Medical Research Council

Somerset NHS Foundation Trust

PINCS

Postnatal Instead of Normally-timed Cervical Screening

Investigating the acceptability and accuracy of cervical screening and self-sampling in women at 6-weeks postnatal

Chief Investigator
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Postnatal Instead of Normally-timed Cervical Screening (PINCS)
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1 LIST OF ABBREVIATIONS

AE	Adverse Event
CA	Competent Authority
CI	Chief Investigator
CIN	Cervical intraepithelial neoplasia/cervical dysplasia
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
HCPs	Healthcare professionals
HPV	Human Papilloma Virus
HR-HPV	High-risk Human Papilloma Virus
IB	Investigator Brochure
ICF	Informed Consent Form
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
LBC	Liquid-based cytology
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NHS CSP	National Health Service Cervical Screening Programme
NHS R&D	National Health Service Research & Development
NSC	National Screening Committee
NTDD	Next Test Due Date
PI	Principal Investigator
PIC	Participant Identification Centre
PIS/PIL	Participant Information Sheet/Letter
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
SSI	Site Specific Information
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

2 TRIAL SUMMARY Phase 1 (PINCS-1)

Trial Title	Investigating the feasibility and acceptability of cervical screening and self-sampling in women at 6-weeks postnatal
Internal ref. no. (or short title)	Postnatal Instead of Normally-timed Cervical Screening-1 (PINCS-1)
Trial Design	A paired feasibility study to investigate the acceptability of cervical screening and self-sampling in postnatal women at 6-weeks and 12-weeks postnatal
Trial Participants	Women and people with a cervix who are 24.5 years old or more, who are pregnant or within 6 weeks of birth
Summary	Consenting participants will have a speculum examination and cervical sample (smear test) taken at 6-weeks and 12-weeks postnatal for HR-HPV testing and liquid based cytology, and urine self-testing using the Colli-pee device for HR HPV testing. We will perform a patient questionnaire after sampling (web-based or paper), at both 6 and 12- weeks, to ascertain acceptability (compliance with protocol), feasibility (ability to recruit), patient-reported outcomes, including discomfort of testing, preferences regarding timing of screening and attitudes to introducing the option of screening at the 6-week postnatal check up in the GP practice. To understand reasons for non-participation and evaluate uptake, a cohort of potential participants will all be approached, and the number who consent of those approached recorded. Reasons given by those that opt to not participate will be fully anonymised.
Rationale	In 2016, the peak incidence of cervical cancer was in the 25 to 30-year age group, coinciding with the average age of a first-time mother in England and Wales (29 years). During pregnancy and the postnatal period women have multiple interactions with healthcare professionals (HCPs) and discussions regarding screening, for both themselves and their baby, at multiple points during and after pregnancy. These contact points are opportunities to inform, educate and facilitate the uptake of cervical screening, helping women to make informed choices. Focus groups, involving women who have recently been through a pregnancy and General Practice teams, agreed that cervical screening at the 6-week postnatal check-up was preferable and that women were more likely to take up the offer of cervical screening. This is compared to the current situation where screening is only available from 12-weeks postnatal.

	There is currently little evidence to support or refute the efficacy of a cervical screening test 6-weeks postnatal. To evaluate this a large study is needed. However, the best design of this study in terms of feasibility and efficiency is not clear. The aim of this study is to determine the acceptability and feasibility of a design where each woman is sampled twice, at 6- and 12-weeks postnatal.	
Planned Sample Size	Acceptability based on recruitment of at least 100 participants who complete the first sample at 6 weeks postnatal. Uptake evaluated using a sample of at least 100 participants who are approached and invited to participate. These will provide precision of at most 5% on the estimated parameters (proportions), which we judge sufficient to evaluate feasibility and acceptability of the design.	
Planned Trial Period	36-48 months	
	Objectives	Outcome Measures
Primary	To evaluate the acceptability and feasibility of a paired study design to evaluate: Acceptability: 1) Whether women are willing to undergo cervical screening at 6-weeks postnatal and 2) If they would be prepared to have cervical screening at both 6 and 12 weeks postnatal Feasibility 3) How many women need to be approached for one to consent.	Acceptability a) Number of participants attending for 6-week postnatal test of those who consent. b) Number of participants attending for 6 and 12-week postnatal test of those who consent. Feasibility c) Recruitment rate (number of participants recruited out of 100 potential participants approached, in subset)
Secondary	1. Evaluate acceptability of clinician-taken sample and urine self-screening tests in those who decline, and in those who consent both at 6- and 12-weeks using questionnaire data. 2. Assess the quality of cervical samples from clinician-taken samples at 6-weeks postnatal. 3. To determine the agreement	a) Acceptability of postnatal testing using questionnaires by: (i) those choosing not to participate; (ii) participants following appointments (both 6 and 12 weeks); (iii) acceptability of Colli-pee testing b) Adequacy rate and reason for inadequacy of HPV testing and

	in HR HPV status at 6- and 12-weeks postnatal between clinician-taken cervical samples and self-testing using urine tests.	cytology at 6-weeks postnatal and 12 weeks postnatal (6-weeks after a previous sample) c) Agreement in HPV test positivity between 6- and 12-week postnatal clinician-taken cervical sampling d) Proportion of clinician sample HPV-positive tests that are also positive using urine self-sampling, at 6 and 12 weeks. e) Proportion of clinician sample HPV-negative tests that are positive using urine-self sampling, at 6 and 12 weeks.
Sites	Multiple sites across England, including those whose Gynaecological Cytology is processed at the Severn Pathology, Manchester Cytology Centre or Derbyshire Pathology labs.	

3 STUDY BACKGROUND

3.1 DRIVER FOR STUDY QUESTION

The NHS Cervical Screening Programme (NHS CSP) standard for cervical screening coverage is 80% uptake to achieve the aim of preventing cancer and deaths from cancer (1). The national audits of women with invasive cervical cancer demonstrates that women who do not attend for screening make up a disproportionate number of cases of cervical cancer; around 60% of women diagnosed with cervical cancer were either never screened or overdue for screening (2). By 2019, overall cervical screening coverage rates in England were around 70%, although in some parts of the country this was as low as 50%, and screening rates were the lowest they had been since the NHS CSP was introduced in 1988 (3, 4). Women with children aged less than 5 years are less likely to have attended their most recent screening invitation (5).

Due to the success of cervical screening the peak age of incidence of cervical cancer in the UK is now aged 25-30 years, which coincides with the age that the many women enter their first pregnancy (6, 7). Cervical screening uptake in this age group is lower than the programme standard (~60%) (4) and pregnancy provides several points of contact for promoting public health in general and cervical screening in particular; an opportunity that was being missed.

A retrospective cohort study in Somerset identified that 50% of women were not up to date with their cervical screening by the end of their pregnancy (8). However, at 6 months postnatal, 50% of the women who were not up to date in pregnancy had still not had cervical screening (8).

A quality improvement project, including focus groups involving new mothers, midwives and primary care teams, identified causes for poor uptake and generated several ideas for change. One key idea for change to improve uptake, suggested by both women and primary care teams, was to move the postnatal smear to coincide with the 6-week postnatal check-up (8). This would make it easier for both women and their primary care teams, reducing need for additional appointments. Self-testing was also suggested to improve screening uptake for busy new mums.

3.2 EVIDENCE FOR CURRENT GUIDANCE OF PERFORMING CERVICAL SCREENING AFTER 12 WEEKS POSTNATAL

We performed a literature search to determine the evidence for this recommendation. We found that there are minimal data from the liquid-based cytology era to support the current guidelines for recommending cervical screening should be performed at minimum of 12-weeks after childbirth. One study using conventional cytology, compared Papanicolaou smears taken at 4, 6 and 8 weeks postnatal (9). They found that there were increased inflammatory changes in those taken earlier, leading to more false-positive, low-grade smears. However, this pre-dates HPV triage and liquid-based cytology. Current recommendations to delay smears until 12-weeks postpartum are therefore based on long-held perceived wisdom, based on out-dated tests, rather than sound evidence of differences in diagnostic test accuracy (DTA).

