PROTOCOL

The impact of HPV-based cervical screening incorporating the choice of a vaginal self-test or a clinician-taken cervical sample in the NZ primary care setting

Let's test for HPV (and prevent cervical cancer)

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Version History	**Notes**
1, Date:26/4/22	Submitted as part of original application to HDEC
2, Date: 10/6/22	Submitted as part of response to HDEC following provisional approval
2A, Date: 6/7/22	Updates to inclusion/exclusion criteria. Updates to reduce patient contact to 3 texts/letters/emails. Update to remove requirement for kits to be provided subsequent to consent. Updates to practical aspects of the study, in alignment with Operations Manual. Clarifications to the text of Appendix 7. Updates resulting from Pacific Steering Committee Meeting #1 feedback. For further detail see Pacific Steering Committee response letter (dated 6/7/22).
2B, Date 14/7/22	Clarification of inclusion criteria (to allow people due for screening without a cervix to be included). Reformatting of age group criteria for data presentation. Clarification regarding Good Clinical Practice training requirements. Inclusion of brochure and poster in recruitment process.
2C, Date 16/11/22	Ability for Support to Screen outreach services to act on behalf of participating GP clinics. Addition of text regarding Māori and Pacific community engagement (as per request of our Pacific Steering Committee), acknowledgement that there may be more than one type of education brochure available, addition of an educational video. Updated guidance regarding patients who are due to exit the national cervical screening programme (Appendix 6). Clarification to Appendix 7.
2D, Date 1/3/23	Clarified that patients can be eligible to take part in the study if they are within 4 months of being due for their cervical screening, as per NCSP screening criteria (detail removed from inclusion criteria in Version 2A). Change of colour on flow chart in Appendix 6 to make it clearer and addition of urgency criteria to legend. The urgency criteria align with the wording in the text of the protocol. Please note that deletion of the prior version of the figure has not been tracked- to view it, please see Protocol V2C. The following updates to improve clarity, based on feedback from Beverly Lawton: - Use of term “self-test” rather than “self-sample” for ease of reading.

	- Clearer wording around role of Support to Screen services. - Correction to full term for NCSPR (from 'record' to 'register'). - Replacement of 'unscreened' with 'underscreened' in the following sentence: "The NSU will also be informed of patients that remain unscreened" - Removal of repeated statement: "* Nurses who are not accredited as cervical screeners will need have undertaken a study education package as approved by the Study Team." - Clearer wording regarding recommendation for care of patients with HPV 16/18. - Addition that screening for patients with prior cervical abnormalities is also referred to as a "Test of Cure". - Clearer wording about how test results are presented and how participants are informed. - Addition of cost to the patient as an example of a barrier to screening. Formatting updated for consistency e.g. Contents table update.

Contents

Background

Cervical cancer is an almost entirely preventable disease.[1] New Zealand (NZ) has a successful National Cervical Screening Programme (NCSP), however annually ~170 women are diagnosed with cervical cancer and over 50 die from it.[2] It is also notable that Māori and Pacific women have a significantly higher cervical cancer incidence and mortality compared with non-Māori and non-Pacific women.[2] Cervical cancer incidence per 100,000 women in 2017 was 9.7 for Māori women, 6.1 for Pacific women, 5.5 for Asian woman, and 5.7 for other women.[2] Mortality due to cervical cancer per 100,000 women in 2016 was 2.9 for Māori women, 3.5 for Pacific women, 1.9 for Asian woman, and 1.3 for European/Other women.[2] A review of the cervical screening histories of women diagnosed with cervical cancer (2008-2012) revealed that around half of women with cervical cancer had not had a cervical screen in the 5 years prior to diagnosis. Many women however had been screened and their screen reported as normal.[3] It is therefore clear that cervical cancer prevention can be improved by (1) ensuring patients participate in regular screening and (2) improving the sensitivity of the test.

Compared with a traditional cervical cytology test, the high risk human papillomavirus (hrHPV) test has been shown in a number of randomised clinical trials to offer greater sensitivity for the detection of precancerous abnormalities and greater protection against cervical cancer.[4] The NCSP has therefore signalled its intention to introduce hrHPV testing as the primary screening test with cervical cytology used to triage hrHPV positive patients to immediate investigation or repeat screening. Recent evidence demonstrates that a self-taken vaginal swab (self-test) offers equal sensitivity to a clinician-taken cervical sample,[5] but, at the present time, for effective triage, many patients who have a positive hrHPV result following a vaginal self-test need to be recalled for a cervical cytology sample.[6]

As a self-test is often more acceptable to patients than a clinician-taken cervical test, self-testing has been shown as an effective tool to improve participation in the screening program in un- or under-screened women[7] and particularly in under-screened Māori women.[8] The hrHPV self-test therefore has the potential to reduce the incidence of cervical cancer and reduce inequities in this disease for NZ patients.

It has previously been identified that a source of screening failure is delayed or inadequate response to an abnormal cervical screening test (*manuscript in preparation*). Delayed access to specialist assessment has also been identified as a source of inequity in NZ (*manuscript in preparation*). It is expected that hrHPV screening will identify more patients with cervical abnormalities than cytology screening so this will increase the imperative that assessment of patients following an abnormal test is effective and equitable.

It is also important to acknowledge that even with cytology triage, the introduction of primary hrHPV testing will increase demand on colposcopy services and that an overloaded colposcopy service will further reduce access to specialist assessment. An important focus of this study therefore is to document patient's access to cytology triage and colposcopy and the potential impact on colposcopy services.

The implementation of primary hrHPV screening incorporating self-testing is an important cancer control initiative. In order to implement this strategy, studies are needed to explore the uptake, efficiency, and equity of the strategy in a range of NZ populations. This study is designed to supply the NCSP and the NZ public with information that will assist the nationwide implementation of hrHPV testing.

Goal

The purpose of this study is to describe the impacts of implementing primary hrHPV-based cervical cancer screening incorporating the choice of vaginal self-testing or a clinician-taken cervical test in a diverse range of NZ primary care settings.

The impacts will be assessed by observing the events in the screening pathway from invitation to diagnosis of a precancerous change and identifying at which points, and for whom, the screening pathway fails.

Aims

To enrol a minimum of 15 primary care providers in differing environments throughout NZ to the study and offer the option of hrHPV screening to patients enrolled with their practice who are due for or overdue a cervical screen.

To include the options of recall coordinated from within participating practices and centralised recall coordinated by the Primary Health Organisation (PHO).

To screen at least 3000 patients using their choice of one of the following tests:

- Vaginal hrHPV self-test performed at home or other suitable location
- Vaginal hrHPV self-test performed at the General Practice (GP) clinic (with or without nurse or kaiāwhina-led support)
- Clinician-taken cervical liquid-based cytology sample.

To implement NCSP-agreed care pathways for abnormal hrHPV screening results utilising cervical cytology, colposcopy and repeat screening.

To implement NCSP-agreed screening and care pathways for patients with previous abnormal cytology.

Objectives

Primary

To describe the impact of hrHPV testing (by demographics and screening history when numbers permit) in terms of:

- Proportion of patients screened by each method
- Proportion of patients who complete or do not complete each step of the appropriate screening pathway (including uptake of screening, cytology triage, and colposcopy assessment) and referral back to primary care
- Time to completion of the appropriate screening pathway
- Screening outcomes in patients with prior abnormalities in relation to transition guideline recommendations
- Number of colposcopy referrals, their indication, and outcomes.

To describe the disease burden detected in the study population, in terms of:

- HPV positivity rate by HPV 16/18 or other hrHPV, by demographics
- Incidence of CIN2+ in patients with HPV 16/18 by cytology result
- Incidence of CIN2+ in patients and with other hrHPV with abnormal cytology.

Secondary

To describe uptake of screening by mode of invitation:

- Centralised PHO or practice-based recall.

To describe resource utilisation (e.g. number of contacts, type of contact, engagement of other agencies, cost to patient) to achieve completion of the screening pathway:

- To achieve hrHPV screen
- In the event of an abnormal hrHPV screen, to achieve cervical cytology and/or colposcopy.

To report the rate of unsatisfactory hrHPV samples or documentation.

Equity

Compared to the general population, Māori and Pacific patients are less well served by the NCSP based in traditional primary care practices. The reason for introducing the HPV self-test is to reduce the incidence of cervical cancer and reduce inequities by providing a more sensitive test and reducing barriers to cervical screening.

There is inequity in access to the current cervical screening programme. A/P Sykes and colleagues recently completed the 2008-2017 Case Review of Cervical Cancer which found that Māori and Pacific women are less likely to have adequate cervical screening prior to their cervical cancer diagnosis when compared to people identifying as "European/other".

