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KING'S College LONDON

STUDY PROTOCOL

SELF-SAMPLING FOR HPV TESTING IN CERVICAL SCREENING NONATTENDERS IN LONDON

Version 9.0 dated 12 Oct 2021

Short title	*A London HPV Self Sampling Pilot*
Acronym	*ALOHA – A LOndon HPV Self SAmpling Pilot*
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Clinical Trials Unit	*Cancer Research UK King's College London Cancer Prevention Trials Unit (CPTU)*

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REVISION HISTORY

Protocol version	Protocol date	Minor or substantial amendment	Date approved by Ethics	Date approved by HRA	Comments and description
V1.0	04/08/2017	N/A Initial version	N/A	N/A	N/A
V2.0	06/09/2017	N/A – part of initial submission	N/A – requested changes	N/A – requested changes	Updated as per request of JRMO. Additional information re the online ordering kits added along with additional detail re confidentiality.
V3.0	16/11/2017	N/A – part of initial submission	27/11/2017	18/01/2018	Updated as per request of the REC to correct typographical errors and to provide more detail on the consent processes.
V4.0	08/06/2018	SA 1	14/06/2018	28/06/2018	Updated with the detail that only two patient identifiers are now required on the sample label (was previously three)
V5.0	28/01/2019	SA 2	03/04/2019	04/04/2019	Update and refining of study aims & objectives including change to stand-alone feasibility pilot, update with new clinical pathway for follow up of HPV positives, change in study Sponsor (and associated data handling changes), reduced passive follow up period to duration of study only, revised study end date to 31 March 2020, updated how residual samples will be stored and handled. Updated details of third-party vendors, specifically Preventx who will take over the laboratory role from The Doctors Laboratory and new responsibilities for PSL Print Management Ltd.
V6.0	09/10/2019	SA 3	17/12/2019	24/12/2019	• To update the label of the sample tube in the opportunistic kits to include two identifiers • To add additional advice to the protocol and accompanying study documents for pregnant women.

Protocol version	Protocol date	Minor or substantial amendment	Date approved by Ethics	Date approved by HRA	Comments and description
					• To update the wording in HPV results letters • To add extra information and clarification around the data required for the trial and purpose of obtaining the different types of data • To add a note to the PIS, and the self-sample instruction leaflet for the participant to contact the study team if they haven't received their test result within two weeks
V7.0	27th April 2020	Minor amendment 3	N/A	N/A not submitted for HRA approval as per COVID guidance at the time	• Extension to passive follow up end date • Further details/clarification (and accompanying participant correspondence) added to the post study follow up procedures under care of GP
V8.0	23rd June 2021	Minor amendment 4	25th June 2021	TBC	• Update to end of trial definition
V9.0	12th Oct 2021	Minor amendment 5	N/A	TBC	Upon study completion study records will be kept for 5 years as per agreement with Sponsor.

GLOSSARY OF TERMS AND ABBREVIATIONS

CCG	Clinical Commissioning Group
CI	Chief Investigator
CIN	Cervical Intraepithelial Neoplasia
GP	General Practitioner
GSTT	Guy's and St Thomas' NHS Foundation Trust
HCA	Health Care Assistant
HCP	Health Care Practitioner
HPV	Human Papillomavirus
JRMO	Joint Research Management Office
KCL	King's College London
NHAIS	National Health Authority Information System
NHSCSP	National Health Service Cervical Screening Programme
NHS REC	National Health Service Research Ethics Committee
PI	Principal Investigator
QMUL	Queen Mary University of London
REC	Research Ethics Committee
SSK	Self-Sampling Kit

SIGNATURE PAGE

Chief Investigator Agreement

The clinical study as detailed within this research protocol **(Version 9.0, dated 12 Oct 2021)**, or any subsequent amendments will be conducted in accordance with the UK Policy Framework for Health and Social Care Research (2017), 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: Professor Peter Sasieni

Chief Investigator Site: King's College London

Signature and Date:  12 November 2021

STUDY SYNOPSIS

Short Title	*A London HPV Self Sampling Pilot*
Methodology	*A pragmatic, factorial cluster randomised controlled pilot study (a 2 x3 factorial design, with the 3-way (individual level) randomisation nested within the 2-way (GP-level) randomisation.* *GP practices will be randomised 1:1 to either offering self-sampling kits (SSK) opportunistically to women overdue (>6 months) cervical screening when they present for any reason (intervention arm) or usual care (control arm).* *The second (nested) randomisation will be individual level randomisation of women within each GP practice who have never been screened or who reach the 15- or 27-month anniversary of the date their last cytology test was due without being screened (by self-sample or cytology). 2:1:1 to either: Group A Usual care (control). Group B Receiving a letter inviting them to order a kit, or Group C: Receiving a kit in the post.*
Research Sites	*~13 GP practices in London*
Aim	*To assess feasibility and optimal approaches for offering self-sampling to cervical screening non-attenders in London to increase coverage.*
Objectives	A summary table of study objectives, endpoints and method of assessment is located in Appendix 1.
Number of participants	*For GP-level randomisation:* *~8420 women in total will be eligible (i.e. >6m overdue cervical screening) within 13 GP practices of which we estimate the following:* • *~500 will be offered SSKs opportunistically (330 will accept and ~210 will return a self-sample)* *For individual-level randomisation:* • *~5000 (i.e. never screened or 15- or 27-month anniversary of the date their last cytology test) will be individually randomised* • *~2500 will receive an SSK or letter inviting them to order an SSK via individual level randomisation of which 175-300 will return a self-sample*
Inclusion criteria	*GP-level randomisation* 1. *Women aged 25-64 years who are eligible for cervical screening and are least 6 months overdue (i.e. no cervical cytology recorded in the GP records in the past 3.5 years if aged 25-49 or 5.5 years if aged 50-64)*