According to the literature, HPV infection status does not differ between pregnancy and the postnatal period. However, these studies performed HPV tests at varying time periods postnatally, ranging from 45 days post-natal (10) to 6-months postnatal (11).

An Irish observational study, including 556 postnatal women, reported no difference in inadequate smear rates (2.5%) when the smear was taken at 6 weeks postnatal using liquid-based cytology compared to a non-pregnant gynaecological population consisting of 1429 women (2.7%) (12). The incidence of unsuitable smears reported in the overall population was 3.2% and therefore using liquid-based cytology appears to negate the previously held belief that post-natal smears should be performed at 12 weeks post-natal. HPV-testing was not compared in this study.

3.3 SELF-TESTING IN POSTNATAL WOMEN

Many women struggle to undergo cervical screening, especially those in higher-risk and socioeconomically disadvantaged groups (13). HPV primary testing, using self-sampling methods, offers an alternative to conventional speculum examination and liquid-based cytology for initial screening and improves screening uptake in under-screened women (14). Urine testing with Colli-pee device has ~70% concordance for HPV positivity from urine and cervical samples in some studies (15). However, previous diagnostic test accuracy studies have not specifically targeted postnatal women, where desire to avoid vaginal sampling may be increased, due to traumatic birth experiences. Our study provides an opportunity to test the DTA of self-testing using the Colli-pee sampler at 6- and 12-weeks postnatal (16, 17). These data will further inform national screening programmes.

3.4 RATIONALE

Between 2016-17 the Somerset NHS Foundation Trust local Invasive Cervical Cancer Audit identified six pregnant or recently postnatal women who were diagnosed with cervical cancer. Some of these women had been eligible for cervical screening in pregnancy or postnatally but had not had screening. Overall, 14 of the 24 women diagnosed with a cervical cancer were out of date for cervical screening, the majority of whom had had a pregnancy previously. This correlates with the results of the latest Public Health England Invasive Cervical Cancer Audit, which found that people diagnosed with cervical cancer were statistically less likely to be up-to-date with screening than controls (20 to 27% compared with 63%).

Focus groups, involving women who have recently been through a pregnancy, and general practice teams, agreed that cervical screening at the 6-week postnatal check-up was preferable and that women were more likely to take up the offer of cervical screening. This is compared to the current situation where screening is deferred until after 12-weeks postnatal. We are currently investigating the acceptability of cervical screening earlier in the postnatal period in a quantitative and qualitative attitudes study. Preliminary data, from this ongoing study, suggest that 67% of respondents would be willing to take part in a clinical study of earlier clinician-taken cervical screening and 79% would be willing to take part in a study of self-testing with urine samples in the postnatal period (unpublished results; n = 299).

4 STUDY OBJECTIVES

This is a two-phase study with a paired sample study design (PINCS-1) with samples performed at 6 and 12-weeks postpartum, followed by a randomised two-arm feasibility study in phase 2 (PINCS-2), comparing sampling at 6 or 12 weeks postnatal. The study protocol will be updated via a substantial amendment with the details for phase 2 prior to recruitment for PINCS-2 commencing. An outline of PINCS-2 is available in the appendix.

4.1 PRIMARY OBJECTIVE (PINCS-1):

- To evaluate the acceptability and feasibility of a paired study design to evaluate:
    - Acceptability:
        - Whether women are willing to undergo cervical screening at 6-weeks postnatal; and
        - If they would be prepared to have cervical screening at both 6 and 12 weeks postnatal?
    - Feasibility
        - How many women need to be approached for one to consent?

4.2 SECONDARY OBJECTIVES (PINCS-1):

- Evaluate acceptability of clinician-taken cervical samples and urine self-screening tests in those who decline, and in those who consent both at 6- and 12-weeks using questionnaire data.
- Assess the quality of cervical samples from clinician-taken samples at 6-weeks postnatal.
- To determine the agreement in HR HPV status at 6- and 12-weeks postnatal between clinician-taken cervical samples and self-testing using urine tests.

4.3 OUTCOMES (PINCS-1)

4 Primary outcomes (PINCS-1)

4.3.1.1 Acceptability

- Number of participants attending for 6-week postnatal test of those who consent.
- Number of participants attending for 6 and 12-week postnatal test of those who consent.

4.3.1.2 Feasibility

- Recruitment rate (number of participants recruited out of 100 potential participants approached, in subset)

4 Secondary outcomes (PINCS-1)

- Acceptability of postnatal testing: described by those choosing not to participate, or drop out between study visit 2 and 3; reported on questionnaires by participants following appointments (6 and 12 weeks); acceptability of Colli-pee testing; factors that influence acceptability and uptake
- Adequacy rate and reason for inadequacy of HPV-testing and cytology at 6-weeks postnatal and 12 weeks postnatal (6-weeks after a previous sample)
- Agreement in HPV test positivity between 6- and 12-week postnatal clinician-taken cervical sampling

- Proportion of clinician sample HPV-positive tests that are also positive using urine self-sampling, at 6 and 12 weeks.
- Proportion of clinician sample HPV-negative tests that are positive using urine-self sampling, at 6 and 12 weeks.

5 STUDY DESIGN (PINCS-1)

We will perform a study to assess acceptability and feasibility of a paired diagnostic accuracy study design.

Cervical screening will be performed with clinician-taken cervical screening samples, for HPV testing and cytology at 6-weeks postnatal, with repeat testing at 12-weeks postnatal. This will inform us as to whether participants are prepared to undergo cervical screening with a speculum examination at 6 and 12-weeks postnatal. It will also inform us as to the feasibility of a pair-wise diagnostic test accuracy study, using repeat testing in the same participant, or whether alternative study designs should be employed. Participants will be offered self-testing using Colli-pee collectors at both time points, to ascertain the agreement with clinician-taken sampling and the acceptability to participants at both time points.

We will recruit women during, or within 6 weeks of completion of, pregnancy, regardless of screening status, to maximise participation. NHS CSP screening schedules (Next Test Due Date – NTDD) will not be re-set for those who have normal testing and were previously up-to-date on screening. Those that were out-of-date on their cervical screening will have their NTDD reset according to the most abnormal of either their 6 or 12-week study results, in accordance with NHS CSP guidelines.

The 6-week sample will undergo initial steps in the laboratory, to allow for safe storage, and saved for processing once the 12-week sample is due. The sample that demonstrates the higher-grade abnormality will determine the ongoing pathway, according to NHSCSP management guidelines. If either sample demonstrates HR HPV positive and abnormal cytology, a non-screening colposcopy referral will be made by the local study team, even if a direct referral is generated, as a failsafe. NTDD will be reset following colposcopy, as per NHSCSP guidelines. If either sample demonstrates HR HPV positive, but normal cytology, either a non-screening referral to colposcopy or reset of NTDD will be made, depending on previous results, as per the NHS CSP screening protocol. The study team will write to the lab as a non-screening referral to reset the NTDD, even for those who generate a direct referral, as a failsafe.

Those with abnormal cytology, but negative for HR HPV, will be referred to colposcopy as a non-screening referral by the local study team (i.e., not a direct screening referral from the cytology laboratory). These results will not be uploaded to the NHS Cervical Screening Administration Service (NHS CSAS) and non-screening referrals will be made by the local study team, outside of the direct referral system for HR HPV-positive samples.

If a participant attends for their 6-week sampling, but withdraws from the study and does not attend for their 12-week sample, the 6-week sample will be processed, and the result communicated to the patient/their GP. Colposcopy referral/NTDD reset will be generated, if appropriate, as above.

The results from the urine HPV testing will not be conveyed to the patient or the GP. There will be no clinical or patient management actions taken on the urine HPV test results.

Participants must be eligible for the cervical screening programme. This requires them to be 24.5 years to 64 years old and have a cervix. Potential participants will be informed of the study and given the study patient information, and if interested in participating, self-refer or referred to a member of the research team.