Te Tiriti o Waitangi is the founding document of NZ outlining the relationship between Māori and Crown representatives. Article three of Te Tiriti guaranteed equality for Māori and British. However, the many disparities in NZ health statistics have been noted as being evidence that our health system breaches the principles of Te Tiriti o Waitangi. We acknowledge that the current NCSP does not result in equitable outcomes. It is therefore essential that changes to the NCSP do not perpetuate this. Patients, and in particular Māori patients, experience many barriers to cervical screening, among these are economic considerations, cultural considerations (including building trust and relationships), and reluctance to undergo or even fear of a speculum examination. There is evidence that a self-test is more acceptable for Māori patients than a speculum examination and that the use of the self-test can, with an appropriate approach from health services, lead to a marked improvement in participation for under-screened Māori patients.[8,9] Barriers have also been identified in Pacific patients, for which the use of self-sampling has been demonstrated to significantly improve screening uptake when compared with standard cervical cytology.[9] We also acknowledge that access to further investigation following an abnormal screening test is a source of inequity. Further study of the acceptability of and compliance with secondary cytology triage is of particular importance as the introduction of an extra step in the clinical pathway may inadvertently introduce more barriers for those patients at greatest

risk. In addition, A/P Sykes and colleagues 2008-2017 Case Review of Cervical Cancer found that compared with Māori and Pasifika women, other women who did not identify as Māori and Pasifika experienced substantially less delay to cervical cancer diagnosis following an abnormal cytology.

In addition to Māori and Pasifika people, other people who are less well served by the current screening programme include non-English speaking and migrant groups, people with disabilities, non-binary people who have a cervix or vagina, and older people. It is essential that approaches and support structures are culturally safe and appropriately designed to have maximum engagement with underserved populations.

Article one of Te Tiriti gave the right to kāwanatanga, to govern and the power to protect Māori interests, while Article two promised tino rangatiratanga, Māori's right to authority of their own affairs. Thus, these articles affirm the right for Māori to be actively involved in developing and determining health programmes affecting Māori. All protocols, information sheets, and educational material will be developed in consultation with our representative Māori advisory groups and in partnership with Māori providers.

In recognition of the health inequities also observed for Pasifika women, materials will also be developed with consultation with our Pacific advisory group.

It has been identified by our Māori and Pacific Advisory groups that engagement of Māori and Pacific patients solely through practices, may not result in equitable outcomes. Practices are encouraged to work with community organisations that they are associated with, to ensure that Māori and Pacific patients have the greatest opportunity to be informed about the benefits of hrHPV testing and hence, take part in this study.

It is important to acknowledge this research is not performed in isolation. NZ research already performed has demonstrated that the hrHPV self-test is acceptable to Māori and Pacific patients and enables increased participation in screening for under screened Māori and Pacific patients.[8,9] In addition, there is ongoing research exploring more aspects of hrHPV screening in NZ. We will work in cooperation with other researchers, in particular our collaborators at Te Tātai Hauora o Hine, and build on research already completed and ongoing research. Dr Beverly Lawton is a co-investigator on this project. We intend to share knowledge and resources with these research teams to ensure optimal engagement for all eligible people. This collaboration will enable an optimal understanding of the issues. As a consequence, this will result in an efficient and consistent approach for Māori and our advice to the Ministry of Health.

Gender Identity

We recognise that not all people who have a cervix or vagina identify as women.

Methods

This is a prospective study observing the impact of the change from cervical screening utilising cervical cytology with a speculum examination to the implementation of hrHPV testing including the option of vaginal self-testing, in the primary care setting. This will include at least 15 general practice clinics in 3 regions of NZ and aims to screen at least 3000 people. The study team wish to take a pragmatic

approach and intend to work collaboratively with local providers and their Māori advisors to assist the introduction of the changes. We will collect real world data that will inform the wider implementation of hrHPV screening to the NCSP. This will be done without additional resource other than support for study consent and data collection. Operational procedures and clinical management of the patients will be determined by the providers involved within guidelines agreed between the study team and the NCSP on a business as usual basis. Prospective data collection will be performed by providers and supported by the study team. As this is not a comparative study, data analysis will be largely descriptive. The data will be presented in the context of historical coverage data available from the NCSP.

As the NCSP Register (NCSPR) is not currently able to manage the results of hrHPV screening, this information will be overseen by the study team. The study team will act in place of the NCSPR to provide reminders to the practices when patients are overdue further investigations or repeat testing, and to ensure management recommendations are correct. Following colposcopy or on completion of the study when the NCSPR is able to manage these patients, information they will be referred back to the NCSPR. This surveillance and tracking will be in addition to the normal recall processes used by individual practices.

Practice selection

Consent to participate in the Study will be sought from approximately 15 practices with an aim to recruit approximately 3000 patients over 6 months. The 15 practices will be selected from 3 regions with 5 practices each being selected from the Whanganui, Capital & Coast, and Canterbury District Health Board (DHB) regions. For patients eligible for cervical screening, the selected practices will offer a choice of hrHPV-self-testing within the practice or at home or a clinician-taken cervical hrHPV test.

The study aims to include patients from a cross-section of demographic characteristics. To ensure representation from practices with a higher proportion of Māori and Pacific patients, from rural locations, and with higher levels of social deprivation, the demographic characteristics of each practice was investigated and categorised by the following variables:

- Rural location
- Urban location + higher proportion of women with a mixed/high socioeconomic index
- Urban location + higher proportion of women with a low socioeconomic index
- Proportion of Māori women enrolled at or higher than the overall proportion of Māori in the NZ population (16.5%)
- Proportion of Pacific women enrolled at or higher than the overall proportion of Pacific in the NZ population (8.1%)

In Whanganui, following discussion with iwi representatives, five practices were selected by the Whanganui Leadership Team which represent the 6 iwi in the region. Screening for cervical cancer using hrHPV testing is seen as significant opportunity to address existing and emerging inequality. This screening approach has the capacity to improve participation for Māori and other under-screened populations. The hrHPV pilot provides an opportunity for Māori patients and other under-screened patients to be included in community engagement with the research study. The development of a

locality leadership approach in Whanganui provides the opportunity for an integrated iwi, community and GP clinic approach for screening to develop. The Whanganui hrHPV study steering group has included GP clinics in the study that will reflect this approach and demonstrate an emerging integrated model of care.

The Whanganui population has a high representation of Māori women and rural practice. In order to provide a balance in demographics, as reported in the aims, in Capital & Coast and Canterbury, four practices from each region would be selected at random, but an additional practice in each region would be chosen at random from within practices with a higher than population level of eligible Pacific women enrolled. In all cases, if a selected practice does not consent, then another practice with a similar demographic profile will be randomly selected.

It is acknowledged that providers may be small or large, and that the number of practices may need to be revised to ensure that the screen sample is of adequate size. Resources will vary between practices and financial support to practices will be proportional to the number of patients recruited.

Practices must hold a screening register/ recall system from which eligible patients can be identified and historical comparison can be made (5 years preferable).

Practices and PHO staff must agree to take part according to study protocol.

Within each practice (or group of small practices) a site lead and a principal screener will be identified.

Support to Screen outreach services will also conduct the study on behalf of selected practices (including,consent, hrHPV testing, and hrHPV test result follow up) . In these circumstances a formal process for clinical responsibility between the outreach service, GP clinic, and the University of Otago study team will be agreed.

Patient selection

Inclusion Criteria

People enrolled in the practice who are eligible for cervical screening as part of the NCSP* and are recalled for cervical screening or opportunistically attend the provider and are due for a cervical screen within the study enrolment period.

Participants are eligible to take part from four months prior to when their cervical screen is due, as per NCSP eligibility.

Participants must provide full informed consent.

Notes

Patients who are recalled for screening but report symptoms at the time of their screening test will be eligible for the study, however a strong recommendation for a clinical assessment will be made.

Patients who are invited to participate in this study can do so if they agree to participate within 3 months of the completion of the recruitment period (i.e., before 1 April 2023).

Patients attending for investigation of symptoms who are not due for screening are not eligible for the study. Note that cervical cytology may be taken as clinically indicated.

Patients who are unable or unwilling to provide informed consent will be recorded, but not included as study participants.

Common reasons a patient may be ineligible for NCSP cervical screening include:

- Total hysterectomy and no further cervical screening required
- Moved overseas
- Serious illness and further screening is not indicated
- Declined screening
- Referred to secondary care services / colposcopy
- Under specialist care
- Other (e.g. unable to consent to screening, never sexually active)

*For full details of inclusion for NCSP screening, please refer to the 2020 Ministry of Health Clinical Practice Guidelines for Cervical Screening in New Zealand at www.nsu.govt.nz.