	Individual-level randomisation 2. Never-screened women & women who reach the 15 months* of last smear due date (and not screened by smear or self-sample)
Exclusion criteria	1. Women unable to provide informed consent (e.g. because of learning difficulties) 2. Women who are documented in the GP records as being a Type 2 objector (i.e. who have objected to disclosure of identifiable data by NHS Digital for secondary purposes) will not be individually randomised.
Statistical Methodology and Analysis	*We will calculate summary statistics for groups of interest (e.g. uptake of self-sampling by mode of approach). Screening uptake between the three arms of the individual level randomisation will be compared by a Chi-square test (2 degrees of freedom).*
Proposed Start Date	*Initial start date: April 2018 (halted on June 2018)* *Re-start date: March 2019*
Proposed End Date	*March 2020 (Recruitment period)* *April 2021 (Follow up)*
Study Duration	*Up to 12 months (active recruitment)* *6 months follow up (from date last HPV positive result on an ALOHA self-sample is reported)* *Please note: In light of the Coronavirus pandemic cervical screening services are currently restricted and/or paused (the situation differs locally). This has a knock-on effect to the 6 month follow up period (as per the secondary objective) and therefore this period will need to be extended accordingly.*

1. BACKGROUND

London consistently has the lowest cervical screening coverage nationally (68.4% versus 73.5% across England in 2015) [1]. Women who are inadequately screened are at the highest risk of developing cervical cancer. Despite efforts to increase screening uptake, coverage in London continues to decline (70.3% in 2014) and there is an urgent need to address this growing problem. The issue of falling coverage is not exclusive to London, cervical screening attendance has been declining nationally for over a decade.[1]

The fact that the human papillomavirus (HPV) causes virtually all cervical cancers [2] has led to the development of HPV testing for high-risk (oncogenic) infection as a form of cervical screening. Self-sampling for HPV testing enables women to take their own sample, in private and at a time and place of their choosing, thereby addressing common screening barriers (e.g. fear or dislike of the pelvic examination, being too busy and difficulty making appointments)[3]. Further advantages include savings in clinician time and (potentially) in overall clinic costs. Self-samples are slightly inferior to clinician HPV samples (similar specificity but lower sensitivity to high-grade CIN disease)[4] but are roughly on par with good quality cytology on clinician samples[4]. Therefore, self-sampling is not recommended for primary screening but is an appealing approach to improving uptake in non-attenders. Studies in other countries[5-15] have fairly consistently shown that offering HPV testing on self-collected samples increases screening uptake in non-attenders (30-40% response in most studies), and that most women (~80%) who test HPV positive attend follow up investigations (cytology or colposcopy). As a result, self-sampling is already being offered to non-attenders in the Dutch national cervical screening programme. The picture in the UK is less clear; only 6%-8% of cervical screening non-attenders returned a self-sample when kits were posted to them [16, 17] and 5-20% when asked to request kits or when kits were posted directly.[18] The reasons underlying these comparatively lower uptake rates are unknown. Moreover, the associated kit attrition rate is likely too high to be acceptable. This prompted us to assess an approach that had not yet been tried; offering self-sampling opportunistically when screening non-attenders consult GP primary care for any reason. Our pilot study at 6 London GP practices and found that 9% of non-attenders who consulted were offered and returned a self-sample.[19] Given these mixed results, it seems likely that in the UK a multifaceted approach for offering self-sampling would work best.

In 2016 the Public Health Minister in England announced that primary HPV testing will replace cytology for cervical screening by 2019. With the switch to primary HPV screening it is likely

that self-sampling (for non-attenders) will also eventually be incorporated. Given the longstanding issues with low coverage, London is an ideal population to assess the potential for self-sampling and to provide the evidence-base for its implementation in England.

In our study of opportunistic offering of self-sampling in primary care we found substantial variation in the offering of self-sampling both between GP practices (11%-36%) and between individual GPs (0% to >50% offered in the practice) [19]. Moreover, despite large variation in the proportion of women offered kits between GP practices, the proportion of women offered who returned a self-sample was constant. This suggests that uptake could be improved if more women were offered kits and that we need to find ways to encourage GPs to offer more kits.

This will be a pilot study to assess feasibility and optimal approaches for offering self-sampling to cervical screening non-attenders in London in GP primary care.

3. AIM, OBJECTIVES AND ENDPOINTS

2.2. Aim

To assess feasibility and optimal approaches for offering self-sampling to cervical screening non-attenders in London to increase coverage.

2.3. Objectives

A summary table of study objectives, endpoints and method of assessment is located in Appendix 1.

2.3.1. Primary

To estimate the proportion of women who provide a self-sample when:

(i) Offered kits opportunistically

(ii) Sent a kit directly (opt-out)

(iii) Invited to order a kit (opt-in)

2.3.2. Secondary

1) To estimate the proportion of eligible women who test HPV positive on a self-sample and attend for follow up (cytology or colposcopy) within 6 months of testing HPV positive

2) To assess the logistics of testing samples, recording results and giving women their results in a timely manner.

2.3.3. Exploratory

- To pilot a variety of approaches to encourage GP practices to offer self-sampling opportunistically to women who are overdue cervical screening consult for any reason.
- To pilot a variety of approaches to facilitating women who wish to order a self-sampling kit.
- To compare demographic and cervical screening status (never screened, overdue, up-to-date) between responders and non-responders
- To examine the consultation rates and response rates (numbers offered, accepted, declined and returned as a proportion of total number of eligible women, reasons for declining kits, kit offers by health professional type) for eligible women in the opportunistic (intervention) arm.
- To assess the impact of offering self-sampling on cervical coverage using passive follow up data
- To carry out analysis on residual samples that could help inform management for cervical screening in the future

2.4. Primary Endpoint

Uptake of self-sampling following different interventions.

2.5. Secondary Endpoints

1) The proportion of eligible women who test HPV positive and
   (i) attend for follow up (cytology or colposcopy) within 6 months of testing HPV positive on a SS and
   (ii) who are diagnosed with CIN2+;
2) Turnaround time for HPV testing and reporting of results

3. STUDY POPULATION

3.2. GP practices

GP practices from within the Hounslow Clinical Commissioning Group (CCG) will be invited to take part. Hounslow CCG was selected because cervical screening (age-appropriate) coverage is low (64.4% in 2015/16)[20].

3.3. Inclusion criteria

A participant will be eligible for the study if all of the following criteria apply:

1. Women aged 25-64 years old, and
2. Eligible for cervical screening, and
3. At least 6 months overdue cervical screening. (i.e. no cervical cytology recorded in the GP records in the past 3.5 years if aged 25-49 or 5.5 years if aged 50-64)
4. Never-screened women & women who reach the 15 months* of last smear due date (and not screened by smear or self-sample)

3.4. Exclusion criteria

A participant will not be eligible for the study if any of the following criteria apply:

1. Women unable to provide informed consent (e.g. because of learning difficulties)
2. Women who are documented in the GP records as being a Type 2 objector (i.e. who have objected to disclosure of identifiable data by NHS Digital for secondary purposes) will not be individually randomised.

