PROTOCOL TITLE:

A PILOT STUDY TO ASSESS THE FEASIBILITY AND ACCEPTABILITY OF OFFERING CERVICAL SCREENING WITHOUT A SPECULUM TO INCREASE UPTAKE IN LAPSED ATTENDERS AGED 50-64

IRAS Number: 242943

Research Ethics Committee Reference:18/LO/1175

Protocol Version: 3.0 dated 18th March 2019

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SIGNATURE PAGE

Chief Investigator Agreement

The clinical study as detailed within this research protocol **(Version 3.0, dated 18th March 2019**, or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Chief Investigator Name: Dr Anita Lim

Chief Investigator Site: King's College London

Signature and Date: _____ __ __ / __ __ __ / __ __ __ __

STUDY SYNOPSIS

Full Title	A pilot study to assess the feasibility and acceptability of offering cervical screening without a speculum to increase uptake in lapsed attenders aged 50-64
Short Title	Cervical screening without a speculum for women aged 50-64.
Protocol Version number and Date	3.0 dated 18th March 2019
Study Duration	14 months
Study population	Women aged 50-64 who are cervical screening lapsed attenders (at least 12 months overdue but screened at least once in the last 15 years)
Study Design	A cross-sectional pilot study in 10-12 GP practices in the Barts NHS Health catchment area. Eligible women will be randomised (1:1) to either: **A.** Intervention arm - A letter offering the choice of: (i) Booking an appointment with their GP or nurse for a non-speculum clinician sample or, (ii) Ordering a self-sampling kit *OR* **B.** Control arm – Usual care (cervical screening reminder letter)
Sponsor/Co-sponsors	Kings College London
Chief Investigator	Dr Anita Lim
REC number	18/LO/1175
Aim	To assess the feasibility and acceptability of non-speculum sampling approaches for HPV testing in lapsed attenders aged 50-64
Number of Subjects	Intervention arm (n=350) Control arm (n=350)
Main Inclusion Criteria	Women aged 50-64 who are eligible for cervical screening and are at least 12 months overdue but have attended at least once in the past 15 years according to their GP records (i.e. lapsed attenders at least 1 year overdue screening).
Statistical Methodology and Analysis	We will calculate summary statistics for groups of interest (e.g. the proportion of women who have a non-speculum test (taken by a clinician or return a self-sample). A descriptive analysis of questionnaire data will be used to assess acceptability of each approach, swab-taker experiences, patients' future screening preferences and intention to take part again in the future if invited.

GLOSSARY OF TERMS AND ABBREVIATIONS

ASR	Annual Safety Report
CCG	Clinical Commissioning Group
CI	Chief Investigator
CIN	Cervical Intraepithelial Neoplasia
CIN 2+	High-grade disease / Cervical Intraepithelial Neoplasia 2 or worse
EMIS	Egton Medical Information Systems
GAfREC	Governance Arrangements for NHS Research Ethics Committees
GP	General Practitioner
HCA	Health Care Assistant
HCP	Health Care Practitioner
HPV	Human Papillomavirus
HPV Triage	The process whereby HR-HPV testing is used to determine whether women with low grade cervical abnormalities require further assessment.
HR-HPV	High-risk HPV
ICF	Informed Consent Form
ISRCTN	International Standard Randomised Controlled Trial Number
KCL	King's College London
LBC	Liquid Based Cytology
NHAIS	National Health Authority Information System
NHSCSP	National Health Service Cervical Screening Programme
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIS	Patient Information Sheet
QMUL	Queen Mary University of London
Subject	An individual who takes part in a clinical trial
REC	Research Ethics Committee
SDV	Source Document Verification
SOP	Standard Operating Procedure
SS	Self-Sampling