Centralised or practice-based recall

In collaboration with the involved PHO's, participating practices will determine the mode of recall utilised for their patients. This may be recall based in the practice or co-ordinated regionally by PHOs.

Identification of eligible patients

All patients enrolled in participating practices eligible for screening according to NCSP guidelines who are due or overdue for a screen within the study timeframe will be considered eligible to participate in the study.

Eligible patients will be identified from the following sources:

- National Screening Unit (NSU) monthly report
- Practice recall registry
- Practice patient information system (eligible but not enrolled including patients over 24.5)
- Opportunistic drop in of unscreened but eligible patients or patients due for a screen who would otherwise be eligible.

A list of eligible patients, date of birth, ethnicity, date of last screen, and date of screen will be kept by participating practices and/or PHOs. The number and date of attempts to contact patients will also be recorded.

Identified data collected for participating patients and deidentified data collected for non-participating patients will be analysed centrally.

Practice-based recall and recruitment

A lead screener will be identified in each practice. Recall practice will be determined by the participating practice however at a minimum will include the following safeguards.

- Patients who are eligible be identified as above. If eligible they will be sent a written invitation (letter or email) and/or a text invitation to undergo screening and offered enrolment in the pilot study.*
- If patients do not respond, a second and, subsequently, a third invitation by letter, email text and/or direct contact.
- Any further intervention to enrol will be determined by the standard practice of that provider. This includes the option to use a poster, as approved by the Health and Disability Ethics Committee.
- Referral to screening support services may also occur consistent with individual practices.

The number of attempts and nature of these attempts will be documented.

The NSU will also be informed of patients that remain underscreened.

To undergo screening, patients will require an appointment with a medical practitioner (Doctor or Nurse)* who is able to discuss the screening test options and study information. They will also consent for the study, screen for symptoms and take a screening history. This appointment may be face to face or by phone with these options and a mechanism to make the appointment included in the recall. Kaiāwhina are encouraged to be involved in this process in a supportive and educational role.

A Screening pack including testing kit, Participant Information Sheet and consent form will be given to the participant, sent to their address or, if indicated, the participant may be advised to attend their primary care provider.

* Nurses who are not accredited as cervical screeners will need have undertaken a study education package as approved by the Study Team.

Opportunistic screening

Patients who attend the clinic who are enrolled in the practice and eligible to undergo screening within the study period will also be invited to be screened and take part in the study.

The number of patients invited to take part in the screen but who decline will also be documented.

Centrally-coordinated recall

Centralised recall can be organised at the PHO level, if practices request this, and it can be accommodated. For GP practices in Whanganui, the recall process is centralised by the PHO, carried out by staff from Whanganui Regional Health Network.

Eligible patients will be identified in the manner described above.

Up to 3 invitations to screen by letter, email and/or text will be sent to patients. Patients who do not initially respond will be approached three times at least unless they request not to be contacted further.

To undergo screening patients will require an appointment with a medical practitioner (Doctor or Nurse)* who is able to discuss the screening test options, and study information. They will also consent for the study, and screen for symptoms and take a screening history. This appointment may a phone appointment with a practitioner working on behalf of the PHO. Alternatively, it may be face to face

or by phone at the practice. A mechanism to make the appointment will be included in the recall. Kaiāwhina are encouraged to be involved in this process in a supportive and educational role.

A Screening pack including testing kit, Participant Information Sheet, and consent form may be sent to their address or the participant is advised to attend primary care provider (provider informed to arrange appointment with the participant).

Opportunistic screening will also occur in those practices utilising centrally-coordinated recall as per above. There is an option for practices to use a poster approved by the Health and Disability Ethics Committee to aid recruitment.

Non-responders

Patients due or overdue for their cervical cancer screen who do not respond to invitation for screening will remain with the responsibility of the NCSP. They will be referred to screening support services as per regional protocol and if not screened by the end of the study NCSP will be informed.

Consent

(See Patient Information Sheet and Consent Form)

All patients taking part in the study will give informed consent

While informed consent is essential, it is important that the consent process does not represent a barrier to screening or deviate significantly from normal practice (there is precedent for a brochure type patient information form and verbal consent for telehealth appointments). It is anticipated the patient information and consent will be discussed with the potential participant by a screener. That in the case of a face to face appointment the consent will be signed at this time. For telehealth appointments verbal consent will be. A consent form and Participant Information Sheet will accompany the test kit. Participants are required to read or have read to them the Participant Information Sheet as part of full informed consent. There will also be an opportunity for participants and potential participants to ring a screener within working hours to answer questions.

Brochures and a video approved by the Health and Disability Ethics Committee will be available. These provide general information on hrHPV and hrHPV screening. Study staff can use the brochures at their discretion to support patient education.

Consent forms will be collected at the practice and sent to study centre or collected by the laboratory and sent to study site.

Key issues of consent

The NCSP is introducing hrHPV screening in 2023 and this is a pilot implementation project. This study is funded by the NCSP.

hrHPV screening is a more sensitive than cytology screening but no screening test is 100% sensitive.

Participants have the option of vaginal self-sample in a patient nominated location, vaginal self-sampling performed at the General Practice (GP) clinic, or clinician-taken cervical sample.

hrHPV self-testing is painless and will not cause any harm.

A cervical hrHPV sample taken by a clinician is exactly the same procedure as for a current standard of care cervical cytology and may be associated with some discomfort.

A vaginal hrHPV self-test is as effective as a clinician-taken cervical hrHPV sample in the detection of precancer abnormalities.[10]

If self-testing is utilised and the test is positive (we expect one in 10), the participant may be recommended to return for a clinician-taken cervical cytology test.

The hrHPV test may incur costs but these costs will not be greater than a routine traditional cervical cytology test if a second test is required. Of note, the study payment to GP clinics is to cover the time and resources required to provide study information for full informed consent, this cost must not be passed on to patients.

The hrHPV test only detects hrHPV which is the cause of cervical cancer and cervical precancer but does not detect any other pathology.

There is evidence HrHPV testing results in more patients being referred to colposcopy because of positive test results. Particular groups of patients find colposcopy very challenging, including younger patients, under screened patients, patients who have experienced abusive relationships and those who have delayed having children. All patients should be treated with courtesy, respect and care. Clinicians and study staff should be aware of the research that exists in order to minimise a patient's anxiety around testing positive for HrHPV, and undergoing colposcopy.

Most patients who have an hrHPV positive test will not have any abnormality that needs treatment, but further investigation or observation will be required. Some patients who have hrHPV will have precancerous or rarely cancerous abnormalities that require further treatment.

Patients with symptoms, particularly post-menopausal bleeding, intermenstrual bleeding, post coital bleeding, persistent pelvic discomfort or pain, or abnormal vaginal bleeding, will be asked to discuss these with their doctor or nurse because other investigations may be indicated. At the time of consent, patients will be asked if they have any relevant symptoms.

We request consent to access clinical screening records, NCSP records, and hrHPV vaccination records.

Currently the National Cervical Screening Programme Register (NCSPR) is not structured to record an hrHPV screening test. However, the result and follow up recommendation following an hrHPV test will be shared with the NCSP.

Patients will be asked if they would provide consent to be approached to take part in online survey or structured phone interview about hrHPV screening (consent is optional and not a requirement to be in the study).

Screening tests

Please see flow charts in Appendix 6.

Most patients enrolling in the study will have 3 options regarding their screening test:

1. Vaginal hrHPV self-test at home or other suitable location
2. Vaginal hrHPV self-test at practice
3. Clinician-taken cervical sample (liquid-based cytology specimen) which will be tested for hrHPV.

In exception to this, patients who have been under follow up of a previous abnormality and according to agreed guidelines require cervical cytology in addition to hrHPV testing. They will be advised to have a clinician taken cervical sample, this will be tested for hrHPV and cytology. Patients who report symptoms will also be recommended to undergo a cervical sample that will be tested for hrHPV and cytology in addition to any other investigations that are deemed necessary by the care provider.

Vaginal hrHPV self-tests will be taken utilising a dry floq swab inserted in the vagina and transported in a sterile sealed container.

Cervical hrHPV tests will be taken under direct visualisation by an accredited cervical screener (smear-taker) using a cervibroom or equivalent and placed in liquid-based cytology medium.

The hrHPV test will be performed utilising an accredited laboratory and an hrHPV assay validated for cervical hrHPV screening.

A modified clearly distinguishable study laboratory request form will be utilised.

Tests will be logged in the practice or at the central study site.

A clinician responsible for the screen result will be designated.

Vaginal hrHPV self-test at home

If a participant indicates this choice, they will be given or sent by mail or courier a sample pack containing instructions consent form, a floq swab, sterile container and prepaid courier pack.

The participant will also have a phone number of the lead nurse from the practice and the study nurse and contact hours to ask any questions.