3.5. Pregnancy

Although pregnant women are not excluded, they are advised not to participate in the study. This is because if a pregnant woman tests HPV positive it is more complicated to ensure adequate follow up within the study lifetime. It is important to note that there are no safety concerns related to pregnant women self-collecting a vaginal swab.

If a pregnant woman still decides to collect a self-sample for the study, they do so with the knowledge that if they test HPV positive they may need to wait until postpartum for full follow up investigations. As this is likely to be after the 'end of the study', the patient's management will be at her GP's discretion.

4. STUDY DESIGN

A randomised controlled pilot in GP primary care using a 2x3 factorial design, with the 3-way (individual-level) randomisation nested within the 2-way (GP-level) randomisation (see Figure 1 Study Schematic**Figure 1 Study Schematic**).

Approximately 13 GP practices in Hounslow CCG (Clinical Commissioning Group) will be included initially. Additional GP practices and CCGs may be added as the study progresses.

The first randomisation will be GP practices in the ratio 1:1 to either:

1. Intervention arm - Offering self-sampling kits opportunistically to women overdue cervical screening by at least 6 months when they present to GP primary care for any reason, and
2. Usual care (control) – women will receive the usual smear reminder letter.

Practices will be randomised in a single block of 12 (with 6 in each arm) using computer-generated random numbers. We may stratify by list size if there are large differences between participating practices.

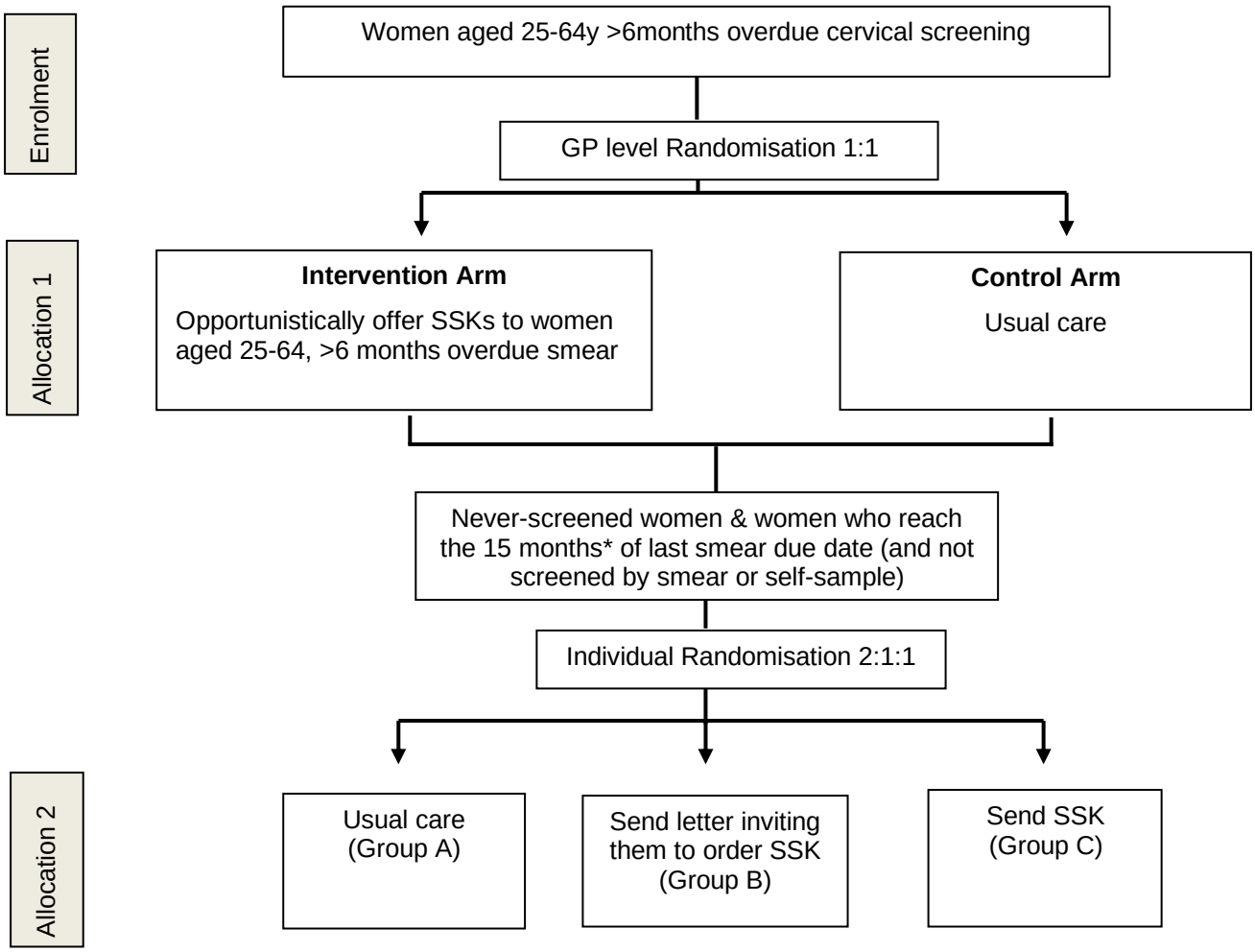
The second (nested) randomisation will be individual level randomisation of women within each GP practice who have never been screened or who reach the 15-month anniversary of the date their last cytology test was due without being screened (by self-sample or cytology). Women who are already past the 15-month anniversary of their last test due date at study start will be randomised if they reach the 27-month anniversary (i.e. women who are between 16 and 27 months past their last test due date). This will allow all women who are overdue screening by at least 15 months to be randomised while avoiding inviting women to self-sampling too close to their next invitation (women aged 25-49 are invited every 36 months). Randomisation at the 27 month anniversary of last test due date will only take place for the first 12 months of the study. This will avoid women being randomised more than once. Never screened women will be randomised in batches throughout the study (e.g. according to birth month or by counting 15m from their last test due date if they had attended when invited), rather than all at a single time point.