5.1 NON-PARTICIPANT SUB-STUDY

To understand reasons for non-participation and establish an up-take rate, a cohort of 100 potential participants will be approached, and the acceptance rate recorded. The reason given by those who choose not to participate will be recorded anonymously for those who agree to have their views recorded.

5.2 STUDY VISIT 1 (PINCS-1)

At study visit 1, potential participants will discuss the study with a member of the research team, and, if willing to take part, consent will be obtained and they will complete a brief questionnaire.

For those who are pregnant when consenting to the study, a member of the study team will contact the participant after delivery to confirm ongoing willingness to participate and arrange a 6-week screening appointment. Access to maternity and medical records will be included in the study consent, to allow for notification of delivery and follow up of cervical screening results and ongoing management via colposcopy. Participants will receive appointment reminder notifications in advance of their appointments.

5.3 STUDY VISIT 2 (PINCS-1)

At study visit 2 at 6-weeks after delivery, consent will be confirmed, and the participant will perform self-testing with a Coli-pee sampler. A speculum examination will then be performed, and a cervical sample taken using a cervical broom. Samples will be collected, in accordance with the NHS CSP guidance, by members of the study team who are registered on the Cervical Sample Takers Database.

The appointment plan for 12-week screening will be confirmed, and further appointment made. Following the appointment, the participant will complete a questionnaire (web-based or paper). A reminder notification will be conveyed in advance of the next appointment.

5.4 STUDY VISIT 3 (PINCS-1)

At study visit 3 at 12-weeks postnatal, ongoing consent will be confirmed. A Colli-pee urine sample and cervical sample will be taken, as above. The participant will be informed of the management process in the case of an abnormal screening result. Following the appointment, the participant will complete a questionnaire (web-based or paper).

The cervical samples will be transported to the research site's usual cytology lab following standard processes. Participants will receive a letter containing their cervical screening results, and information on continuation of care under the NHS CSP, with a copy sent to their GP (and the cytology laboratory if the NTDD is to be changed).

The urine samples will be sent for laboratory analysis at the Manchester Cytology Centre. The urine results will form part of the study data analysis, but the results will not be available to the study team or study participants during the study. No clinical action will be required based on the results of the urine tests, and the results will not affect the NHS CSP Next Test Due Date (NTDD).

6 PARTICIPANT ELIGIBILITY CRITERIA

6.1 PATIENT IDENTIFICATION AND SCREENING

Potential participants will be identified by members of patient's existing clinical care team including general practitioners, community or hospital midwifes, health visitors, practice nurses or obstetricians, as part of routine schedule of pregnancy-related appointments. Potential participants may also self-identify through publicity literature in recruitment sites and via social media of gynaecological cancer charities (e.g. Jo's Cervical Cancer Trust, GO Girls) and local and national social media groups for new mothers (e.g. Mumsnet). Publicity would be in the form of posters and leaflets, distributed via social media, at antenatal events, and at routine appointments or shared through the electronic maternity care record. Potential participants will be pregnant or within 6 weeks of delivery. Potential participants will be given a patient information leaflet and if interested in participating they will be referred to a member of the study team.

A sub-study of at least 100 potential participants, approached in pregnancy or within 6 weeks of delivery by a member of the research team, will record anonymously whether the potential participant accepted or declined participation, to ascertain likely future study recruitment rates. Reasons for declining to be involved will be recorded, with verbal consent, anonymously, including the setting potential participant approached (in pregnancy/postnatal; hospital or community setting).

6.2 INCLUSION CRITERIA

- 24.5 years (24 years and 183 days or greater on day of consent)) to <65 years old
- Women and people with a cervix
- Currently pregnant or within 6 weeks of delivery at the time of recruitment
- Able to give informed consent

6.3 EXCLUSION CRITERIA

- Absence of a cervix
- Not eligible for the NHS CSP
- Unable to give fully informed consent

6.4 WITHDRAWAL CRITERIA

A participant has the right to withdraw from the study at any time.

Participants who withdraw from the study will have all their data included in the study analysis, up to the date of withdrawal of consent, unless requested by the individual not to include it. Any stored samples remaining on withdrawn participants will be either destroyed or remain within the laboratory for future testing, depending on the participant's wishes.

If participants withdraw, we will confirm their permission to check their future cervical screening and colposcopy results, if they have these performed via the NHS CSP, within the study period.

The reason for withdrawal will be recorded in the CRF, using the pre-6-week and post-6-week withdrawal questionnaires, or the reason recorded will be "not given" if not provided by the participant.

The Principal Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason.

7 STUDY PLAN (PINCS-1)

7.1 VISIT SUMMARY (PINCS-1)

The study will consist of a screening and consent appointment followed by two study visits.

- Appointment 1 (during pregnancy or within 42 days of delivery), patient information and consent (may be at the same time as patient identification, provided sufficient time has been given to read the patient information sheet and understand the study).
- Appointment 2 (at >37 but ≤56 days postnatal), cervical sample for LBC/HR HPV testing (speculum and broom) and urine sample for HR HPV testing. Web-based/paper questionnaire after sample collection.
- Appointment 3 (at > 42 days after first test and ≥84 days but <24 weeks postnatal), cervical sample for LBC/HR HPV testing (speculum and broom) and urine sample for HR HPV testing. Web-based/paper questionnaire after sample collection.

7.2 SCREENING AND CONSENT VISIT (STUDY VISIT 1) (PINCS-1)

Potential participants will be assessed against the above inclusion and exclusion criteria and will be asked if they wish to participate if they are eligible for the study.

All eligible individuals will be given a Patient Information Sheet and provided with an explanation of the study. This will detail what the study will involve, why it is being carried out, any benefits and/or risks related to participation and details of renumeration for participation. They will have as much time as they need to consider whether they would like to participate or not (at least 1 hour). Potential participants will be informed that participation is voluntary, and their clinical care will not be affected if they choose not to participate, or if they withdraw their consent at any point. Participants will be informed that participation may lead to a referral to colposcopy, or an earlier repeat cervical screening test, if the test results are abnormal.

Participants will give informed consent through a signed and dated declaration of consent. Once they have consented, participants will be allocated a unique study ID and added to the enrolment log. The participant will complete a (web-based or paper) questionnaire (5-10 minutes) with help from a member of the study team, if required. Paper forms will be transcribed to the electronic clinical research file (eCRF) by a member of the study team and the original paper copy kept in the site file.

The eCRF will include:

- Age
- Ethnicity
- Main languages spoken
- Sexual orientation and gender
- Cervical screening history (including previous abnormal cervical screening and any treatments)
- Smoking status
- Self-reported HPV vaccination history
- Obstetric history (parity, mode of previous and most recent deliveries, dates of deliveries), pregnancy complications (including any perineal/vaginal tears or infection) and perception of birth trauma
- Number of children in their care
- Number of days since delivery
- HIV status
- Immunosuppressants
- Relationship status
- Educational level completed
- Occupation and employment status
- Residential post code to calculate Index of Multiple Deprivation
- Time from home to the hospital
- Mode of travel from home to the hospital
- How much time is allowed to get from home to research appointment
- Time from home to their GP
- Local family support with childcare

This screening visit can be performed at the time of patient identification, and routine clinical appointments, or as an additional study visit depending on participant preference.

7.3 POSTNATAL CONTACT (PINCS-1)

After delivery, a member of the study team at the local site will contact the participant to confirm ongoing willingness to participate and arrange a 6-week screening appointment. A reminder notification will be conveyed in advance of the appointment, including **instructions to avoid urinating 1 hour before the appointment** to facilitate taking the urine sample.