1 INTRODUCTION

Annually, around 20% of new cervical cancer diagnoses in the UK occur in women aged 65 and over [1] and around 50% of the deaths.[2] Most of these cases occur in women who are not adequately screened when aged 50-64.[3] Women aged 65 who have had regular screening (i.e. 3 consecutive negatives) have a much lower risk of developing disease compared to those who have not been screened between ages 50-64.[3] Additionally, the consistent fall in screening coverage [the rates of cervical cancer in older women are likely to rise] of the NHS Cervical Screening Programme (NHSCSP) is a cause for concern. As of March 2017, coverage was 74.5% of women aged 50–64 compared with 78% in 2011.[4] This falling coverage among older women, coupled with the projected increase in life expectancy, [5] means there is clear need to increase screening coverage in older women. [4]

Cervical screening non-attendance in older women is associated with perceptions of low risk of cervical cancer and low levels of knowledge about cervical screening.[6] However, a key barrier, in older women, is the speculum examination due to increased discomfort from musculoskeletal problems and vaginal atrophy [7] [8] .

Almost all cervical cancers are attributable to persistent infection with human papillomavirus (HPV),[9, 10] with around 70% of cervical cancer cases caused by HPV16 and HPV18.[11] Advances in molecular biology techniques has enabled testing for high-risk HPV infection to be used as a form of cervical screening. HPV testing is better than cytology (previously known as a 'smear test') at detecting high-grade disease, [12] and HPV primary screening will replace cytology in England in 2019.[13]

HPV testing has introduced the possibility of new cervical screening approaches that are likely to be more acceptable to older women, as sampling from the cervix is not necessary. HPV testing on self-collected samples has the potential to overcome most barriers to conventional screening.[14-16] Women can take the sample themselves in private without needing to be examined, at a time and place of their choosing. Self-samples are slightly inferior to clinician HPV samples (similar specificity but lower sensitivity to high-grade CIN disease) [17] but are roughly on par with good quality cytology on clinician samples.[17] Therefore, self-sampling (SS) is not recommended for primary screening but is an appealing approach to improving uptake in non-attenders. Self-sampling is already being offered to non-attenders in some countries such as The Netherlands, Australia [18] and Italy. The main drawbacks are that self-sampling is slightly less sensitive than clinician-collected HPV samples to CIN2+ [19] and many women worry about not taking a good quality sample. [20-23]

HPV testing on clinician-collected vaginal samples without a speculum is another possibility. Although test performance is likely to be similar to self-sampling it may be more appealing to women who want the reassurance of a clinician-taken sample without the discomfort. Unlike self-sampling, the dialogue between women and screener is maintained. Findings from a recent qualitative study suggest that non-speculum clinician sampling for cervical screening could be an appealing option for older women, particularly for those who may have been put off screening by the speculum examination.[7]. In this study we will offer lapsed attenders (i.e. at least 12 months overdue but have attended at least once in the past 15 years) a choice of non-speculum clinician sampling or self-sampling. The results will provide some evidence on what approach may be effective in increasing screening uptake in non-attenders. Focusing on lapsed attenders as opposed to non-attenders is likely to be more effective for this study as women who have never attended screening by age 50 are likely to be entrenched in their decision to not attend [8] (regardless of what test is offered). This novel approach could be an excellent way of attracting women (who stopped when it became uncomfortable) back to the screening programme.

This study is the final in a series of studies which are part of a larger project looking at the acceptability, test performance and feasibility of HPV testing on non-speculum clinical collected samples in older women for cervical screening. The first study comprised of focus groups in women aged 50-64 and found that non-speculum clinician sampling would be welcomed by both cervical screening non-attenders and by women with a dislike of the speculum. The second study was a cross-sectional study in GP primary care and colposcopy to assess the test performance and (actual) acceptability of non-speculum clinician samples for HPV testing. This study, the final component of the project, is a pilot study which aims to assess the feasibility, acceptability and experiences of non-speculum approaches to HPV testing in the target population (lapsed attenders aged 50-64).

2 STUDY AIM, OBJECTIVES AND ENDPOINTS

2.1 Aim

To assess the feasibility and acceptability of non-speculum sampling approaches for HPV testing in lapsed attenders aged 50-64.