Individual-level randomisation of women will be in the ratio of 2:1:1 to either:

- Group A: Usual care (control).
- Group B: Receiving a letter inviting them to order an SSK
- Group C: Receiving an SSK in the post.

The planned pilot trial duration is up to 12 months for the active recruitment phase.

Figure 1 Study Schematic



*Or 27-month anniversary if between 16m and 27m overdue at study start
SSK=self-sampling kit

5. STUDY PROCEDURES

5.1. Pre-randomisation

At study start, baseline information will be collected at each GP practice by the research team using an anonymous search of electronic patient records. This will only include high level aggregate data such as 5-year cervical screening coverage for the previous year (before census date) and the number of eligible women. We will also check to ensure that it is possible to identify the number of women who have reached our census date of 15.0-15.99 months or 27.0-27.99 months past their last test due date.

5.2. Cluster randomisation

5.2.1. Intervention arm - Opportunistic offering of self-sampling

GP practices randomised to the intervention arm will have an alert set up on their electronic patient record (EPR) software to automatically flag potentially eligible women when their record is loaded. Specifically, EPR systems will be programmed to flag women aged 25-64 who are at least 6 months overdue cervical screening (i.e. no cervical cytology recorded in the past 3.5 years (if aged 25-49) or 5.5 years (if aged 50-64) and no codes for hysterectomy or amputation of cervix).

Doctors, nurses and healthcare assistants (HCA)/assistant practitioners (AP) will be asked to offer self-sampling kits to women who have been flagged when they consult for any reason. In practice, this will be done on a case-by-case basis at the discretion of the healthcare professional consulted (e.g. SSKs will not be offered to women who are terminally ill). The study invitation will comprise a brief conversation (~2 minutes) at the end of the consultation. Once eligibility has been confirmed, women who agree will be given a self-sampling kit.

A study template will be set up in the GP electronic patient record system. When eligible women are offered kits, the consulting health professional will use the template to record:

1) Whether or not the study kit was accepted.
2) Study kit number (if accepted).
3) Reason for declining (if applicable)

5.2.2. Control arm - Usual care

GP practices randomised to the control arm will follow their normal procedures for reminding women to attend cervical screening (i.e. usual care).

5.3. Individual-level randomisation

Eligible women will be identified on a monthly basis using GP records (i.e. date of last cytology test entered will be used to calculate time since last test). This will be carried out by a member of the GP practice admin team using a pre-written search of the electronic GP records. All eligible women in participating GP practices who have never been screened or who reach the 15 month (or 27 month) anniversary of their last test due date and have not been screened (by cytology or self-sample) will be randomised (2:1:1) to receive usual care (Group A), a letter inviting them to order a self-sampling kit (Group B) or a self-sampling kit

(Group C). This will include women who have been offered self-sampling opportunistically in the intervention arm GP practices.

GP practices will randomise eligible women either using a computer-generated list of random numbers that will be provided by the study team or using the in-built randomise function in the EPR. We will use a mailing company (PSL Print Management Ltd) to assemble kits and subsequently distribute letters and kits to women on the GP practices' behalf. This vendor is fully ISO27001 and GDPR compliant. It will be recommended to GPs that they should put a data notice on their website / in the practice stating that patient's data may be submitted to a third-party organisation as part of a cervical screening research study.

A patient information leaflet, a self-sample instruction sheet and an HPV information leaflet will be included with the invitation letters sent to women in Groups B and C.

Women invited to order kits (Group B) will be able to choose from different options for ordering kits. The currently planned options include:

- Ordering kits online (from a secure website)
- Ordering kits by returning a mail order form (using a freepost envelope)
- Ordering kits by text message

The inclusion of ordering kits by text message will depend on each GP practices preferences and existing text message software. There are several different platforms available for text messaging at GP practices, capability/functionality varies, and some practices may not use text messages at all. We envisage that the process will comprise a weekly email of text message replies (auto-generated by the text message platform) that is sent to a member of the GP practice admin team who will then send out kits.

5.4. Study website

A study website will allow women who are sent letters inviting them to order an SSK

(Group B) to order kits online. The site will be hosted by Queen Mary University of London (QMUL) where the research team were based during initial study set up. The research team moved to King's College London in January 2018, however it was agreed the website and the associated database would remain at QMUL. Women who opt to order self-sampling kits via the study website will be required to input a unique ID number (pre-printed on their

invitation letter), their name, address, postcode and date of birth onto the website. Entering their email address (to receive an email confirmation) will be mandatory. These data will be encrypted and stored on a secure database held at Queen Mary University of London and will only be accessible to designated staff at PSL Print Management Ltd or their third party suppliers. PSL will receive an automated email to alert them when new orders have been placed. They will then access the encrypted data containing details of women who have placed an order online using an individual login (username) and password. PSL staff will then send out study kits to women who complete their details on the site with a valid unique ID number.

The study team will use this website to monitor and conduct measurements of study outcomes (e.g. number of women who placed an order but did not return a kit) but will not have access to patient identifiable information on the website.

Women will be asked to provide consent for their data to be stored and transferred (as described above) as part of the online kit ordering process. A pop-up window will clearly outline what they are agreeing to by placing their order and women will be required to click a button to confirm their agreement.

5.6. Text message reminders

We plan to ask GP practices that already use patient-care messaging software to send text message reminders to women approximately 7 days after they have been given a kit (opportunistic or sent kits directly) or invited to order a kit. Wording of text messages will be generic (i.e. will not contain any personal information) and will be agreed with the GP practices.

We will explore the possibility of adding a hyperlink in the text message that will link to the study website for ordering self-sampling kits (for women invited to order kits – Group B).

5.7. GP endorsement

GP endorsement will be included on study invitation letters that offer self-sampling as this has been shown to increase participation in colorectal screening (and would be cost neutral).[21]

5.8. Self-sampling kits

Self-sampling kits will be;

- enclosed in a freepost return box (UN3373 compliant & pre-addressed to the laboratory)

and will include:

- A flocked swab (Copan FLOQswab™) in a tube with a re-sealable lid
- Pictorial and written instructions for self-collecting the vaginal sample
- A patient information leaflet
- An HPV information sheet
- A Lab Request/Consent form

5.9. Post-study follow-up under care of the GP

Figure 2 Post-study Management summarises the post-study follow-up management plan of women who return a self-sample in the study.