7.4 STUDY VISIT 2 (6 WEEKS POSTNATAL) (PINCS-1)

- Confirm consent to continue in study (verbal). We will record the number who choose to withdraw from the study, with reasons, if given. The reason for withdrawal will be recorded in the CRF, or the reason recorded will be “not given” if not provided by the participant.
- Check if any adverse events (AEs) since last visit. Study team to record any AEs in eCRF.
- If consenting to self-test, give Colli-pee sampler with instructions (as per manufacturer). A link to a video will be made available to study participants prior to and at the appointment. https://sites.manchester.ac.uk/aces/.

- Participant performs urine test with Colli-pee sampler - check that participant has not passed urine within the last hour and delay taking sample until an hour has passed.
- Check sample sealed and container is clearly labelled with study details, study ID number and study request card on pink paper.
- **After** taking the urine sample, perform speculum examination with water or carbomer free lubrication.
- Take a cervical sample:
    - Place the tip of a cervical broom into the os of the cervix and rotate 360° 5 times; Place the Cervex-Brush™ / broom as it is into the LBC fixative (ThinPrep);
    - Push the Cervex-Brush™ / broom into the bottom of the vial using a vigorous swirling motion. Do this at least 10 times, forcing the bristles apart. Firm pressure is necessary or the cells will cling to the Cervex-Brush™ / broom;
    - Inspect the Cervex-Brush™ / broom for any residual material and remove any remaining by passing the Cervex-Brush™ / broom over the edge of the fixative vial;
    - Make sure the material reaches the liquid to preserve it;
    - Tighten the cap so that the torque line passes the torque line on the vial;
    - Shake the vial if you wiped any material on the edge;
    - Label the vial. The broom can then be discarded.
- Make sure the LBC container is clearly labelled with study details, study ID number and study request card on pink paper. Place sample in study sample collection bag for transfer to the cervical screening laboratory.
- If the appearance of the cervix is consistent with cervical cancer, refer to colposcopy via cancer wait time pathway.
- Book further appointment for 12-week cervical screening test.
- Complete and send GP letter, informing of study participation, if participant consents.
- Participant completes the questionnaire in the clinic (5 minutes) about acceptability of testing methods and timing, either via a web-based form or on a paper form, if preferred, with help from a member of the study team, if required. Any paper or electronic forms will be transcribed to the eCRF by a member of the study team and the original paper copies kept in the CRF.
- Study team member to record visit and details of tests performed and ensure questionnaire results uploaded to eCRF.
- Study team member to send cervical screening sample and urine sample to the local cervical screening laboratory. Urine samples will be forwarded from the local cervical screening laboratory to the centralised testing centre.

7.5 STUDY VISIT 3 (12-WEEKS POSTNATAL) (PINCS-1)

- Confirm consent to continue in study (verbal). We will record the number who chose to withdraw from the study, with reasons, if given. The reason for withdrawal will be recorded in the CRF, or the reason recorded will be “not given” if not provided by the participant. If participants withdraw, we will confirm their permission to check their future cervical screening results, if they have these performed via the NHS CSP, within the duration of the study.
- Check if any AEs since last visit. Study team to record any AEs in eCRF.

- Check participant has not passed urine within last hour and delay urine collection until this time has passed.
- If consenting to self-test, give Colli-pee sampler with instructions (as per manufacturer). A link to a video will be made available to study participants prior to and at the appointment. https://sites.manchester.ac.uk/aces/.
- Check sample sealed and container is clearly labelled with study details, study ID number and study request card on pink paper.
- **After** urine sample taken, perform speculum examination with water or carbomer free lubrication.
- Take a cervical sample:
    - Place the tip of a cervical broom into the os of the cervix and rotate 360° 5 times; Place the Cervex-Brush™ / broom as it is into the LBC fixative (ThinPrep);
    - Push the Cervex-Brush™ / broom into the bottom of the vial using a vigorous swirling motion. Do this at least 10 times, forcing the bristles apart. Firm pressure is necessary or the cells will cling to the Cervex-Brush™ / broom;
    - Inspect the Cervex-Brush™ / broom for any residual material and remove any remaining by passing the Cervex-Brush™ / broom over the edge of the fixative vial;
    - Make sure the material reaches the liquid to preserve it;
    - Tighten the cap so that the torque line passes the torque line on the vial;
    - Shake the vial if you wiped any material on the edge;
    - Label the vial. The broom can then be discarded.
- Make sure the LBC container is clearly labelled with study details, study ID number and study request card on pink paper. Place sample in study sample collection bag for transfer to the cervical screening laboratory.
- If the appearance of the cervix is consistent with cervical cancer, refer to colposcopy via cancer wait time pathway.
- Before the participant leaves clinic ensure you have their preferred means of contact to receive their results.
- Participant completes the questionnaire in the clinic (5 minutes) about acceptability of testing methods and timing, either via a web-based form or on a paper form, if preferred, with help from a member of the study team, if required. Any paper or electronic forms will be transcribed to the eCRF by a member of the study team and the original paper copies kept in the CRF.
- Study team member to record visit and details of tests performed and ensure questionnaire results uploaded to eCRF.
- Study team member to send cervical screening sample and urine sample to the local cervical screening laboratory. Urine samples will be forwarded from the local cervical screening laboratory to the centralised testing centre.
- Local PI and study team check on cervical screening result, communicate with participant and GP, and ensure follow up and next text due date NTDD reset, as per NHS Cervical Screening Programme guidance.

7.6 MANAGEMENT OF CYTOLOGY AND URINE SAMPLES

Cytology samples performed following a HR HPV positive test will be dual labelled with patient identifying information and study details/study number and stored and managed in accordance with NHS CSP guidance.

Cytology samples taken out of normal NHS CSP protocol, purely for the purposes of the study for (HR HPV negative samples) and will be labelled with study details and study ID number only and will be destroyed at the end of the study. Results of the cytology on HPV negative samples, which would not ordinarily be performed as part of the NHS Cervical Screening Programme, will not be uploaded to the NHS Cervical Screening Administration Service (CSAS), but will be recorded for the purposes of the study and acted on within the study protocol.

Urine samples will be labelled with a study details and study ID number only and will be destroyed after testing and communication of results with the study team.

7.7 DEFINITION OF END OF STUDY

Recruitment will end when at least 100 recruited participants have attended and completed clinician-sample screening at their six-week appointment and have attended, or declined to attend, their 12-week appointment. If participants withdraw before the 6-week sample, further participants will be recruited, so that at least 100 participants have their 6-week samples performed. The study will end once all patients have completed follow up, as described above, and data have been collected and analysed. In the instance of low recruitment, an earlier end point may be initiated following discussion with the Independent Trial Steering Committee.

8 PINCS-2

PINCS-2 - Postnatal Instead of Normally-timed Cervical Screening-2 (PINCS-2) is the second phase of the PINCS Feasibility Study. This is a feasibility study of 100 participants to test the feasibility of individual consent and randomisation to LBC screening at 6- (arm A) or 12-weeks (arm B) postnatal. Self-testing will be offered at the time of LBC screening, as well as at 12-weeks for those in arm A. This will inform whether further studies can be individually randomised, requiring smaller sample sizes for adequate statistical power, or whether a cluster randomised design will be needed, to test the effect on uptake rates of screening and longer-term clinical effects on subsequent screening outcomes and development of CIN.

For both feasibility studies we will recruit women regardless of screening status at the end of pregnancy, to maximise participation. NHS CSP screening schedules will not be re-set for those who have normal test results. However, those with abnormal results will be treated according to NHS CSP guidance. Both studies will collect paired LBC samples and self-collected samples for HPV testing. We will perform a participant questionnaire after sampling at both 6 and 12- weeks to ascertain participant-reported outcomes. This will help to inform changes to the subsequent study designs & ultimately the NHS CSP screening schedule.

We will update the PINCS protocol, via a substantial amendment, prior to beginning recruitment to the second phase of PINCS (PINCS-2), with separate PIS and consent forms. We will start recruitment once either recruitment to PINCS-1 has completed. If recruitment to PINCS-1 is poor, showing that a paired sample design is not feasible, a decision to start PINCS-2 will be made

following review of the anonymised data and recruitment by the Independent Trial Steering Committee, subject to ethical approval of amendments.