2.2 Objectives

Primary Objective	Endpoint
To estimate the effect of offering non-speculum sampling to lapsed attenders aged 50-64 on cervical screening uptake	Proportion of women screened at 4 months from randomisation (according to GP records) in the intervention (non-speculum) vs control arm (standard screening).

2.3 Secondary objectives

Secondary objectives	Endpoints
To assess whether any increase on uptake observed at 4 months is maintained at 12 months (i.e. long term cervical screening coverage).	Coverage at 12 months from randomisation (using GP records) in each arm.
To assess the acceptability of non-speculum sampling approaches for cervical screening in among women aged 50-64 who are lapsed attenders.	A descriptive analysis of patient questionnaire data.
To assess the acceptability of clinician-sampling without a speculum versus self-sampling in lapsed attenders aged 50-64.	The proportion of women who undergo clinician-taken sampling without a speculum versus the proportion who request and return a self-sample.
To assess the feasibility of offering non-speculum approaches for cervical screening in lapsed attenders aged 50-64	The proportion of eligible women who test HPV positive and a) attend for follow up (cytology or colposcopy) within 6 months of testing HPV positive on a non-speculum sample and b) who are treated for CIN2+
To assess the acceptability of non-speculum sampling for cervical screening among the clinical staff who took non-speculum samples from eligible women at GP practices participating in this study.	A descriptive analysis of swab-taker questionnaire data.

3 STUDY POPULATION

3.1 Inclusion Criterion

1. Women aged 50-64 who are eligible for cervical screening who are at least 12 months overdue but have been screened at least once in the past 15 years according to their GP records (i.e. lapsed attenders at least 1 year overdue screening).

3.2 Exclusion Criterion

1. Women unable to provide informed consent.

4 STUDY DESIGN

4.1 Overall design

This is a pilot study in primary care which will involve 10-12 GP practices within the Barts Health Catchment area. Eligible women will be randomised (1:1) to:

A. Intervention arm - A letter offering the choice between two different non-speculum sampling tests for cervical screening:
    i. Booking an appointment with their GP or nurse for a non-speculum clinician sample or
    ii. Ordering a self-sampling kit

OR

B. Control arm - Usual care - cervical screening reminder letter

All GP practices in the Barts Health catchment area use Egton Medical Information Systems (EMIS) web for electronic patient records. EMIS web has built-in search, alert and template functions which will be used to identify eligible women.

4.2 Intervention arm

Women who have a non-speculum clinician collected sample

Women randomised to the intervention arm who choose to have a non-speculum vaginal sample by their GP or nurse will contact their GP practice to book an appointment where they will have the sample taken. Depending on the preferences of the GP practice, women will be able to book appointments in at least one of the following ways; by calling the practice (an EMIS alert will be set up to prompt the reception staff about the study), online via EMIS Web 'Patient Access' and by text messaging.

Acceptability questionnaire

Clinical staff who take non-speculum study samples at participating GP practices will be asked to complete a short questionnaire to assess the acceptability of non-speculum sampling. These data will provide information on the practical use of non-speculum sampling and barriers and facilitators to future implementation. (See section 5.8 for further details).

Women who return a self-sample

Women who are randomised to the intervention arm and choose to order a self-sampling kit will be able to do so either by returning a form (included with a freepost envelope in the mail-out) or by phone. The kit will consist of a participant information leaflet, a flocked swab (Copan FLOQswab™) with an instruction leaflet explaining (written and pictorial) step by step how to collect a sample, a laboratory request/ consent form, a HPV information leaflet, a study questionnaire and a freepost return envelope. The participant information leaflet will inform the women about the possible results of the self-sample.

Both non-speculum clinician collected samples and self-samples will be sent to the Barts Health NHS Trust cytology laboratory where HPV testing will be performed. (See section 6.1 for further details)

Results will be obtained from the laboratory, by the study team (with the women's consent) (see section 9.2 Data Collection)

Participants will also be asked to complete a short questionnaire to assess the acceptability of non-speculum sampling (non-speculum clinician sampling and self-testing) and future screening preferences. (See section 5.7 for further details).