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 self-samples in the national cervical screening database, women who test HPV negative on a self-sample will continue to receive the usual smear reminder letters (i.e. will remain on normal recall). Note: If a sample with a negative result is returned after the validation period as confirmed by the lab (30days) the participants will be advised (by letter) to attend their GP practice for a cervical cytology test (i.e. routine screening with liquid based cytology).

Women who test HPV positive will be advised in their results letter to have a cervical cytology test 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).

Pregnant women who test HPV positive will be advised to contact their GP to discuss follow up investigations which may have to be had when the woman is postpartum.

Self-sampling studies have found that most (~80%) women who test HPV positive attend follow-up cytology.[6, 10, 15-17] In our previous study of opportunistically offered SSK in London, 85% of women who tested HPV positive on a self-sample attended for follow-up investigations. We will collect details of follow up tests for HPV positives (cervical cytology, histology) from the women's GP (with the women's permission).

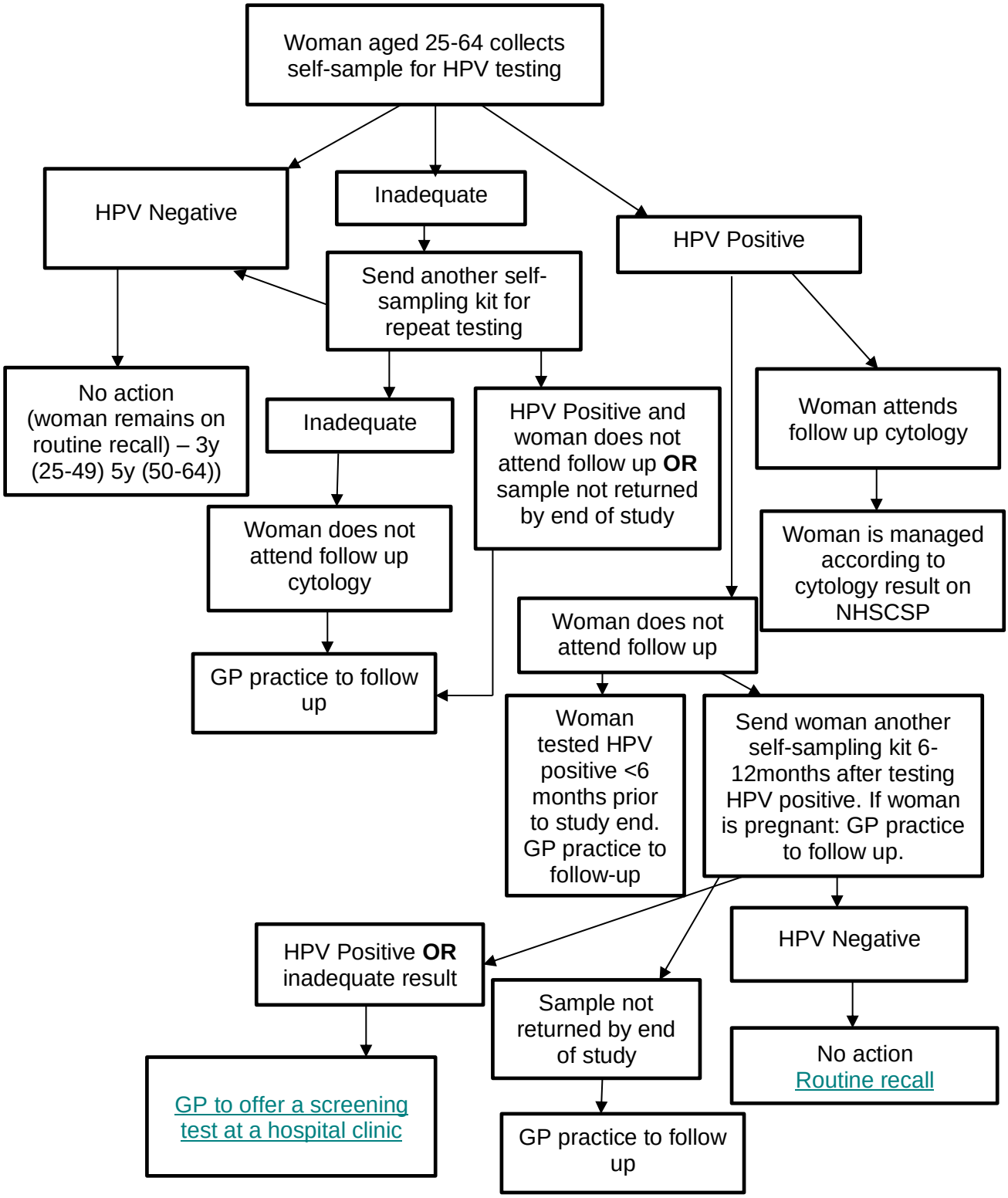
As an additional safety-net, women who have not attended for a follow up cervical cytology test by 6-12 months after testing HPV positive (on a self-sample) will be sent a further self-sampling kit for repeat HPV testing. Relevant women will be identified by the participating GP practices (designated study administrator) using a pre-written search of the GP records. The GP practices will send the list of the participant's names and DOBs to the study team

(securely via NHS.net to NHS.net email) who will send the kits to women. Women who test HPV positive or inadequate on their repeat sample (1st sample HPV positive) will be offered another screening test at a hospital clinic (colposcopy clinic). Women who test HPV negative will be advised that they are not required to do anything further. For women who do not return a sample for repeat HPV testing, the study team will ask the women's GP to manage their follow up by either contacting them to remind them to come for a follow up test (standard screening test) or offering them another screening test at a hospital clinic (colposcopy).. For women who test HPV positive or have an inadequate result on a self-sample who have been recruited at the latter stages of the trial, the study will have ended before they would have been sent a repeat kit. At the end of the study, these individuals will be highlighted to the GP practices who will manage the follow-up of the participant, either by contacting them to remind them to come for a follow up test (standard screening test) or offering them another screening test at a hospital clinic.

Note: Where a participant is referred to a hospital clinic (colposcopy) for another screening test it will be at the clinician's discretion whether they do a full colposcopy examination or a cervical cytology test (i.e. routine screening with liquid based cytology).