8.1 STUDY FLOW CHARTS

8 PINCS-1 Participant flowchart

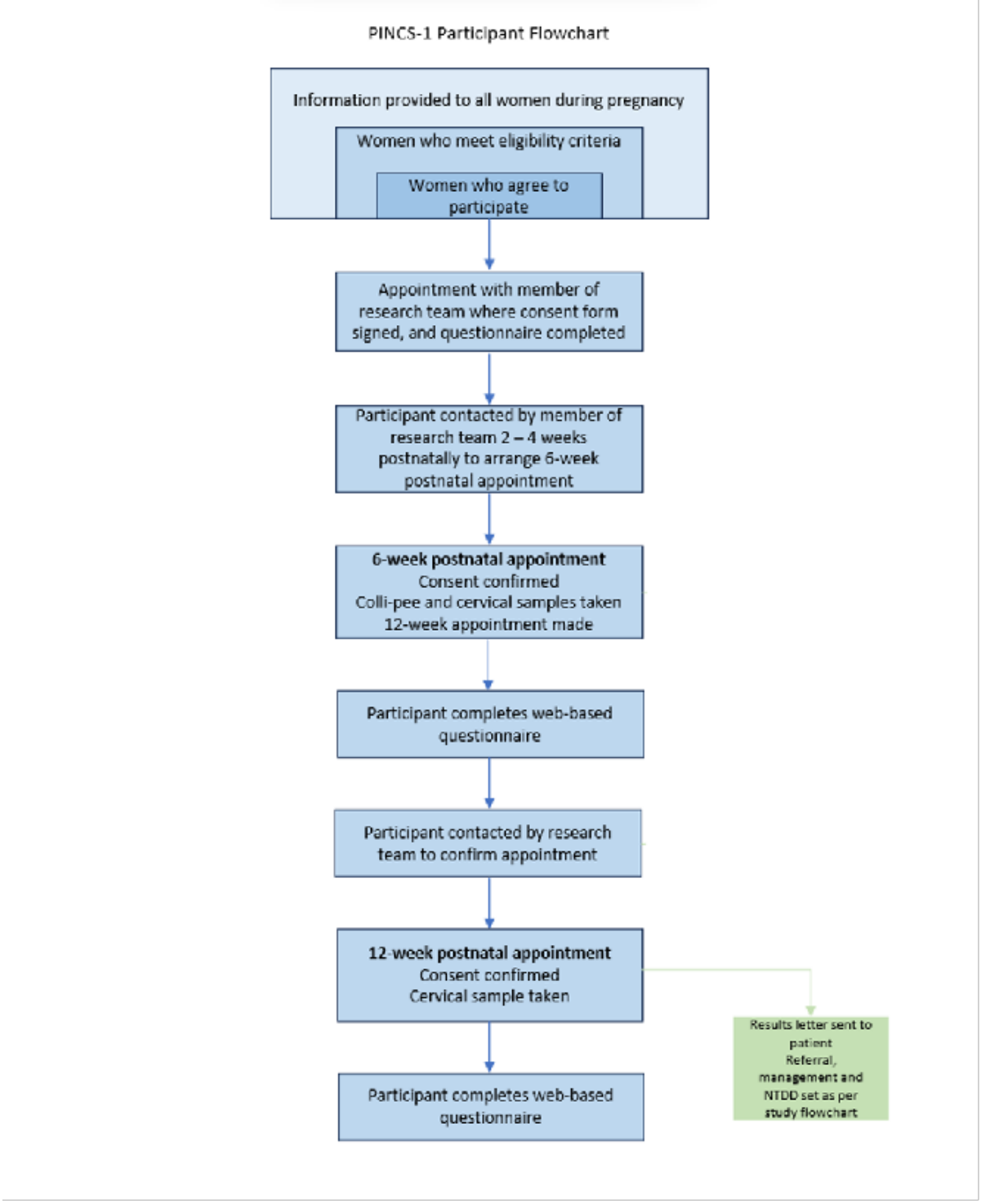

Figure 1 PINCS-1 participant flowchart NTDD = Next Test Due Date

8 PINCS-1 Study flowchart

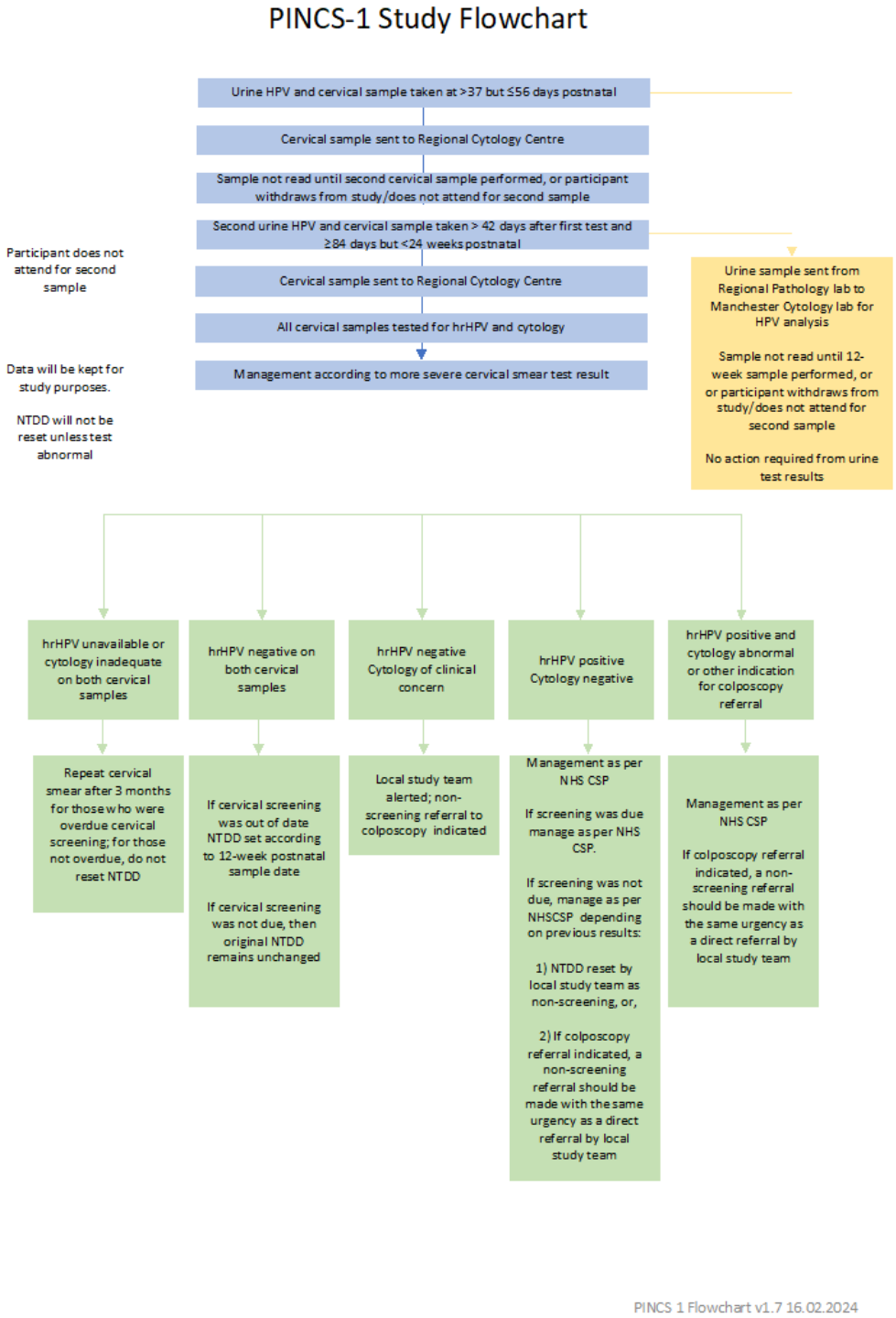

Figure 2 PINCS-1 study flowchart NHSCSP = NHS Cervical Screening Programme; NTDD = Next Test Due Date; hrHPV = high risk human papilloma virus; DTA = diagnostic test accuracy; PROM = patient reported outcome measures