4.3 Control arm (usual care)

Women who are randomised to the control arm will receive the usual cervical screening reminder letter.

4.4 Study Schematic

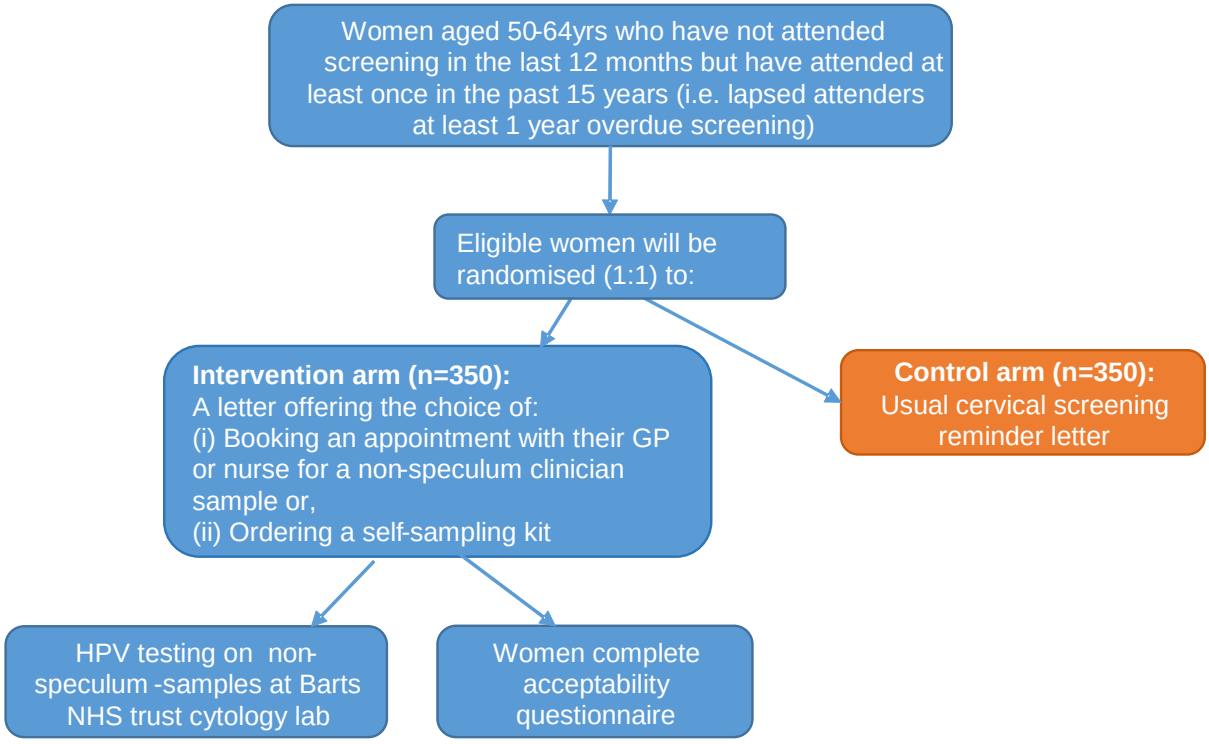

Figure 1: Study schematic

5 STUDY PROCEDURES

5.1 Identifying and inviting eligible women

Eligible women will be identified using an electronic search of EMIS Web (the GP record software system). The search will be pre-written by the study team and will be carried out by GP practice administrative staff on an agreed census date. Eligible women will be randomised by the GP practice using computer-generated random numbers (provided by the study team) in a ratio of 1:1 to either the intervention or control arm (see section 5.2). GP practices will send women who are randomised to the intervention arm the study documentation (invitation letter, patient information leaflet and HPV information sheet) via the post. Women who are randomised to the control arm will receive their usual cervical screening reminder letter from the screening programme.