All women who return a self-sample and who are individually randomised will be passively followed up for the duration of the trial, to obtain data on cervical cytology tests and histology results. Individual participant follow-up length will depend on the point in which they are enrolled and will be up to 21m. Only anonymous aggregate data will be collected for women who are individually randomised but do not return a self-sample (i.e. not consented to the study). GP records will be used for this purpose.

Figure 2 Post-study Management Plan


Woman aged 25-64 collects self-sample for HPV testing
HPV Negative
Inadequate
HPV Positive
Send another self-sampling kit for repeat testing
No action (woman remains on routine recall) – 3y (25-49) 5y (50-64))
Inadequate
HPV Positive and woman does not attend follow up **OR** sample not returned by end of study
Woman attends follow up cytology
Woman does not attend follow up cytology
Woman is managed according to cytology result on NHSCSP
GP practice to follow up
Woman does not attend follow up
Woman tested HPV positive <6 months prior to study end. GP practice to follow-up
Send woman another self-sampling kit 6-12months after testing HPV positive. If woman is pregnant: GP practice to follow up.
HPV Positive **OR** inadequate result
HPV Negative
Sample not returned by end of study
No action
Routine recall
GP to offer a screening test at a hospital clinic
GP practice to follow up

5.10. Screening status on the National Database

Self-sampling is currently not available on the cervical screening programme (CSP) in England. Therefore, returning a self-sample for the study will not affect the women's screening status in the national database (unless they attend for cytology).

5.11. Inadequate samples

Women whose samples cannot be analysed (this is normally due to insufficient DNA) will be asked to collect another sample. Based on our previous self-sampling study we expect this will be in the region of 2%[19] of all returned samples. The study team will send women another self-sampling kit with an accompanying letter explaining that their sample was inadequate and asking them to collect another sample. 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. If the second sample is not returned by the end of the study the patient's GP practice will manage their follow up.

6. SAMPLE COLLECTION AND PROCESSING

Women who accept a self-sampling kit in their GP practice (opportunistic) will have the option of collecting their sample in the clinic bathroom or at home. Samples collected at the GP practice will be posted to the laboratory by the GP practice staff.

Women who are sent kits directly (Groups B and C) will collect their sample at home.

All samples collected by women at home will be posted to the laboratory for analysis (using a freepost, pre-addressed UN3373 compliant box or envelope that will be provided with the kit). Women will be asked to post the sample as soon as possible after taking it.

6.1. Sample labelling

6.1.1. Opportunistically offered kits

Sample tubes will be pre-labelled with a Preventx 'SK' number and barcode (standard barcode or two-dimensional barcode/Quick Response Code (QR code)). PSL will maintain a log of what 'SK' numbers were sent to each site.

The label will have space for the participant's name (first name and surname), date of birth and the date the sample was taken.

The GP, nurse or HCP handing out the kit will be required to write the 2 identifiers on the label (first name, surname and date of birth (DOB)) and will be required to affix the

Preventx barcode to the Lab Request/Consent form. Women will be required to write the date the sample was taken onto the swab label and laboratory request form (supplied by GP with participants name, address and DOB prepopulated).

6.1.2. Kits sent to / ordered by women

Sample tubes will be pre-labelled with a Preventx 'SK' number and barcode (standard barcode or two-dimensional barcode/Quick Response Code (QR code)). The Preventx 'SK' number and barcode will also be affixed to the Lab Request/Consent form and a unique ID number will be merged to print on the form. The unique ID number is generated by the coordinating centre and supplied to PSL. The unique ID number serves 2 purposes:

1. allows the coordinating centre to identify whether the participant is from Group B or Group C) .
2. Allows Group C participants to complete their self-sampling kit web or postal order

Women will be instructed to write the date the sample was taken on the sample tube and Lab Request/Consent form (participants name, address and DOB prepopulated)

6.2. Sample transport and storage

Samples will be transported dry and stored at room temperature.

6.3. Residual samples

Residual samples will comprise of residual DNA stored in Roche transport media. After HPV results have been reported residual samples will be stored at room temperature by Preventx. Throughout the study, residual samples will be sent to the Molecular Epidemiology lab (MEL) at the Wolfson Institute of Preventive Medicine, Queen Mary University of London where they will be stored. Preventx will pseudonymise the samples and will retain a data linkage file (using the Preventx 'SK' number). The study team will then amalgamate this file with relevant data (age & histology from GP records) to provide to the QMUL laboratory for their analysis. In this way, the residual samples will be analysed anonymously by the MEL team, but the study team will be able to link the residual sample data to HPV result and final histology (if available).

At the end of the study residual samples will be stored in linked-anonymised format at the Molecular Epidemiology Laboratory at Queen Mary University of London, Wolfson Institute of Preventive Medicine, Charterhouse Square, London EC1M 6BQ under the institutional HTA storage license pending storage for possible future ethically approved analysis.

Potentially, residual samples will be made acellular before the end of the REC approval, in which case they would become not relevant material and will not require cover by the institutional HTA storage license. Results will not impact clinical management for women in the study.

7. LABORATORY

HPV testing for the study will be performed by Preventx, Meadowhall Business Park, Carbrook Hall Road, Sheffield, S9 2EQ.

7.1. HPV testing

Preventx will use Roche cobas® 6800 platform for HPV testing. The cobas® 6800 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

HPV testing will be performed using the Roche's CE marked HPV test kits. Samples will be prepared into PCR Media, following the Roche guidelines and to the applicable standards outlined in the laboratory quality manual. Testing will be carried out in the Preventx Laboratory (Preventx, Meadowhall Business Park, Carbrook Hall Road, Sheffield, S9 2EQ).

The laboratory will aim to process samples and send out results within 5 working days of receipt. Results will be reported via Preventx's integrated testing platform and will be accessible via Preventx's secure online reporting tools.

7.2. Reporting of HPV test results

Preventx will send HPV test results to the study team via a secure results reporting platform. The team will then personalise a pre-determined 'HPV result' letter and send to the study participant in the post. The HPV positive result letter will be accompanied with the study specific HPV Information Sheet for their reference. HPV results will be sent to the participant's GP on a weekly basis via NHS.net accounts and hard copies will follow in batches on a monthly basis by post. Study HPV test results will be entered on the GP medical record system as Read codes by the practice administrative staff.