Once the sample is taken this can either be returned by mail or dropped off by the participant to the designated collection point.

If a consent is logged and the study team does not receive an HPV result from the lab within 10 working days, the study team will contact the practice to determine the reason for this e.g. the participant may not have sent the sample back. If the participant has experienced difficulties these will be addressed where possible. The participant will be offered self-swab in the clinic or clinician-taken alternatives.

Vaginal hrHPV self-stest in clinic

The participant will be given self-test pack and instructions, a nurse or kaiāwhina will go over the instructions with the participant and they will be provided with a private space to perform the test.

If the participant requests assistance the nurse or kaiāwhina is able to provide hands on assistance or support. In fact, in some circumstances the participant may request that the nurse or doctor takes the vaginal test.

Such requests and support will be documented.

The test will be logged in the practice and sent to the lab.

Clinician-taken cervical sample

If a clinician-taken sample has been requested, this will be performed in the usual manner from the cervix under direct visualisation.

This is a liquid-based cytology test, but it will be processed for hrHPV testing and cytology only performed if hrHPV is detected.

The sample however will be logged as a research sample by the practice and sent to the appropriate lab.

If the patient is due for screening and is enrolled but the patient has been recommended to undergo a speculum examination and the test has been taken as part of this examination, the patient will be included in the study but the reason for this recommendation will be documented. If symptoms or other clinical concerns exist, a cytology test can also be requested. The reason for this will be documented. If a cytology test is recommended to the patient by the practitioner, the reason for this will be documented.

Off-study cytology tests

A patient may choose not to take part in the study and have a conventional cytology test at the participating practice. This will be reported and managed by the NCSP as per normal practice.

A patient may have a cytology test performed as part of investigation of symptoms.

A patient may choose to have a cytology test at another practice.

These occurrences will be logged in the practice where possible and identified from the NCSPR on completion of the study.

If a patient undergoes an off-study cytology test they will receive no further invitations for screening as part of the study.

Cytology triage (risk stratification)

As the incidence of hrHPV is higher than the incidence of CIN2 + and the risk of CIN2 or greater varies by the hrHPV type and cervical cytology findings, in most hrHPV screening programs, cytology is used to triage patients prior to colposcopy referral.

Reflex cytology process

If the sample has been performed as a clinician-based cervical sample, a liquid-based cytology examination will be performed in the reporting laboratory in the routine manner on the same specimen without further request. Reporting will be as per modified Bethesda (NZ) as per NCSP

recommendations. The pathologist's recommendation will be made as per NCSP guidelines, but it will also be noted that the patient is participating in the pilot study and study recommendations may vary from this. The report will be forwarded to the NCSP.

If a self-test hrHPV has been performed and hrHPV is detected, the patient will be recommended to undergo a clinician-taken cervical sample at their practice. This sample can be taken by any cervical screener. The cervical cytology will be performed in a routine manner at an accredited laboratory. The sample will be marked that the patient is taking part in the pilot study and the result of the hrHPV test. Reporting will be as above.

A patient with HPV16/18 will be referred directly to colposcopy. Because cytology is considered helpful to the colposcopist and to exclude other pathology a cervical cytology test is recommended for these participants, however it is not required and should not create a barrier for the participant. Patients who are experiencing symptoms should undergo a speculum examination cervical cytology and investigations as indicated.

Patients may choose to have the reflex cytology done at a non-participating practice. This is discouraged as it will make correlation of results more difficult. The cytology will then be performed and reported as per NCSP guidelines. The reporting pathologist may not be aware of prior hrHPV results and recommendation for referral will be made on the basis of cytology.

Patients with prior cervical abnormalities (Test of Cure)

Patients with a previous high-grade abnormality or glandular abnormality, and who have not completed test of cure are recommended to undergo cytology at the time of hrHPV testing. If cytology or hrHPV testing is abnormal the patient should be referred to colposcopy. If a patient has had a prior low-grade abnormality (and no high grade) or has completed a test of cure they can be managed as per patients undergoing routine screening. When reporting the test, the laboratory will have access to the prior screening history. If a cervical cytology test (test of cure) is indicated but has not been taken, this will form part of the report.

Handling of specimens

Specimens will be delivered to the participating practice or central study location or the practice in person or by return courier envelope. The specimens will be logged and then sent on to the participating laboratory by courier or other suitable delivery mechanism. In some circumstances if a home test has been performed the specimen will be delivered directly to the laboratory. In this case consent forms will be collected by the laboratory and returned to the study centre. It is recommended that samples are sent to the lab within 48 hours of being taken. Results are to be reported within 5 working days of being received by lab.

Clinical responsibility for cervical tests

hrHPV tests organised by practice staff will be the responsibility of that practitioner (cervical screener).

hrHPV tests organised by the central recall system will be deferred to the designated lead in the practice. A method of coordination between the practice and the central recall will be determined. The centralised recall will be responsible for ensuring the designated practice is aware of the test and

the result. Patients with a positive result will require a face to face or a telehealth appointment to discuss the result.

Test Results

Test results will be reported according to normal locality and service-based protocols. The report will be issued to the clinician responsible for the test. A copy of the report will also be provided to the central study coordinator.

hrHPV results may be reported as follows

- Unsatisfactory test
- hrHPV Negative
- hrHPV Positive
- HPV 16 and or 18 and or HPV other(non-16 non 18 types) (extended genotyping may be reported if available)

A recommendation for management will be included on the report according to the agreed management protocol after consideration of the patient's screening history and recorded presence or absence of symptoms.

Informing patients

Central recall (mail out)

If the test kit has been supplied directly from the central recall team, participants will be informed of their result by the central study nurse by a combination of letter, phone call, or text (preference will have been requested at the time of taking).

Practice taken or practice coordinated.

The patient will be informed of their result by the practice coordinating nurse or the patient's cervical screener by phone or text or letter as per normal practice.

Unsatisfactory

The test needs to be repeated at the patient's earliest convenience.

Negative hrHPV

A very low risk of cervical abnormality. Repeat screening test at normal recommended interval (*currently 3 years however will increase to 5 years with the new program*). However, if the patient has symptoms they should consult with their doctor. An exception to this is patients due to leave the NCSP screening programme. Please see Appendix 6.

Positive hrHPV (no reflex cytology)

The test has detected the presence of hrHPV. This indicates an increased likelihood of a cervical abnormality. Cervical cancer is very unlikely but further investigation is strongly recommended

HPV16/18

Participants positive for HPV 16 18 will be referred directly to colposcopy without delay. A cervical cytology test at this point is recommended but is not required.

HPV other

The patient will be advised to please make an appointment to undergo an examination and a cervical cytology test (smear) within 2 weeks by a cervical screener of their choice.

The making of appointments will be facilitated by the informant. The patient will be informed that there may be a charge for that appointment.

At this point a patient with a positive result may be referred to colposcopy if cytology triage is considered to be an unacceptable barrier, but the patient agrees to attend colposcopy.

Positive hrHPV with reflex cytology

If a cervical hrHPV sample has been taken and cytology triage has been performed, then this information and or the need to undergo colposcopy can be communicated with the patient face to face or by phone.

Referral to colposcopy

(See flow chart in Appendix 7)

Referral to colposcopy guidelines are in accordance with planned NSU recommendations with the additional safety that patients with low grade cytology and hrHPV other who will be referred to colposcopy.

Referral to colposcopy is indicated for patients with a significant risk of high-grade cervical abnormalities. The recommendations in this pilot study have been agreed with the NCSP and take into consideration the current recommendations for colposcopy referral, risk of CIN2+, colposcopy service capacity, access to colposcopy for underserved populations, and the requirement of data collection from this study in a timely manner to inform implementation of the NCSP. It is important to acknowledge that these recommendations may differ to the final NCSP recommendations and time frames on the basis of this and other information yet to be determined.

Patients with hrHPV other and low-grade cytology are referred to colposcopy in this study because the burden of disease in this group is not documented in NZ. Within this study we are unable to follow up this group via repeated testing, in addition patients over 30 with low grade cytology and hrHPV are currently referred to colposcopy and laboratories are obliged to put this advice on their cytology reports. It is anticipated in the new program that these patients will undergo repeat testing at 12 and 24 months as per the Australian program.

Risk of CIN2+ can be stratified as below:

Low risk

- Other HPV positive, cytology normal or unknown

Intermediate risk

- HPV 16/18 positive with normal cytology
- Other HPV with ASCUS/low grade cytology (the risk for this group in NZ is unknown and may be low)

High risk

- HPV 16/18 positive with ASCUS/low grade/high-grade/AGC cytology
- Other HPV with high-grade/AGC cytology

Patients stratified as low risk will be recommended to have a repeat screen in 12 months.