5.2 Participant enrolment

Participant enrolment (i.e. randomisation) will be recorded in women's GP record with the allocation. The list of eligible women randomised to the study (with allocation) will be retained at the GP practice and pseudonymised copy will be kept in the investigator site file.

5.3 Informed Consent Procedures

5.3.1 Women randomised to the intervention arm

Women who are randomised to the intervention arm will receive the patient information sheet and an information leaflet on HPV with their study invitation letter.

Women who have a non-speculum clinician collected sample

For women who opt to have a non-speculum clinician-collected sample at their GP practice, the sample-taker will explain the study and obtain written consent prior to the study sample being taken.

Women who return a self-sample

For women who choose to self-collect a sample, consent will be implicit by return of a self-sample along with the laboratory request/consent form which is included in the kit. This form will contain the women's details (to identify the women) and statements detailing precisely what the study involves and what they are agreeing to by returning a self-sample (e.g. regarding permission for the study team to access to medical record data).

5.3.2 Women randomised to usual care (control group)

Women who are randomised to usual care (control group) will not provide consent for the study. Only anonymous aggregate data will be collected for these women.

5.4 Participant withdrawal

In the event that a patient withdraws their consent from the study all samples and data collected up to that date will be used in the study but no further data will be collected.

5.5 Clinical management & follow-up

Study HPV results will be mailed by the study team to the women and their GP. Women who test HPV negative will be advised in their results letter that they are not required to do anything further for the study. As we are unable to record non-speculum HPV samples in the national cervical screening database, women who test HPV negative on a non-speculum sample will continue to receive the usual smear reminder letters (i.e. will remain on normal recall).

Women who test HPV positive will be advised in their results letter to have a cervical cytology test (i.e. conventional cervical screening with liquid based cytology) in a primary care clinic (e.g. GP surgery or family planning clinic). These women will be managed according to their cytology results as per routine clinical care under the NHS Cervical Screening Programme (CSP). Self-sampling studies have found that most (~80%) women who test HPV positive attend follow-up cytology.[6, 10, 15-17]

As an additional safety net, women who test HPV positive on a non-speculum sample who have not had a follow-up test by the end of the study will be invited to a study colposcopy clinic.

All women who are randomised in the study will be passively followed up for 12 months to obtain data on cervical cytology tests and histology results. Only anonymous aggregate data will be collected for women in the control arm or women in the intervention arm who do not have a study sample (i.e. not consented to the study). GP records will be used for this purpose.

5.6 Inadequate samples

Women whose non-speculum samples cannot be analysed (this is normally due to insufficient DNA) will be asked to collect another sample using the same method. Based on a previous self-sampling study we performed, we expect this will be in the region of 2% [24] of all returned samples. Women who had a non-speculum clinician collected sample will be asked to book an appointment for another clinician sample. Women who returned a self-sample will be sent another self-sampling kit with an accompanying letter. If the second sample is also inadequate the woman will be advised to make an appointment at her GP practice to have a routine cytology test taken.

5.7 Acceptability – participating patients

All women who have a non-speculum sample taken for HPV testing will be asked to complete an anonymous self-complete questionnaire to assess the acceptability of non-speculum sampling for HPV testing, and future screening preferences. Completed questionnaires will be handed back to GP practice staff (non-speculum clinician taken samples only) or posted to the study team (using a self-addressed postage paid envelope which will be provided).

5.8 Acceptability – swab-takers

All relevant clinical staff (nurses, nurse practitioners, GPs) at participating GP practices who have taken a non-speculum sample as part of this study will be asked to complete a short anonymous online (Survey Monkey) questionnaire to assess the acceptability of non-speculum sampling for HPV testing, from their point of view. The swab-takers will be approached approximately 6 months after the start of the study at their practice, long enough to allow sufficient experience of non-speculum swab-taking, but soon enough to ensure the experience is still relatively fresh in their memory.