9 STUDY PROCEDURES

9.1 SPECULUM EXAMINATION AND CERVICAL SAMPLE (SMEAR TEST)

Cervical sampling will only be performed by accredited professionals, who have undergone required training, and who hold a cervical screening sample taker code, as per NHS CSP criteria. The collection technique will follow standard practice for cervical sampling:

- A speculum examination will be performed with the use of minimal KY lubricating jelly. A cervical sample will be obtained by placing the tip of a cervical broom into the os of the cervix and rotating 360^0 5 times;
- Place the tip of a cervical broom into the os of the cervix and rotate 360° 5 times; Place the Cervex-Brush™ / broom as it is into the LBC fixative (ThinPrep);
- Push the Cervex-Brush™ / broom into the bottom of the vial using a vigorous swirling motion. Do this at least 10 times, forcing the bristles apart. Firm pressure is necessary or the cells will cling to the Cervex-Brush™ / broom;
- Inspect the Cervex-Brush™ / broom for any residual material and remove any remaining by passing the Cervex-Brush™ / broom over the edge of the fixative vial;
- Make sure the material reaches the liquid to preserve it;
- Tighten the cap so that the torque line passes the torque line on the vial;
- Shake the vial if you wiped any material on the edge;
- Label the vial. The broom can then be discarded.

The risks to the participant are discomfort from the speculum examination and cervical sampling, and a small risk of light vaginal bleeding after the procedure. Speculum examination is safe following birth, including following perineal repair, and no additional risks are anticipated. A small number of women may find the examination painful. Participants will be able to stop the examination at any point, should they experience pain or wish to not continue.

9.2 URINE SAMPLE

Urine samples will be collected by participants using the Colli-Pee self-sampling urine-collection device. This allows for volumetric and standardised collection of first-void urine. This will be used for HR HPV testing at 6-weeks and 12-weeks postnatal.

There are no additional foreseen risks to the patient from urine self-sampling, as clinical management will be based on clinician-taken samples.

10 ADVERSE EVENTS

10.1 DEFINITIONS

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant of the study.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: ● results in death ● is life-threatening ● requires inpatient hospitalisation or prolongation of existing hospitalisation

	● results in persistent or significant disability/incapacity ● consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

10.2 REPORTING ADVERSE EVENTS

In all cases AEs and / or laboratory abnormalities that are critical to the safety evaluation of the participant must be reported to the Sponsor; these may be volunteered by the participant, discovered by the investigator questioning or detected through physical examination, laboratory test or other investigation.

Potential AEs will be recorded at assessments and during communications with the research team when arranging appointments. Participants may contact the research team (e.g., over the phone) at any time point during the study to report potential AEs. AEs will be recorded as part of the eCRF for the previous study visit (e.g., an AE occurring between assessment 1 and 2 will be recorded as part of the study visit 1.

Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

10 Non serious AEs

All such events, whether expected or not, should be recorded.

10.2.1.1 Serious Adverse Events

All SAEs occurring from the time of written informed consent until final visit with the trial team must be recorded on the Case Report Form and sent to the Sponsor **within 24 hours** of the research staff becoming aware of the event. Once all resulting queries have been resolved, the Sponsor will request the original form should also be posted to the Sponsor and a copy to be retained on site.

For each SAE the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality, in the opinion of the investigator
- whether the event would be considered anticipated.

Any change of condition or other follow-up information should be sent to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

11 RESPONSIBILITIES

11.1 PRINCIPAL INVESTIGATOR (PI)

1. Checking for AEs when participants attend for tests / follow-up.
2. Using medical judgement in assigning seriousness, causality and whether the event/reaction was anticipated.
3. Ensuring that all SAEs are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
4. Ensuring that AEs are recorded and reported to the sponsor in line with the requirements of the protocol.
5. Ensuring results of cervical screening are communicated with participants and abnormal results acted upon in accordance with NHS CSP guidance and additional study guidance, for HPV-negative samples.

11.2 CHIEF INVESTIGATOR (CI)

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol.
3. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs.

11.3 SPONSOR

1. Central data collection and verification of AEs and SAEs according to the trial protocol onto a database.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit.
3. Reporting safety information to the independent oversight committees identified for the trial.
4. Preparing standard tables and other relevant information in collaboration with the CI and ensuring timely submission to the REC.

12 STATISTICS AND DATA ANALYSIS

12.1 SAMPLE SIZE

We will recruit at least n=100 participants who attend their 6-week study visit, and there will be at most 5% precision on two acceptability measures (number attending for 6-week test of those who consent; number attending both 6 and 12-week tests). We also judge these to be sufficient precision for the primary analysis on acceptability of the intervention.

Uptake to the study will be estimated using a sub-sample of at least n=100 people who are approached. This will provide standard error on overall uptake at most 5% which we judge sufficient for evaluating feasibility for recruitment to a larger study.

12.2 STATISTICAL ANALYSIS PLAN (SAP)

Full details of the statistical analysis will be described in a SAP that will be written and finalised before data lock. Any subsequent amendments will be documented. The statistical aspects of the study are summarised below.

12.3 METHOD OF ANALYSIS

- **Primary analysis:** The primary outcomes are binary variables. We will estimate 95% CIs for each using Wilson's method.

	Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary	To evaluate the acceptability and feasibility of a paired study design to evaluate Acceptability: 1) Whether women are willing to undergo cervical screening at 6-weeks postnatal and 2) If they would be prepared to have cervical screening at both 6 and 12 weeks postnatal Feasibility 3) How many women need to be approached for one to consent.	Acceptability a) Number of participants attending for 6-week postnatal test of those who consent. b) Number of participants attending for 6 and 12-week postnatal test of those who consent. Feasibility c) Recruitment rate (number of participants recruited out of 100 potential participants approached, in subset)	6-weeks postnatal 12-weeks postnatal During antenatal/postnatal recruitment
Secondary	1) Evaluate acceptability of clinician sample and urine screening tests in those who decline, in those who consent both at 6- and 12-weeks using questionnaire data.	a) Acceptability of postnatal testing using questionnaires by: (i) those choosing not to participate; (ii) participants following appointments (both 6 and 12 weeks);	During antenatal recruitment, 6-weeks and 12-weeks postnatal

	2. Assess the quality of cervical samples from clinician-taken samples at 6-weeks postnatal. 3. To determine the agreement in HR HPV status at 6- and 12-weeks postnatal between clinician-taken cervical samples and self-testing using urine tests.	(iii) acceptability of Colli-pee testing b) Adequacy rate and reason for inadequacy of HPV-testing and cytology at 6-weeks postnatal and 12 weeks postnatal (6-weeks after a previous sample) c) Agreement in HPV test positivity between 6- and 12-week postnatal clinician-taken cervical sampling d) Proportion of clinician-taken sample HPV-positive tests that are also positive using urine self-sampling, at 6 and 12 weeks. e) Proportion of clinician-taken sample HPV-negative tests that are positive using urine-self sampling, at 6 and 12 weeks.	6-weeks and 12-weeks postnatal 6-weeks and 12-weeks postnatal 6-weeks and 12-weeks postnatal 6-weeks and 12-weeks postnatal

Table 1 – outline of statistical analysis plan

13 DATA MANAGEMENT

The plan for the data management of the study is outlined below.

13.1 SOURCE DATA AND DOCUMENTS

Data and records will be managed in accordance with data laws and guidance.

Source documents are where data are first recorded, and from which participants' eCRF data are obtained. These include, but are not limited to, hospital records, clinical and office charts, laboratory and pharmacy records, diaries, radiographs, and correspondence.
eCRF entries will be considered source data if the eCRF is the site of the original recording (e.g., there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

13.2 ACCESS TO DATA

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

13.3 DATA HANDLING AND RECORD KEEPING

Each participant will be assigned a unique Participant Study ID following confirmation of consent to participate in the study.