Patients with intermediate risk will be referred to colposcopy as a semi urgent referral (for the purpose of the study we request these patients are seen within 3 months).

Patients with HPV 16/18 who do not undergo cytology may be referred as high risk because their risk is undetermined and may be high risk.

Patients with high risk of CIN2+ are referred for colposcopy (20 working days).

Patients with suspected cancer will be seen within 10 working days and treated accordingly as per regional practice.

Clinical override will upgrade the urgency of referral including patients with an abnormal appearing cervix, symptoms, are under-screened or who have perceived barriers will be referred to colposcopy urgently at the discretion of the cervical screener.

Colposcopy and pathology records will be sourced via the provider (with permission of the patient).

Patients with positive hrHPV may be referred to colposcopy in the absence of cytology triage as follows: Pacific and Māori patients, under-screened patients, and patients with HPV16/18.

As identified by the Māori Steering Committee, cervical cytology testing is a probable barrier for Māori patients (https://www.heiahurumowai.org.nz/_files/ugd/b7edfc_621f3417d3b84349be2ed6372d479d30.pdf). It is particularly important to fully discuss the indications for cervical cytology with patients and to explain that they are able to opt for direct referral to colposcopy without cytology screening, if they would prefer it.

Previous cervical abnormality may also be an indication for referral in the presence of an abnormal hrHPV test.

Colposcopy

Colposcopy will be performed as per standard practice guidelines. Patients who have had no cytology in the last 3 months or normal cytology should have a cytology performed. If feasible at least 1 biopsy should be taken of any visible lesion or the cervical transformation zone. Treatment protocols will adhere to NCSP guidelines. Relevant colposcopy and treatment data will be retrieved to be included in the study dataset.

Patients who do not attend for recommended cytology or colposcopy

The management of these patients should be consistent with normal practice.

Non-attendance for colposcopy is associated with a risk of cancer and every effort should be made to ensure attendance. Where possible a medical practitioner should discuss this with the patient and make an individualised plan for their follow up. The NCSP will be notified.

Patients with hrHPV other following a self-test who decline cytology may be referred to colposcopy. If this is declined where possible a medical practitioner should discuss this with the patient and make an individualised plan for their follow up. The NCSP will be notified. Support to Screen services will be utilised as per normal practice.

Data management

A detailed Data Management Plan is available as a separate document.

All patient data are confidential, and for Māori patients, data are recognised as taonga.

Data from participating patients will be collected within participating practices and from the central study site on a secure web-based REDCap database stored on a secure University of Otago server.

Data sources include practice screening registry, NCSPR, consent, practice records, and laboratory results (cytology, histology, hrHPV, colposcopy records). Data will be anonymised prior to analysis.

Specimen storage /disposal

Specimen storage /disposal will be as per NCSP/ laboratory protocol (please see Tissue Management Plan for detail).

Outcome measures

HrHPV TESTING
The number (and percentage) of participants with: 1,2,3 or >3 attempts to be contacted prior to their hrHPV test.
The mean, median and range for time from the first study appointment to an hrHPV test being conducted, for each participant.
The mean, median and range for time from the first contact attempt to an hrHPV test being conducted, for each participant.
The number (and percentage) of participants who were successfully contacted to take part in the study by: - Letter - Text - Opportunistic invitation at their GP clinic - A face to face appointment with a staff member at their GP clinic - A phone call with a staff member from their GP clinic - Other form of contact.
The mean, median and range for the time from the first study appointment to an hrHPV test being conducted, for each participant.
The mean, median and range for the time from an hrHPV test being undertaken to being received by the laboratory for analysis, for each participant.
The number (and percentage) of participants that undertook a: - Vaginal test at home - Vaginal test at their GP clinic without staff assistance - Vaginal test at their GP clinic with staff assistance - Cervical test without concurrent cytology - Cervical test with concurrent cytology.
The mean, median and range of charges (NZD) for each type of hrHPV test listed under the outcome above. This will be reported by whether the tests were subsidised or not.
The mean, median and range for the time from an hrHPV test to the results report being issued.

UNSATISFACTORY hrHPV TESTS
In participants who underwent hrHPV testing and had an unsatisfactory result, the reason for that result: - Incorrect labelling - Sample unsatisfactory

- Other
In participants who underwent hrHPV testing and had an unsatisfactory result, the number (and percentage) that: - Did have a repeat hrHPV test - Did not have a repeat hrHPV test.
In participants who underwent hrHPV testing and had a repeat test, the mean, median and range for time from the first hrHPV test and the repeat hrHPV test.

hrHPV RESULTS
The number (and percentage) of participants who had the following hrHPV result: - HPV 16 - HPV 18 - Other hrHPV (listed by genotype where available) - hrHPV not detected.

CYTOLOGY
The reason cytology was performed in participants that had cytology results issued from the sample taken during a cervical hrHPV test: - Requested by GP due to previous high grade lesion (test of cure) - Requested by GP due to previous abnormal cytology - Requested by GP due to symptoms - Requested by GP for other reason - Performed by laboratory due to detection of hrHPV (not GP requested) - Performed by laboratory due to identification of need to test for cure (not GP requested), - Other reason.
The reason cytology was performed in participants that had cytology performed after an hrHPV test and before colposcopy: - Positive for hrHPV result - Other reason. Data to be presented separately for participants negative for hrHPV, participants positive for HPV16 and/or 18, and participants positive for hrHPV other than 16 or 18.
The mean, median and range for the time from an hrHPV test result report being issued and the participant being informed of the result. Data to be presented separately for participants negative for hrHPV, participants positive for HPV16 and/or 18, and participants positive for hrHPV other than 16 or 18.

The number (and percentage) of participants informed of their hrHPV result by: - Face to face appointment with a staff member at their GP clinic - Phonecall with a staff member from their GP clinic - Text - Other form of contact. Data to be presented separately for participants negative for hrHPV, participants positive for HPV16 and/or 18, and participants positive for hrHPV other than 16 or 18.
The number (and percentage) of participants with 0*, 1, 2 or 3 invitations for a cytology appointment, in participants who are recommended to have cytology. Data to be presented separately for participants negative for hrHPV, participants positive for HPV16 and/or 18, and participants positive for hrHPV other than 16 or 18.
The reason for no cytology report (prior to colposcopy) in participants positive for hrHPV and had a vaginal hrHPV test: - Cytology not considered feasible by the GP - Participant declined - Participant unable to be contacted - Other. Data to be presented separately for participants positive for HPV16 and/or 18 and participants positive for hrHPV other than 16 or 18.
In participants that had a cytology test prior to colposcopy, the mean, median and range for the time between an hrHPV test result report being issued and a cytology sample being undertaken (prior to colposcopy). Data to be presented separately for participants negative for hrHPV, participants positive for HPV16 and/or 18, and participants positive for hrHPV other than 16 or 18.
In participants that had a cytology test prior to colposcopy, the mean, median and range for the time from a cytology sample being undertaken to the results report being issued. Data to be presented separately for participants negative for hrHPV, participants positive for HPV16 and/or 18, and participants positive for hrHPV other than 16 or 18.

In participants that had a cytology test prior to colposcopy, the number (and percentage) with a result of:

- Negative for dysplasia or malignancy
- ASC-US (atypical squamous cells of undetermined significance - excluding ASC-US possible high grade)
- LSIL (low grade squamous intraepithelial lesion)
- ASC-H (atypical cells of undetermined significance, possible high grade)
- HSIL (high grade squamous intraepithelial lesion)
- Cancer (invasive squamous carcinoma of the cervix)
- Adenocarcinoma
- Cancer other
- AGC/AIS (atypical glandular cells / adenocarcinoma-in-situ)
- Unsatisfactory sample

Data to be presented separately for participants negative for hrHPV, participants positive for HPV16 and/or 18, and participants positive for hrHPV other than 16 or 18.

In participants that had a cytology test prior to colposcopy, the mean, median and range for the time from their cytology sample being undertaken to being informed of the result.

Data to be presented separately for participants negative for hrHPV, participants positive for HPV16 and/or 18, and participants positive for hrHPV other than 16 or 18.

In participants that had a cytology test prior to colposcopy, the number (and percentage) informed of their cytology results by:

- Face to face appointment with a staff member at their GP clinic
- Phone call with a staff member from their GP clinic
- Text
- Other form of contact.

Data to be presented separately for participants negative for hrHPV, participants positive for HPV16 and/or 18, and participants positive for hrHPV other than 16 or 18.

COLPOSCOPY

The mean, median and range for the time between an hrHPV test report being issued and GP referral for colposcopy.

Data to be presented separately by whether participants had a cervical or vaginal hrHPV test.