6 SAMPLE HANDLING

6.1 Non-speculum clinician collected samples

Study kits will be provided to the participating GP practices and will contain:

- Participant information sheet
- HPV information sheet
- Informed consent form
- Study patient questionnaire
- Flocked swab (Copan FLOQswab™)
- Specimen bag

At the appointment the GP or nurse will collect a non-speculum vaginal sample using a flocked swab (Copan FLOQswab™). The flocked swab is approximately 12.5 cm long and comes in a tube with a re-sealable lid.

In order for the sample to be processed at the laboratory the sample will have a minimum of two patient identifiers (full name and date of birth) and an accompanying study lab request form.

Study lab request forms will have the following details:

- Full name
- Date of birth
- Address
- NHS number
- Name of sample taker
- GP Practice

An EMIS (the GP record software system) web mail-merge document will be set-up to enable printing of lab request forms that will be auto-populated with the relevant details.

6.2 Self-sampling

Self-sampling kits will be posted to women by the study team and will contain:

- Participant information sheet
- Laboratory Request/ Consent Form
- HPV information sheet
- Instructions on how to take the sample (written and pictorial)
- A flocked swab (Copan FLOQswab™) in a tube with a re-sealable lid
- Study patient questionnaire (with a self-addressed postage paid envelope)
- A UN3373 compliant freepost envelope or box that is pre-addressed to the laboratory

The instructions enclosed with the kits will explain in detail how to take the self-sample and how to return it. The self-sample will be taken by the woman using the flocked swab which is approximately 12.5 cm long and comes in a tube with a re-sealable lid.

Study laboratory request/ consent form will include the following details:

- Date sample was taken
- Full name
- Date of birth
- Address
- Telephone numbers

6.3 Sample Storage and transport

Non-speculum clinician samples (and study lab request forms) will be placed in a specimen bag and stored at room temperature until they are transported dry to the Barts Health NHS Trust Cytology laboratory via the normal Barts specimen collection service.

Self-samples will be posted using the freepost envelope or box provided and will transported dry to Barts Health NHS Trust Cytology laboratory via Royal Mail.

6.4 Sample Receipt/Chain of Custody/Accountability

Upon receipt of the samples, the laboratory should document the receipt of the sample and ensure that the physical integrity of the sample has not been compromised in transit. If physical integrity has been compromised the lab will inform the study team.

7 LABORATORY

The Barts Health NHS Trust Cytology laboratory analyse samples for all cervical screening in the Barts Health catchment area and will perform the HPV testing on the non-speculum clinician collected samples and the self-samples for the study.

Samples will be analysed to determine the presence of infection with high-risk types of HPV DNA.

7.1 HPV testing

The Roche cobas® 4800 platform for HPV testing will be used. The cobas® 4800 Human Papillomavirus (HPV) Test is a qualitative in vitro test for the detection of Human Papillomavirus in patient specimens. The test utilises amplification of target DNA by the Polymerase Chain Reaction (PCR) and nucleic acid hybridisation for the detection of 14 high-risk (HR) HPV types in a single analysis. The test specifically identifies (types) HPV16 and HPV18 while concurrently detecting the rest of the high risk types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) at clinically relevant infection levels.

HPV testing will be performed with the liquid based cytology (LBC) platform ThinPrep at the division of Cellular Pathology laboratory at Barts Health NHS Trust, 80 Newark Street, 2nd Floor, room HIST 234, London, E1 2ES. Samples will be prepared and processed following the Roche company guidelines.

7.2 Retention of residual samples

After results have been reported the residual samples will be anonymised and sent to Professor Attila Lorincz's lab at the Wolfson Institute of Preventive Medicine, Queen Mary University where they will be stored (i.e. labelled only with unique study ID). Analysis of samples will performed anonymously and linked to anonymous clinical data only identified by the study ID. The study team will retain the data linkage file.

Residual samples will be used for further analysis that could help inform management for cervical screening in the future. Specifically, we are interested in assessing triage tests for HPV positive results (e.g. DNA methylation). Results will not impact clinical management for women in the study and therefore, will not be reported to women or their GP.