All trial data will be entered onto a secure web application for managing data (REDCap), which will host the eCRF. The validation process will include naming variables, eCRF design, data verification and validation (range and logic tests), test data entry, and data export verification.

REDCap allows for the main administrator of a project to assign specific rights to individuals to input and/or access data. Local investigators will have the right to input data for the study into REDCap. Those responsible for analysing and monitoring the data will be able to access data and create reports.

Identifiable, personal data will be retained by local study teams. The participants will be identified by a unique trial specific number and/or code in any database for analysis outside REDCap (i.e., they will be excluded from any data exports for data analysis).

Each site will keep a consent log which will keep a record of all participants that have been enrolled onto the study, with study IDs linked to patient identifying information (NHS number, DOB, Name, address), which will be stored in a secure electronic file, which will be password protected, and a paper copy kept in a locked filing cabinet in a secure location. After consent has taken place, the study team member will enter baseline data onto the screening and eligibility case report form. This form can be printed, to be entered electronically later, or entered directly in an electronic version. All electronic versions of the CRF will be stored on secure servers. Any hard copies will be filed locally under patients' unique identifier and stored in locked filing cabinets with access restricted to pre-specified members of the research team at each site.

13.4 ARCHIVING

To ensure participant anonymity is safeguarded and subject to any reasonable and necessary delay, pseudonymised research data will be securely archived to a repository following publication of the results where they will be stored indefinitely. These data may be used in future research, here or abroad.

Prior to database lock, the database will be reviewed to ensure all queries have been resolved and the dataset is complete.
The Data Management will be compliant with Somerset NHS Foundation Trust's policy.

The PI will retain all essential documentation pertained to the study for 10 years as per the Sponsor's policy. This documentation will include copies of protocols, correspondence, CRFs, records of consent, original reports of test results and any other documents related to the conduct of the study. Documents will be stored digitally, or if hard copies, in locked filing cabinets, which will be able to be accessed and data retrieved at a later date if required. Digital forms will be encrypted or stored on Trust secure servers.

No study document is to be destroyed without prior written agreement between the Sponsor and the PI. Should the Investigator wish to assign the study records to another party, or move them to another location then written agreement must be obtained from the Sponsor.

13.5 CONFIDENTIALITY

Confidentiality is governed by principles within the General Data Protection Regulation of 2018, The Caldicott Principles, conditions of Research and Ethics Committee Approvals and 2017 UK Policy Framework for Health and Social Care. Information related to participants will be kept confidential and managed in accordance with these principles.

14 QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and SOPs.

14.1 STUDY MONITORING

All monitoring, audit and inspection of the study will be completed as per the Sponsor's standard operating procedures. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents.

Data will be monitored for quality and completeness by the study's research coordinating team, using established verification, validation and checking processes. Missing data will be chased until they are received, confirmed as not available, or when the trial is at analysis. Study team members from participating centres will also contact participants by telephone to facilitate data completion where appropriate.

The Sponsor reserves the right to intermittently conduct source data verification exercises on a sample of participants, which will be carried out by staff from the Sponsor. Source data verification will involve direct access to patient notes at the participating NHS sites and the ongoing central collection of copies of consent forms and other relevant investigation reports.

Following written SOPs, the monitors will verify that the clinical study is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

14.2 STUDY COMMITTEES

14 Trial Management Committee

The trial management committee will comprise of all named investigators, the trial manager, relevant staff from the Surgical Intervention Trials Unit, patient and public involvement representatives, and other key personnel involved in the trial. It will be responsible for the design of the trial and the day-to-day management in line with the committee's Charter. The Committee will initially meet monthly and the frequency of the meetings will be adjusted depending on progress.

14 Independent Trial Steering Committee

As this is an unblinded trial (with blinded outcome assessment), a separate Data Monitoring and Ethics Committee is not required. The TSC will also assume the role of the Data Monitoring and Ethics Committee. It will comprise of an independent Chair (academic gynaecological oncologist), an independent statistician, a patient and public representative.

15 PROTOCOL DEVIATIONS

15.1 PROTOCOL COMPLIANCE

Protocol non-compliances are departures from the approved protocol. Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and will not be accepted or used.

Accidental protocol deviations can happen at any time. If an accidental protocol deviation is found, this will be reported to the Chief Investigator and Sponsor immediately and documented on the relevant forms.

15.2 SERIOUS BREACHES

A "serious breach" is a breach which is likely to effect to a significant degree –

a. the safety or physical or mental integrity of the participants of the trial; or
b. the scientific value of the trial

Should a serious breach occur then:

- the sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase
- the sponsor of a clinical trial will notify the licensing authority in writing of any serious breach of
  a. the conditions and principles of GCP in connection with that trial; or
  b. the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach

16 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 DECLARATION OF HELSINKI

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

16.2 GUIDELINES FOR GOOD CLINICAL PRACTICE

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

16.3 INTERNATIONAL STANDARD RANDOMISED CONTROLLED TRIALS NUMBER (ISRCTN) REGISTER

We will register the clinical study on the clinical trials ISRCTN registry and update the site regularly. We intend to publish the results of the study within 12 months of completion of each study phase. We will share results widely, including with those responsible for the NHS CSP, to facilitate discussions regarding a larger sentinel site study to test the findings and evaluate whether earlier postnatal screening improves uptake in sentinel site, using QI methodology.

16.4 APPROVALS

Following Sponsor approval, the protocol, informed consent form, PIS and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and HRA (where required) and host institutions for written approval.

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

16.5 DATA PROTECTION AND PATIENT CONFIDENTIALITY

The study will comply with the United Kingdom General Data Protection Regulation (UK GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), with the exception of the secure and encrypted eCRF, where participant identifiable information (e.g. names, contact details, consent form) will be stored. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

16.6 INDEMNITY

NHS indemnity operates in respect of the clinical treatment which is provided. Negligent harm and non-negligent harm policies, which apply to this study, are held by Somerset NHS Foundation Trust.

16.7 PATIENT AND PUBLIC INVOLVEMENT

Patients have been directly involved with the design of research, and will be involved with the undertaking of the research and the dissemination of findings.

This study idea was directly generated by stakeholder groups of new mums, young women who had a cervical cancer diagnosed shortly after pregnancy and primary care staff directly involved in both postnatal care and cervical screening. Supporting this project would therefore be the truest form of public engagement in science. We have also asked pregnant women and those with young children, about the acceptability of this study in a separate quantitative and qualitative study, called pre-PINCS, and adapted our study design accordingly.

The involvement of stakeholders in all phases of this study will dictate future study design and inform changes to the NHS CSP screening schedule.

We will work with Jo's Trust, the UK cervical cancer charity, who recognised our previous work with an innovation award, to publicise the study and encourage recruitment to the survey and DTA study. We will also work with our hospital communications team, using local media and social media channels, to encourage participation. Results will be disseminated with the help of Jo's Trust and our hospital communications team.

17 DISSEMINATION POLICY

This study is designed to support the design of further studies in the NHS CSP regarding timing of postnatal screening and repeat screening after inadequate samples. Data will also inform decisions re self-testing samples for screening. No commercial outputs are expected.

We will publish results in peer-reviewed journals, present data to gynaecological oncology charities for dissemination to women eligible for the cervical screening programme, and though engagement

with social media, e.g., Mumsnet. We will discuss results with NHS England and those responsible for cervical screening in the devolved nations, with a view to further, larger study that would require involvement of the NHS CSP, to test whether this change would lead to an improvement in screening uptake and the effects on screening outcomes, and involve funders, including NIHR and MRC, in order to facilitate taking these plans forwards.

18 ADMINISTRATION

18.1 LANGUAGE

Participant information sheets, consent forms, lay summaries, and any other written materials to be used by subjects will be in language that is easily and clearly understood. CRFs will be in English. We will endeavour to provide written materials in alternative languages, if requested.