Data to also be presented separately for participants negative for hrHPV, participants positive for HPV16 and/or 18, and participants positive for hrHPV other than 16 or 18.

In participants that had a cytology test prior to their colposcopy referral, the mean, median and range for the time between the cytology result report being issued and referral for colposcopy. Data to be presented separately for participants negative for hrHPV, participants positive for HPV16 and/or 18, and participants positive for hrHPV other than 16 or 18.
The number (and percentage) of participants that had a referral for colposcopy by classification of urgency. Data to be presented separately for participants negative for hrHPV, participants positive for HPV16 and/or 18, and participants positive for hrHPV other than 16 or 18.
In participants referred for colposcopy, the number (and percentage) that received 1, 2, 3 or >3 invitations for an appointment. Data to be presented separately for participants negative for hrHPV, participants positive for HPV16 and/or 18, and participants positive for hrHPV other than 16 or 18.
In participants that had a colposcopy, the mean, median and range for time from GP referral to their colposcopy appointment. Data to be presented separately for each classification of urgency. Data to also be presented separately for participants negative for hrHPV, participants positive for HPV16 and/or 18, and participants positive for hrHPV other than 16 or 18.
In participants that had a cytology test during colposcopy, the number (and percentage) with a result of: - Negative for dysplasia or malignancy - ASC-US (atypical squamous cells of undetermined significance - excluding ASC-US possible high grade) - LSIL (low grade squamous intraepithelial lesion) - ASC-H (atypical cells of undetermined significance, possible high grade) - HSIL (high grade squamous intraepithelial lesion) - Cancer (invasive squamous carcinoma of the cervix) - Adenocarcinoma - Cancer other - AGC/AIS (atypical glandular cells / adenocarcinoma-in-situ) - Unsatisfactory sample Data to be presented separately for participants negative for hrHPV, participants positive for HPV16 and/or 18, and participants positive for hrHPV other than 16 or 18.

In participants that had colposcopy, the number (and percentage) that had a visualised result of: - Unsatisfactory, - No abnormality detected - CIN1 - CIN2 - CIN3 - Adenocarcinoma - Squamous cell carcinoma - Other Data to be presented separately for participants negative for hrHPV, participants positive for HPV16 and/or 18, and participants positive for hrHPV other than 16 or 18.
In participants that had colposcopy, the number (and percentage) that had the transformation zone visualised. Data to be presented separately for participants negative for hrHPV, participants positive for HPV16 and/or 18, and participants positive for hrHPV other than 16 or 18.
In participants that had colposcopy, the number (and percentage) that had a biopsy. Data to be presented separately for participants negative for hrHPV, participants positive for HPV16 and/or 18, and participants positive for hrHPV other than 16 or 18.
In participants that had colposcopy with a biopsy, the number (and percentage) that had a visualised result of: - Unsatisfactory - No abnormality detected - CIN1 - CIN2 - CIN3 - Adenocarcinoma - Squamous cell carcinoma - Other Data to be presented separately for participants negative for hrHPV, participants positive for HPV16 and/or 18, and participants positive for hrHPV other than 16 or 18.
In participants that had colposcopy, the number (and percentage) that had each treatment recommendation. Data to be presented separately for participants negative for hrHPV, participants positive for HPV16 and/or 18, and participants positive for hrHPV other than 16 or 18.
In participants that had colposcopy, the number (and percentage) that had each treatment. Data to be presented separately for participants negative for hrHPV, participants positive for HPV16 and/or 18, and participants positive for hrHPV other than 16 or 18.

The mean, median and range for times from colposcopy to initiation of each of the treatments in the outcome above. Data to be presented separately for participants negative for hrHPV, participants positive for HPV16 and/or 18, and participants positive for hrHPV other than 16 or 18.
Incidence of CIN2+ in participants by cytology result. Data to be presented separately for participants negative for hrHPV, participants positive for HPV16 and/or 18, and participants positive for hrHPV other than 16 or 18.

OTHER
Where numbers permit, all outcomes will be presented by: - Screening history (previously undergone cervical treatment/had an abnormal cervical screen, or not) - Age band (<25, 25-34 years, 35 to 54 years, 55-69, >69 years), self-reported ethnicity (NZ European/other, Māori, Pacific Island or Asian) - Socioeconomic deprivation index (Quintiles 1 through to 5) - Region (Christchurch, Wellington or Whanganui and surrounding areas)
Mean, median and range for the per participant cost (NZD) to the participant's GP clinic for each of the following: - hrHPV self-test at home or clinic without support - hrHPV self-test at clinic with support - hrHPV cervical test by a nurse - hrHPV cervical test by a doctor - Cytology test as part of hrHPV cervical test - Cytology test performed separately to the hrHPV test - Colposcopy referral.
The number of patients at participating clinics who are due or overdue for cervical cancer screening during the six-month screening period that did not take part in the study (deidentified data). Of these patients, the number (and percentage) that: did have cervical cytology during the screening period and did not have cervical cytology during the screening period.

Statistical Considerations

The Ministry of Health reported NZ average is one full-time equivalent general practitioner (GP) per 1,650 patients and the average practice size is 3 full-time equivalent GPs. Thus, the average GP practice has 4950 patients on their books. Approximately, 32% of the NZ total population is female and between 25 and 65 years old.[11] Adding patients between 65 and 69 years and excluding patients who have had a hysterectomy, the average GP practice will have approximately 1600 patients who are eligible for 3-yearly cervical screening and thus, approximately 533 patients due for screening in any one year, and 266 patients due for screening per practice over the 6 month recruitment period. Assuming, 25% of patients do not wish to participate in the study, it would be possible to recruit 200

patients per practice over 6 months. We aim to include 15 general practices as recruitment sites. Thus, that would allow us to recruit 3000 patients over 6 months.

The acceptability and uptake of self-testing varies markedly in different studies depending on country, method of invitation, and demographics of the patients involved.[8,12] Irrespective, the majority of hrHPV self-sample studies and surveys involve un- or under-screened patients,[8, 12-14] and the uptake in patients who usually participate in screening may differ. However, based on these previous studies, we estimate that 60-70% of patients may opt for self-sampling, thus we estimate that we will recruit 1800-2100 patients to the hrHPV self-sampling group and 900-1200 patients to the clinician-taken hrHPV test group. Based on previous studies,[4] we estimate that 12% of hrHPV self-sampled tests will be hrHPV positive and an estimated 216-252 patients will need to return to their GP practice so that a follow-up cervical cytology sample can be taken. As this is a key safety concern, the number of patients in the hrHPV self-sample group who do not return for a clinician-taken cervical cytology sample within 3 months following a hrHPV positive result will be assessed. With a sample size of 216, there is 95% power to observe a failure to return rate of 2% or more.

In order to align with current NCSP practices, in terms of database requirements and automatic recall procedures, all patients in the clinician-taken sample group will have a cytology assessment of the sample they have already given, thus, do not need to return for a follow up cervical screen. The two groups, therefore, cannot be directly compared in terms of failure to return for follow up. In addition, as the clinician-taken and self-sample groups are self-selected they will be different and, hence, outcomes from the two groups will be recorded but cannot be directly compared.

Due to the relatively small size of this study and the unlikely outcome of a high-grade cervical abnormality, outcomes related to colposcopy referral will lack the power for stratification. However, the choice of screening method may usefully be able to be stratified.

Transfer of data and patient care to the NCSP.

The NCSPR will be informed of all patients participating in the study.

As the NCSPR is not currently able to manage the results of hrHPV screening this information will be overseen by the study team. The study team will act in place of the NCSPR to provide reminders to the practices when patients are overdue further investigations or repeat testing and to ensure management recommendations are correct. Following colposcopy or on completion of the study when the NCSPR is able to manage these patients' information they will be referred back to the NCSPR

Results of all cytology tests and hrHPV tests and colposcopy records will automatically be referred to the NCSPR. The study team will follow all patients to the end of the study to ensure patients who require colposcopy have been seen.

At completion of the study enrolled patients will fall under the following categories.

- Normal screen, next routine screen to be performed at the normal screening interval (5 years)
- Normal screen but because of previous abnormality follow up recommended in 12 months
- Abnormal screen referred to colposcopy attended follow up dictated by colposcopist and referred back to NCSP

- Abnormal screen colposcopy recommended lost to follow up/colposcopy declined
- Abnormal screen follow-up cytology advised but declined/lost to follow up
- Abnormal screen cytology performed follow up in 12 months recommended

This information will be shared with the NCSP (as far as possible in a manner that is suitable to the NCSP) and patients will be discharged to GP practice and NCSP

Participants who withdraw consent for the study, who transfer their care to a non-participating practice or who are lost to follow up will be regarded as off study. Every reasonable effort will be made to ensure they are aware of their test result and the subsequent recommendation, and that this information is shared with the appropriate health professionals that are involved. The NCSPR will also be informed.