8 STATISTICAL CONSIDERATIONS

8.1 Sample size considerations

This is a pilot study, therefore formal sample size calculations are not appropriate.

A sample of 350 in each arm will provide between 75% and 93% power (with alpha set at 5%) under a range of realistic scenarios (Table 1). In previous UK studies which sent letters to non-attenders "response" rates have ranged between 6%-17.5% in the self-sampling arm and 4.5%-6% in the control arm.[25-27] With an uptake of 4%, 6% or 8% at 4 months, the study will have good power for an absolute increase of 7% or a relative response proportion of 2.4 in the intervention arm.

Table 1: Expected power for different response rates after 4 months in control and intervention arms (non-speculum HPV testing)

Proportion of responders in control arm	**Proportion of responders in intervention (non-speculum HPV testing) arm**	**Power**
4%	8% (i.e. +4%) 10% (i.e. +6%) 12% (i.e. +8%)	54% 84% 97%
6%	10% (i.e. +4%) 12% (i.e. +6%) 14% (i.e. +8%)	44% 75% 93%
8%	12% (i.e. +4%)	37%

	14% (i.e. +6%)	68%
	16% (i.e. +8%)	88%

Note: assuming α=5% and two-sided test.

8.2 Planned analysis

The primary outcome measure is screening uptake at 4m in women offered non-speculum HPV testing vs women sent a cervical screening reminder letter. Secondary outcomes will be: (i) 12m coverage; and (ii) the acceptability of non-speculum clinician sampling in lapsed-attenders aged 50-64.

We will also report: (i) the proportion of women who undergo clinician-taken sampling without a speculum versus the proportion who request and return a self-sample (ii) future screening preferences and (iii) the proportion of lapsed attenders who test HPV positive on a non-speculum sample and attend for (a) follow up (cytology or colposcopy) and (b) who are treated for CIN2+.

The Chi Squared test will be used to determine the differences in proportions between groups. For HPV positive women we will calculate the proportion who have a follow-up investigation within six months. Descriptive statistics will be used to compare demographic and cervical screening status between responders and non-responders.

A descriptive analysis of patient questionnaire data will be used to assess acceptability of each approach and intention to take part again in the future if invited.

A descriptive analysis of swab-taker questionnaire data will be used to assess the acceptability, experiences and practicalities of the non-speculum sampling from the clinicians' viewpoint.

8.3 End of Study Definition

The 'end of study' is defined as 12 months after the last randomisation; i.e. when passive follow up of the last eligible woman has been completed.

9 DATA HANDLING AND RECORD KEEPING

9.1 Confidentiality

All information which is generated in the study will be kept strictly confidential in accordance with the Data Protection Act, NHS Caldicott Guardian, The Research Governance Framework for Health and Social Care and Research Ethics Committee Approval.

All of the above bodies have a duty of confidentiality to the patient as a research participant and nothing that could reveal their identity will be disclosed outside the research site. All data will be stored in a locked room only accessed by authorised personnel.

9.2 Data Collection

Patient identifiable data will be collected by the study team for the following reasons:

- The study team will be sending out the self-sampling kits to the women
- The study team will be sending out the non-speculum HPV result letters to the women and will therefore receive the results from the Barts NHS Cytology lab. Results will be sent securely between nhs.net to nhs.net email accounts (in this way data will be encrypted and sent securely).

The following data will be collected by the study team:

- GP record data
    - Relevant cervical screening data (date and results of cervical screening tests relevant to the study) – only anonymous aggregate data will be collected for women in the control arm or women in the intervention arm without a study sample
- Age (in years)
- Non-speculum HPV test date and result (including HPV type) – *intervention arm only*
- Follow-up test (cytology and/or colposcopy dates and results for women who test HPV positive on a non-speculum sample, including final histology (if applicable) – *intervention arm only*
- Patient questionnaire data – *intervention arm only*
- Swab-taker questionnaire data – *intervention arm only*.