18.2 EXPENSES AND BENEFITS

Participants will receive compensation towards reasonable expenses and travel £30 for completing testing and questionnaires at study visit 2 and 3 (£30 for each visit), in line with NIHR involvement guidance and previous cervical screening studies.

19 APPENDICES

RISK

Risks associated with trial interventions

☒A ≡ Comparable to the risk of standard medical care

☐ B ≡ Somewhat higher than the risk of standard medical care

☐ C ≡ Markedly higher than the risk of standard medical care

Justification: Briefly justify the risk category selected and your conclusions below (where the table is completed in detail the detail need not be repeated, however a summary should be given):

There is minimal risk to participants during PINCS-1.

All personal identifiable information will be stored at local sites in locked filing cabinets and on password-protected NHS secure servers. The research team will adhere to principles of data management laid out in the GDPR, Caldicott Principles and Data Protection Act. Pseudonymised patient information will be input and stored on a case report form on the platform, REDCap, which provides secure storage of data.

Participants will be asked to have a speculum examination performed and to provide a urine sample. It is a safe and commonly part of medical care to have a speculum examination performed post-partum.

There is the possibility of false positive, or false negative results. To minimise this risk, cervical samples will be managed as per current existing guidelines and monitored for quality assurance.

There is a risk of samples being incorrectly labelled, and therefore incorrectly reported. Samples will be labelled as per best practice guidelines which involve verbally confirming details with the patient, and checking with another member of staff.

What are the key risks related to interventions/investigations?		How will these risks be minimised?		
Intervention	Body system/Hazard	Activity	Frequency	Comments

Speculum examination and cervical screening	Risks of discomfort and bleeding	Speculum examination and cervical screening to be performed by experienced, accredited personnel.	Up to twice during each feasibility study	
Urine sample	No additional risks	Colli-pee device and sampler using to ensure adequate urine catch.	Up to twice during each feasibility study	

Outline any other processes that have been put in place to mitigate risks to participant safety (e.g. DMC, independent data review, etc.)

- Data storage, management, and patient confidentiality: any personal identifiable information will be held on encrypted files, which will be accessed on NHS secure servers. Study personnel will adhere to the principles of GDPR, Caldicott principles, and the Data Protection Act in the safe management and storage of data.
- Cervical screening quality assurance will be carried out as per National Guidance, to minimise the risk of inaccurately reported cervical samples.
- To minimise the risk of samples being incorrectly labelled, the labelling of samples will be carried out as per the Standard Operating Procedure guidance for the study. This will include the patient providing verbal confirmation, and this being confirmed by a member of staff.

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PINCS-2

21 PINCS-2

PINCS-2 - Postnatal Instead of Normally-timed Cervical Screening-2 (PINCS-2) is the second phase of the PINCS Feasibility Study. This is a feasibility study of 100 participants to test the feasibility of individual consent & randomisation to LBC screening at 6- (arm A) or 12-weeks (arm B) postnatal. Urine self-testing will be offered at the time of LBC screening, as well as at 12-weeks for those in arm A. This will inform whether further studies can be individually randomised, requiring smaller sample sizes for adequate statistical power, or whether a cluster randomised design will be needed, to test the effect on uptake rates of screening & longer-term clinical effects on subsequent screening outcomes & development of CIN.

We will update the PINCS protocol, via a substantial amendment, prior to beginning recruitment to the second phase of PINCS (PINCS-2), with separate PIS and consent forms. We will start recruitment to PINCS-2 once either recruitment to PINCS-1 has completed, or if recruitment to PINCS-1 is poor, showing that a paired sample design is not feasible. Recruitment will be reviewed on a 2-monthly basis. A decision to start PINCS-2 will be made following review of the anonymised data and recruitment by the Independent Trial Steering Committee.

The study outline for phase 2 is as below:

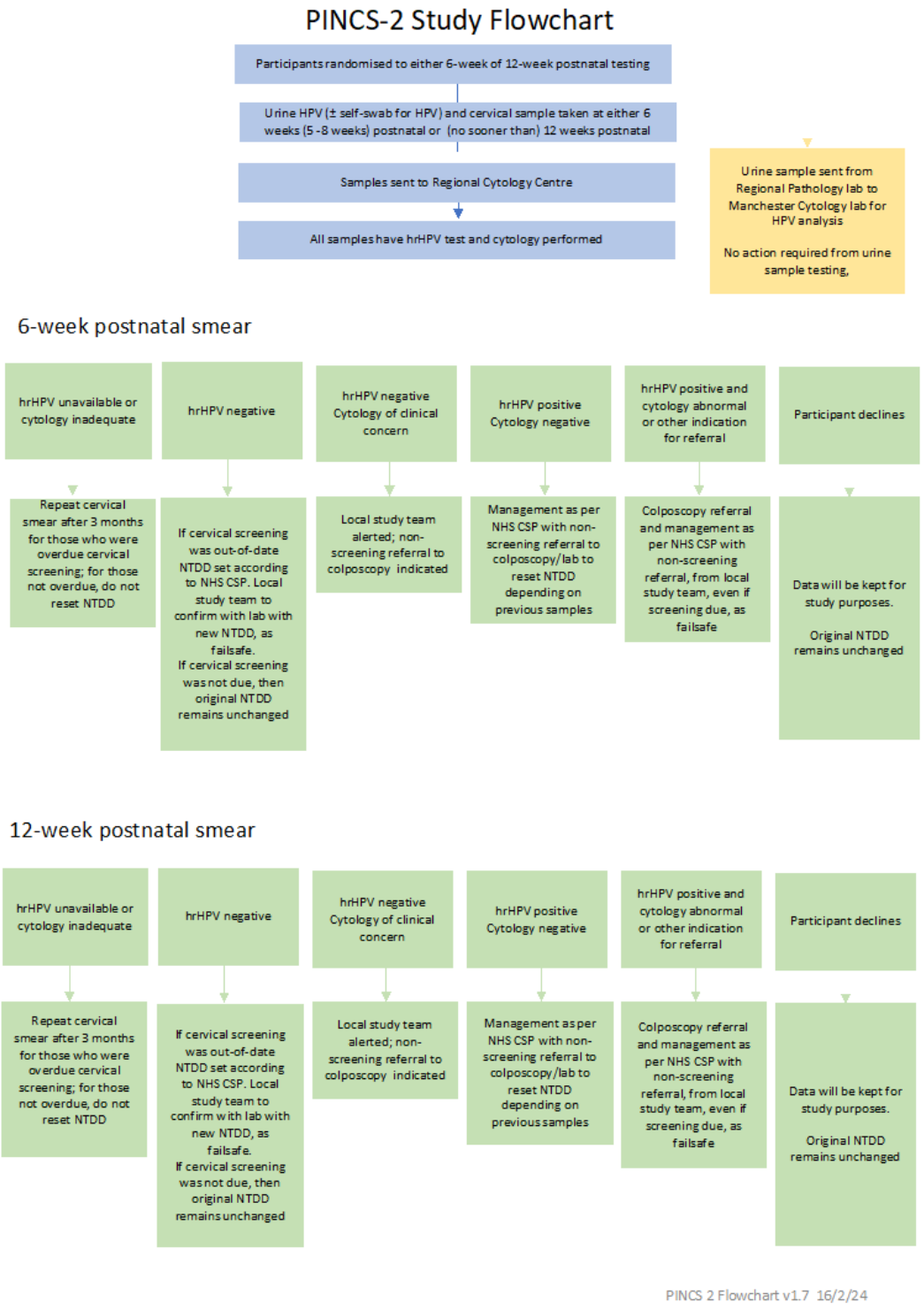

Figure 3 Provisional PINCS-2 flowchart (details to follow in substantial amendment). NHS CSP = NHS Cervical Screening Programme; NTDD = Next Test Due Date; HR HPV = high risk human papilloma virus; DTA = diagnostic test accuracy; PROM = patient reported outcome measures