Financial considerations

The NCSP has indicated it will provide the following support:

- Funded colposcopy in public hospital as per agreed referral criteria
- The laboratory cost of cytology tests
- The financial support of the study grant
- Funding to support screening activities within usual PHO funding

The cost to practices not covered by the study grant will therefore be met by the patient. However, it is unethical for a patient to be charged more for a study cervical screening procedure than for a current NZ standard of care cervical cytology.

The study payment to GP clinics is to cover the time and resources required to provide study information for full informed consent, this cost must not be passed on to patients. The payment also covers the time required for clinic staff to provide data for the University of Otago Redcap database (clinics in the Wellington and Canterbury regions only; in Whanganui this will be conducted by the PHO (Whanganui Regional Health Network) on their behalf).

As the costs of administration and post is covered by the grant, we anticipate that participants taking the self-test at home would only involve the cost of the initial study visit, and would include education on how to undertake an hrHPV self-test.

We anticipate that participants having an hrHPV self-test in the clinic with the support of a nurse may have a facility charge similar to the cost of a nurse visit.

Participants requesting a clinician-taken cervical hrHPV test will have a charge identical for a current NZ standard of care cervical cytology.

Participants who have a positive cytology test following a positive hrHPV screen should not have a total cost greater than for a current NZ standard of care cervical cytology. This cost should be subsidised from elsewhere (other screening activities or screening support funds).

Participants who would normally be eligible for a free cervical cytology screen in that practice should be offered a free hrHPV screen (and, if required, cervical cytology).

Ethical Considerations

As this is a pilot study all participants need to provide informed consent.

The process of Informed Consent should not be a barrier to patients getting screened and therefore should be as simple as possible.

Access to the study must be equitable and appropriate support provided to patients to enable this.

The cost of screening to participants in the study should not exceed the cost for a current NZ standard of care cervical cytology.

Patient safety is paramount and quality assurance is required to optimise this.

All patient information is confidential and must be treated as taonga - see Data Management Plan.

If centrally-coordinated recall is utilised a satisfactory process is required to ensure that patient confidentiality is preserved.

As this is a validated test the study will be covered by ACC legislation.

Conduct of the study may increase demand to colposcopy. The cost of colposcopy will be met by the NCSP and as practices will not be limited to one DHB the impact on any one service should be minimal.

Patients who are hrHPV positive should not be denied colposcopy if they have a significant risk of a high-grade abnormality and there are barriers to having a cytology test. As this is a pilot study, patients with indications for colposcopy referral under current guidelines should be offered colposcopy.

Quality assurance

See Appendix 2 for the quality assurance plan.

All site investigators will compete Good Clinical Practice training. Formal training is to be completed by the lead investigator at each site, who is responsible for training other staff.

Aspects of quality assurance include monitoring of:

Adverse events

Proportion of eligible patients contacted

Equity/ cultural safety

Patient satisfaction

Satisfactory sample rate

Laboratory process will be assured by the laboratory as part of normal process

Communication of results to patients

Accessment of patients to cervical cytology and colposcopy

Audit of data entry

Site visits will occur on commencement and during the study at intervals to be determined

Communications strategy

Principal relationships

Participants and potential participants

NSU

Māori and Pacific patients

Participating PHO and practices

DHBs affected

Laboratory services

RNZCGP

RACP

RANZCOG

Patient and Women's advocacy groups

The medical community

The general population

Plan to identify contacts for above groups and best method of communication

Pre study: communication, consultation and communication with above groups

During study: monthly update newsletter

Post study: dissemination of results and recommendations

Impact of Covid 19

The disruptions associated with the Covid 19 pandemic have had a marked impact on the functioning of many systems including the NZ health service. This has introduced new barriers to screening and screening rates have been impacted. Where barriers exist, the tendency is for inequities of access to be amplified.

Face to face health visits have been intermittently affected and the strain on primary health services has been an addition to an already strained heath sector. These impacts have been varied over time and region and there is likely to be more disruption to come. Self-testing offers opportunities for contactless screening which is a potential advantage in the current circumstances. This contactless approach is a far cry from the face to face hands on supportive approach that has previously been utilised. These changes will result in changes to the patient experience which may impact on engagement with screening.

Historical comparisons within the practice and within the screening program therefore while important will be of limited value. The outcomes therefore must be taken at face value informing us of the impact of this method of screening in these populations at this current time. The results may be utilised to give some indication of which groups did not engage with screening or follow up investigations and the proportion of patients who will be referred to colposcopy in the first screening round. This will therefore guide us to where further resources are required to support the new program.

Limitations of this pilot

There are dangers that this implementation will perpetuate the weaknesses of the current program. Patients who are not registered with a GP or who are not domiciled near the practice they are registered with will be disadvantaged with this system. In addition, patients who experience barriers to screening and colposcopy are likely to do so. Screening support services must be engaged to determine strategies to reduce inequity. Costs to the patient are a limitation in present program.

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Appendix 1 *Data Management Plan (see separate document)*

Appendix 2 Safety and quality assurance plan

Introduction

This study is performed to determine the impact of implementation of hrHPV testing into the NCSP. The aim of screening is to prevent cervical cancer by the identification and treatment of the precursors to cervical cancer. While the NCSP has been a highly successful public heath intervention, screening has its limitations and for individual screening failure can occur, this may be due to the inherent weaknesses of the test, diagnostic and treatment pathways, or failure of the process to be carried out correctly. It is well documented that the major cause of screening failure is non-engagement with the screening program, however, failure of the screening test to detect an abnormality and failure of the diagnostic and treatment pathway are also associated with a significant number of cancer occurrences. In addition, there are a number of service delivery interactions that may significantly affect the quality of a patient's experience which may in turn have an impact on future participation. It is well documented that the impact of these failures is inequitable.

The introduction of hrHPV testing will be associated with an increased sensitivity of the screening test and offers greater accessibility of the test and hence will improve the safety of the program. However, the change in procedures may increase, at least temporarily, the possibility of procedural or administrative errors. It is therefore important to monitor patient safety aspects of this study. This will be done by reporting adverse events, site visits, and auditing of data against source documents.

Identified risks

Major risks

Failure to detect significant abnormality (false negative test)

Patient given wrong result

Patient given inappropriate advice

Patient not informed regarding a positive result

Colposcopy for high grade cytology or HPV 16/18 not attended within 3 months

Inequity associated with participation

Other risks

Eligible patients not invited

Minimum invitation requirements not met

Patient positive for other hrHPV (i.e., non-HPV16/18) does not attend for cytology

Patient with other hrHPV (i.e., non-HPV16/18) does not attend for colposcopy

Serious adverse event reporting

Serious adverse events will be reported to the study management team by filling out a Serious Adverse Event (SAE) report form and emailed within 7 days of the GP practice becoming aware of the event.

Serious Adverse Events include:

- Interval diagnosis of invasive cancer, CIN3, or AIS following a negative hrHPV test
- A screened person being given the wrong result
- A screened person being given the wrong advice following their screen (e.g., not referred to colposcopy or cytology when they should have been)
- A screened person not receiving the result of a positive test

Serious adverse events will be investigated as soon as possible by the study team and the relevant service provider to ensure similar errors do not occur and that there is no systemic case for this error.

The service provider will be responsible for the discussion of this adverse event with the person affected and their whanau and informing other agencies if appropriate. The study team will be responsible for informing the NCSP.

The following other adverse events will also be reported at completion of the study

- A person referred to colposcopy who does not attend within 3 months
- A person with other hrHPV who is recommended to have cervical cytology but who does not attend within 3 months

Site visits

Site visits will be performed either face to face or virtually by at least 1 member of the study management team, prior to commencing invitation to the study and within 3 months of commencing the study. Additional visits will be organised on request of the participating practice or if issues are perceived by the study management team.

The first visit is to ensure mechanisms of enrolment data management and clinical management of patients is understood by all members of the team. In addition, to ensure that systems are appropriate.

The second visit is to understand any issues of concern being encountered by the practice and to ensure ongoing participation of the practice team with screening and study protocols.

Further site visits may occur as required if areas of concern have been identified.

Audit

Prospectively-collected data will be collected in electronic case report forms (e-CRF) within 4 weeks of the event. 10% of data will be audited against source documents. If more than 10% of data is missing or incorrect, further in-depth audit will be undertaken.

Quality assurance

As the NCSPR is not currently able to manage the results of hrHPV screening this information will be overseen by the study team. The study team will act in place of the NCSPR to provide reminders to the practices when patients are overdue further investigations or repeat testing and to ensure management recommendations are correct. Following colposcopy or on completion of the study when the NCSPR is able to manage these patients information they will be referred back to the NCSPR.