8. STATISTICAL CONSIDERATIONS

8.1. Sample size considerations

With 13 participating GP practices there would be approximately 8420 eligible women (i.e. women aged 25-64 eligible for cervical screening who are overdue by at least 6 months).

8.1.1. Intervention arm – Opportunistic offering of self-sampling

With six GP practices randomised to the intervention arm, there would be some 4000 eligible women. Based on a previous study[19]) we estimate that 60% will consult their GP practice over one year, 500 (21%) will be opportunistically offered a self-sampling kit and ~330 (14%) will accept (4000*0.60*0.14). An estimated 210 (9%) (4000*0.6*0.09) would return a self-sample for HPV testing. Therefore, the proportion of women >6m overdue cervical screening who will return a sample when opportunistically offered a kit (i.e. ≈210/2400) could be estimated with a 95% confidence interval of width ±1.0%.

8.1.2. Individual level randomisation

With 13 GP practices we anticipate that some 5000 will be identified as never screened or will reach the 15- or 27-month anniversary of their last test due date during the study. Of these, approximately 2500 women will be randomised to each of the two intervention arms. If we assume that 12% of those who are sent a kit (initially) return an adequate sample, the expected 95% confidence interval would be estimated with approximately ±1%. If about 7% of those offered a kit request one and return an adequate sample, then this could be estimated with approximately ±1%. Therefore, for 13 GP practices approximately 1250 invitation letters will be sent (here, the number of self-sampling kits will depend on the women's willingness to participate) and 1250 self-sampling kits posted.

8.2. Planned analysis

The aim of the pilot study is to assess feasibility and optimal approaches for offering self-sampling to cervical screening non-attenders in London, therefore there is no formal primary outcome measure. Instead, we will calculate measures of feasibility and acceptability such as the proportion of eligible women who are offered kits, accept and return a self-sample for each arm. We will also examine how this differs by GP practice, age and cervical screening status. 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.

We plan to estimate:

Opportunistic arm

1) Using electronic GP record searches: The proportion of eligible women who:
    - consult their GP practice
    - are offered a self-sampling kit
    - accept a self-sampling kit
    - return an adequate self-sample.

We will also examine:

1) reasons why eligible women are not offered the self-sampling kit
2) reasons why eligible women decline self-sampling kits (if offered)

Individually randomised women

1) The proportion of eligible women in Group B who order a self-sampling kit
2) The proportion of eligible women in Group B and Group C who return a self-sample.

All women in the study who return a self-sample

1) The proportion of women who return an adequate sample
2) The proportion of women who test HPV negative who attend for cervical cytology after returning a self-sample
3) The proportion of women who test HPV positive, and of these:
    - The proportion of women who attend for cervical cytology
    - The proportion with abnormal cytology
    - The proportion with CIN2+ on histology

All women who return a self-sample and all individually randomised women

We will examine the passive follow up data to determine if we can extract:

1) Change in cervical screening coverage at each practice (to assess the impact of self-sampling on coverage):

2) Cervical screening status at the end of the passive follow up period (aggregate anonymous data and/or individual anonymous data for women who return a self-sample from GP records)
3) Cytology and histology (if available) results for women who return a self-sample (if applicable)

    - The proportion with abnormal cytology
    - The proportion with CIN2+ on histology

8.3. End of study definition

The study will end once the following have been completed:

- up to 12 months of active recruitment,
- 6 months follow up (from the date the last HPV positive result on an ALOHA self-sample is reported),
- follow-up data monitoring and
- data collection and cleaning.

Please note: In light of the current COVID-19 pandemic the end of follow up date will depend on when cervical screening services are resumed. i.e. those who tested positive on their ALOHA HPV self-sample will need to be given 6 months at a time when services are available to attend for their follow-up screening.

9. DATA HANDLING AND RECORD KEEPING

Study data will be stored securely and made available for audit according to the standard procedures of King's College London.

9.1. Confidentiality

Information related to participants will be kept confidential and managed in accordance with the Data Protection Act 2018, NHS Caldicott Principles, UK Policy Framework for Health and Social Care Research (2017), and the conditions of Research Ethics Committee Approval.

9.2. Data collection

For study management purposes the study team will require access to patient identifiable data for the following reasons;

- to fulfil kit postal orders to be sent – women will have submitted a postal order form
- to send repeat sample kits – women will have returned a sample i.e. consented
- to generate HPV results letters – women will have returned a sample i.e. consented
- to resolve queries i.e. or to confirm the identity of women for samples returned without a lab request form – women will have returned a sample i.e. consented

The study team will also require access to patient identifiable medical record data for monitoring purposes (for those who have returned a sample).

Self-test order forms will be received by the ALOHA study team by post at KCL. The data will be uploaded to PSL print management Ltd web-based SFTP portal and approved third parties (securely via the AIMES Health Cloud). Forms will be stored securely in a locked cabinet in a restricted access office in Guy's Hospital.

Personal data (line-level) will only be downloaded from the GP medical records by the ALOHA trial coordinator for women who return a self-sample i.e. those in the intervention arms who have consented by returning a sample.

Identifiable data will be accessed by the study team on secure web-based reporting platforms using the 'AIMES Health Cloud'. The AIMES Health Cloud is a dedicated virtual environment that enables NHS Trusts to use cloud technologies managing sensitive data in a secure governed environment. The AIMES Health Cloud is only connected to either the Secure NHS Network (N3/HSCN) or directly to individual NHS Trusts with no direct route to the Internet.

At the end of the study personal identifiers will be removed and data will be stored and analysed using the participant's SK number/ unique ID number.

Only anonymous aggregate data or pseudonymised line-level data will be collected for women who are eligible for the study but are 1) in one of the intervention arms but do not return a self-sample or 2) in one of the control groups (at GP level randomisation or individual level randomisation).