Non-speculum HPV results will be sent to the study team by the Barts Health NHS Trust Cytology laboratory with the women's consent. Barts Health NHS Trust Cytology laboratory will send the non-speculum HPV results to the Study Team securely via the Barts Trust network (Dr Anita Lim has a Barts Health NHS Trust account).

10 ASSESSMENT OF SAFETY

We do not anticipate any major safety concerns for the study. Vaginal samples are routinely taken in GP primary care for STI (sexually transmitted infection) tests. Vaginal self-sampling using flocked swabs has been safely performed in several studies. [26-30] Over 250 non-speculum clinician-collected vaginal samples were taken in a previous study with no issues.

10.6 Annual Safety Reporting

This is a low risk study and we do not anticipate any major safety issues.

As per standard practice, the CI will send the Annual Progress Report to the main REC using the NRES template (the anniversary date is the date on the MREC "favourable opinion" letter from the MREC) and to the sponsor.

11 CLINICAL GOVERNANCE ISSUES

11.1 Ethical Considerations

The study will be conducted in accordance with ethical principles Declaration of Helsinki (1996), and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework, Trust and Research Office policies and procedures and any subsequent amendments.

A Research Ethics Committee (REC) will review all appropriate trial documentation in order to safeguard the rights, safety and well-being of patients. Ethical approval for the study will be obtained from a Research Ethics Committee (REC). The REC will be informed of any changes to the conduct of the trial and seek approval for these changes and any amended patient materials.
The study team will maintain an accurate and complete record of all written correspondence to and from the REC and will agree to share all such documents and reports with the sponsor.

11.2 Summary Monitoring Plan

A member of the research team will monitor study procedures on an ad hoc basis (e.g. recruitment, recording of consent, and anonymous data downloads to check data quality). Refer to study monitoring plan for further details.

11.3 Reporting of Serious Breaches in GCP or the Trial Protocol

All sites participating in the trial will notify the study team of a potential serious breach that they become aware of. The CI is responsible for notifying the sponsor within 24 hours of becoming aware of a serious breach.

A “serious breach” is a breach which is likely to effect to a significant degree:

- The safety or physical or mental integrity of the subjects of the trial; or
- The scientific value of the trial.

Participating site should contact the study team for further information.

12 RECORD RETENTION AND ARCHIVING

Study data will be stored securely and made available for audit. Upon study completion study records will be kept for 20 years as per Research Governance Framework and Trust Policy.

13 FINANCE AND PUBLICATION POLICY

13.1 Finance

This study is funded by a project grant awarded by Cancer Research UK to Dr Anita Lim.

13.2 Publication

We plan to disseminate the findings of our research via conference presentations and publication in peer-reviewed journals.

14 INDEMNITY

King’s College London has suitable indemnity to be in place for this study.

APPENDIX 1 – Information with regards to Safety Reporting in Non-CTIMP Research

	Who	When	How	To Whom
SAE	Chief Investigator	Within 15 days of CI becoming aware of the event	SAE Report form for Non-CTIMPs, available from NRES website.	Main REC with a copy to the sponsor
Urgent Safety Measures	Chief Investigator	Immediately Within 3 days	By phone Notice in writing setting out reasons for the urgent safety measures and the plan for future action.	Main REC with a copy sent to the sponsor. The MREC will acknowledge this within 30 days of receipt.
Progress Reports	Chief Investigator	Annually (starting 12 months after the date of favourable opinion)	Annual Progress Report Form (non-CTIMPs) available from the NRES website	Main REC with a copy to the sponsor
Declaration of the conclusion or early termination of the study	Chief Investigator	Within 90 days (conclusion) Within 15 days (early termination)	End of Study Declaration form available from the NRES website	Main REC with a copy to the sponsor
Summary of final Report	Chief Investigator	Within one year of conclusion of the Research	No Standard Format However, the following Information should be included:- Where the study has met its objectives, the main findings and arrangements for publication or dissemination including feedback to subjects	Main REC with a copy to be sent to the sponsor

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