We plan to collect:

- Age / sex / ethnicity breakdown of all registered patients – anonymous aggregate data only

- Age / sex / ethnicity breakdown of all women eligible for the study - pseudonymised line-level for those who do not return a sample
- The number of women aged 25-64 years
- Cervical screening coverage (age-appropriate and 5 year)
- The number of women who are eligible over the study period (i.e. aged 25-64 with a cervix who are (i) at least 6 months overdue cervical screening or (ii) women who have never been screened or reach the 15- or 27-month anniversary of their last cytology due date (both arms).
- The number of eligible women who consulted a GP, nurse or healthcare practitioner at least once during the study period (to calculate the proportion of women invited and response rates) – Intervention arm only
- The proportion of eligible women who order an SSK:
    - Online
    - By returning a form
    - Via text message
- Cervical screening data – all clinical codes relating to cervical screening (cytology and histology) for all women in the study (GP level randomised and individually randomised) – pseudonymous line-level data for those who do not return a sample.
- Passive follow up of cervical cytology tests and histology results for all women in the study (GP level randomised and individually randomised) - pseudonymised line-level data for those who do not return a sample. This data will be collected from the GP records. Depending on GP practice capacity and resource, they may be asked to ensure they have updated the GP records with data from the NHAIS national screening database prior to final data collection.

Record Retention and Archiving Study data will be stored securely and made available for audit. Upon study completion study records will be kept for 5 years as per agreement with Sponsor

10. ETHICS

10.1. Ethics approval

Ethics approval for the study will be obtained from the London - Brighton & Sussex Research Ethics Committee (REC) ref 17/LO/1655).

10.2. Informed consent procedures

The patient information sheet and an information leaflet on HPV will be provided to all women who receive self-sampling kits and all those invited to order kits. As only women who wish to participate will return a self-sample (i.e. opt-in), consent is implicit.

10.3. Opportunistic offering of self-sampling

GP primary care is a busy and time-pressured environment with an average GP consultation length of just 9 minutes.[22] In a previous study of opportunistic offering of self-sampling in GP primary care the consent procedure consisted of a brief (2 min) study explanation and verbal consent. This simplified approach was suggested by the reviewing REC committee (Brighton and Sussex NRES Committee 13/LO/1441) and worked well for the study with no issues raised. Therefore, we intend to use the same verbal consent procedure for this study. Consent to accept a self-sampling kit will be recorded in the women's GP medical record.

10.4. Women randomised to receive or order an SSK in the post

Consent will be implicit by return of a self-sample.

SSKs will come with a form which 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). The form will state clearly what the women are consenting to by returning their sample.

Women who order a SSK online (will only apply to women randomised to Group B who are invited to order a SSK) will be asked to provide explicit consent to storing their personal data (encrypted) on a secure database at QMUL and for this data to be shared with trusted third parties for the purposes of assembling, sending and analysing the kit/sample. . This will be in the format of an online pop up window during the SSK ordering process, and their data will only be saved once they click "I agree". Personal data collected on the website will be stored but not accessed by QMUL, as the PID collected will only be used for SSK order fulfilment (carried out by PSL Print Management Ltd).

10.5. 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.

11. SAFETY CONSIDERATIONS

We do not anticipate any major safety concerns for the study. Vaginal self-sampling using flocked swabs has been safely performed in several studies.[17, 23-26]

12. SAFETY REPORTING

12.1. Annual Safety Reporting

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

13. MONITORING & AUDITING

A member of the research team will audit and monitor study procedures as agreed in the study monitoring plan (e.g. recruitment, recording of consent, and anonymous data downloads to check data quality).

The study may be audited internally by KCL.

14. USER INVOLVEMENT

User representatives will be involved in the study design and review of trial results. We have already sought user feedback for all the study documentation that participants will receive, and this has been incorporated. As the study will be held in GP primary care, we have involved GPs in helping us develop the study processes

15. FINANCE AND FUNDING

The pilot study will be funded by a programme grant awarded by Cancer Research UK to Professor Peter Sasieni.

16. INDEMNITY

The study was initially sponsored by Queen Mary University of London and suitable indemnity was in place during this time. Relocation of the study team to King's College London in January

2018 resulted in the change of sponsorship from Queen Mary University of London to King's College London. King's College London is currently sponsoring the study and has arranged for suitable indemnity to be in place.

17. DISSEMINATION OF RESEARCH FINDINGS

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

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APPENDIX 1 – TABLE OF OBJECTIVES, ENDPOINTS & ASSESSMENT METHOD

Primary Objective	**Endpoints**	**Assessment Method**
To estimate the proportion of women who provide a self-sample when: • Offered kits opportunistically • Sent a kit directly (opt-out) • Invited to order a kit (opt-in)	Uptake of self-sampling within 6 months after invitation	**Opportunistic:** number of eligible women with self-sample returned (using data provided by lab) as a % of total eligible women with Read codes for kits offered as per GP records ***vs*** **Sent a kit directly (opt-out):** number of women returned self-sample (using data provided by lab) as a % of total eligible sent kit directly ***vs*** **Invited to order a kit (opt-in):** number of women returned self-sample (using data provided by lab) as a % of total eligible sent letter (and separately for each method of kit ordering as a % of total eligible sent letter)
Secondary Objectives	**Endpoints**	**Assessment Method**
To estimate the proportion of women who test HPV positive on a self-sample and attend for follow up within 6 months of a positive result	Attendance at follow up (cytology or colposcopy) amongst eligible women within 6 months of testing HPV positive on a self-	Number of eligible women who test HPV positive on a self-sample and (i) have codes for cytology or colposcopy attendance in their GP records within 6 months of HPV positive result and (ii) who have CIN2+ recorded in their GP records; as a % of all eligible women who test HPV positive on a self-sample

	sample and histological confirmation of CIN2+	
To assess the logistics of testing samples, recording results and giving women their results in a timely manner.	Turnaround time for HPV testing and results reporting.	Number of days between sample received at laboratory to results reporting to women and to GPs (data from laboratory & study team).
Exploratory Objectives		
To pilot a variety of approaches to encourage GPs to offer self-sampling opportunistically to women who are overdue cervical screening consult for any reason. Where GP functionality exists text message ordering will also be utilised, but it is unclear how many GP sites will have the functionality to offer this. Availability of additional services will be recorded to see if this is a viable method to take forward into future work		
To pilot a variety of approaches to facilitating women who wish to order a self-sampling kit		
To compare demographic and cervical screening status (never screened, overdue, up-to-date) between responders and non-responders		
To examine the consultation rates and response rates (numbers offered, accepted, declined and returned as a proportion of total number of eligible women, reasons for declining kits, kit offers by health professional type) for eligible women in the opportunistic (intervention) arm.		
To assess the impact of offering self-sampling on cervical coverage using passive follow up data		
To carry out analysis on residual samples that could help inform management for cervical screening in the future		