To ensure the clinical safety of participants. The redcap database will generate reminders to the general practice and to the study management team to ensure that critical parts of the patient care episode are completed. For example, informing patients of results, having a cervical cytology test and attending colposcopy within pre-determined time frames. while the general practice team will hold clinical responsibility for these actions the study management team will act as a safety net and prompt the clinicians involved. Thus, the database and the study management team are offering a greater degree of safety than the NCR, which at this point is unable to process hrHPV screening tests.

In addition, for all patients with an abnormal hrHPV test the recommendation recorded on the database will be cross checked against their result and cervical screening history to ensure this is consistent with guideline. Where this is not correct the inconsistency will be investigated by the study team and the provider.

Appendix 3 Risk assessment by hrHPV and Cytology result

The risk of CIN2 + by hrHPV and cytology.[15, 16]

History	Current HPV result	Current cytology result	*n*	%	CIN 3+ cases	CIN 3+ immediate risk, %	CIN 3+ 5-year risk, %	Recommended Management	Recommendation confidence score, %
Unknown	HPV-negative	NILM	1,388,153	90	1,246	0.00	**0.12**	5-y follow-up	100
Unknown	HPV-negative	ASC-US	25,331	1.6	83	0.04	**0.40**	3-y follow-up	100
Unknown	HPV-negative	LSIL	3,300	0.21	47	1.1	**2.0**	1-y follow-up	100
Unknown	HPV-negative	ASC-H	791	0.05	26	3.4	3.8	Colposcopy[a]	Special situation
Unknown	HPV-negative	AGC	2,275	0.15	27	1.1	1.5	Colposcopy[a]	Special situation
Unknown	HPV-negative	HSIL+	183	0.01	43	**25**	27	Colposcopy/treatment	53
Unknown	HPV-negative	ALL[b]	1,420,033	92	1,472	0.01	**0.14**	5-y follow-up	95
Unknown	HPV-positive	NILM	63,541	4.1	1,798	**2.1**	**4.8**	1-y follow-up	100
Unknown	HPV-positive	ASC-US	30,506	2.0	1,378	**4.4**	7.3	Colposcopy	100
Unknown	HPV-positive	LSIL	23,659	1.5	1,008	**4.3**	6.9	Colposcopy	96
Unknown	HPV-positive	ASC-H	3,766	0.24	863	**26**	33	Colposcopy/treatment	82
Unknown	HPV-positive	AGC	977	0.06	254	26	35	Colposcopy/treatment[a]	80
Unknown	HPV-positive	HSIL+	3,980	0.26	1,700	**49**	53	Colposcopy/treatment	100
Unknown	HPV-positive	ALL[b]	126,429	8	7,001				
		Total[c]	1,546,462	100	8,473				

		CIN3+			CIN 2+		
	Total	*N* (cases)	Risk	95%CI	*N* (cases)	Risk	95%CI
All HPV positive[a]							
ASC-US	717	154	21.5	18.7 24.7	223	31.1	27.9 34.6
LSIL	333	99	29.7	25.2 35.0	146	43.8	38.7 49.4
High-grade[b]	554	359	64.8	60.9 68.8	397	71.7	67.9 75.4
≥ASC-US	1604	612	38.2	35.8 40.6	766	47.8	45.3 50.2
HPV16							
ASC-US	132	51	38.6	30.9 47.5	63	47.7	39.6 56.6
LSIL	79	37	46.8	36.6 58.4	49	62.0	51.5 72.6
High-grade	189	143	75.7	69.4 81.5	153	81.0	75.1 86.2
≥ASC-US	400	231	57.8	53.0 62.6	265	66.3	61.6 70.9
HPV18							
ASC-US	53	11	20.8	12.1 34.3	18	34.0	22.9 48.4
LSIL	22	6	27.3	13.3 50.9	11	50.0	31.6 71.8
High-grade	52	34	65.4	52.6 77.9	38	73.1	60.7 84.2
≥ASC-US	127	51	40.2	32.3 49.2	67	52.8	44.4 61.6
Other high-risk HPV[c]							
ASC-US	498	90	18.1	15.0 21.7	138	27.7	24.0 31.9
LSIL	225	55	24.4	19.4 30.6	84	37.3	31.4 44.0
High-grade	294	174	59.2	53.6 64.8	198	67.4	62.0 72.6

		CIN3+			CIN2+		
	Total	*N* (cases)	Risk	95%CI	*N* (cases)	Risk	95%CI
Baseline HPV Result							
HPV-positive[a]	1278	102	8.0	6.6 9.6	154	12.1	10.4 14.0
HPV16	201	40	19.9	15.0 26.1	49	24.4	19.0 30.9
HPV18	74	8	10.8	5.6 20.5	12	16.2	9.6 26.8
Other high-risk HPV[b]	981	54	5.5	4.2 7.1	92	9.4	7.7 11.4

Without triage			
HPV negative	cytology unknown	risk of CIN3	0.01%
HPV positive	cytology unknown	risk of CIN3	6%
With triage			
HPV 16	normal cytology	risk of CIN2+	24%
HPV 16	ASCUS	risk CIN2+	47%
HPV 16	HSIL	risk CIN2+	81%
HPV other	normal cytology	CIN2+	9.4%
HPV other	ASCUS /LSIL	CIN2+	28%/37%
HPV other	HSIL	CIN2	67%

Data is limited from New Zealand. Rates vary from different populations and age groups and studies and rates of CIN3 are lower. However, patterns remain constant across studies. CIN3 has a greater risk of progression to cancer and a lower rate of spontaneous regression.

While to some extent it can be argued that all patients who are hrHPV positive should undergo colposcopy, these resources in NZ are limited and cytology triage is appropriate to limit the number of referrals and urgency. Low risk patients can safely be monitored with repeat tests and intermediate risk patients may be safely managed with non-urgent colposcopy. Australian data suggests that patients with other hr HPV and low-grade cytology have a low risk of CIN2+ (similar to the risk for patients with normal cytology). As a result, Australian guidelines recommend follow up hrHPV tests for 2 years prior to referral to colposcopy. As this is inconsistent with data from NZ and Europe and we have no data on completion of follow up, we aim to document the proportion of patients with CIN2+ in this group following referral to colposcopy.

HPV screening data is limited in NZ and this pilot study aims to acquire data on real world hrHPV screening in New Zealand and the utility of cytology triage in a program utilising self-testing. As such, we propose that all hrHPV positive patients are recommended to undergo cytology triage. However, it is acknowledged that for some patients this will represent a barrier and therefore in some circumstances it may be appropriate to refer to colposcopy without a cytology triage. These circumstances may include unscreened patients, patients unable or unwilling to undergo speculum examination, and populations at increased risk. If referral without cytology triage occurs, triage will take place on the basis of the hrHPV result and circumstances will be documented.

Appendix 4 The impact of hrHPV screening pilot on colposcopy services

Currently, NCSP data suggests approximately 1.5% of cervical cytology reports are high-grade (HSIL, ASCH, or AIS) while 5.5% of reports are low-grade (ASCUS {2%] or LSIL {3.5%]).

Patients with a high-grade cervical cytology are referred to colposcopy urgently (20 working days). Patients with a low-grade cervical cytology require a repeat cervical cytology or an hrHPV test prior to referral and are referred as semi-urgent to be seen within 26 weeks.

HPV tests are currently not recommended for patients under 30 years but are currently performed for over 90% of screened patients over 30 years with low grade cytology. On average, 61% of patients with LSIL cytology are hrHPV positive as are 23% of patients with ASCUS cytology.

According to the most recent NSCP report there are around 1600 referrals to colposcopy for high-grade abnormalities and 3200 referrals for low-grade abnormalities each year. Based on these figures, we estimate that approximately 1.5% of patients undergoing cytology are currently referred to colposcopy urgently and 3% are referred semi urgently. Thus, for 1000 patients screened with cytology, approximately 15 patients would be referred urgently and 30 patients referred semi-urgently.

Based on overseas studies, for primary hrHPV screening, we expect a hrHPV positivity rate of approximately 7% but this could vary from 5-10%. hrHPV positive samples will be divided into those that are positive for HPV 16 or 18 positive and those that are positive for other khrHPV genotypes. We have poor data on the proportions of these in the screening population in NZ, however, real-world data from Norway indicates we may expect about 25% of positives to be HPV 16 or 18.

Based on the Norwegian data, we can estimate that approximately 30% of patients with HPV 16 or 18 positive samples will have normal cervical cytology. For patients with other hrHPV positive samples, an estimated 45% will have a normal cervical cytology and 35% will have a low-grade cervical cytology.

Thus, if all patients with (a) HPV 16/18 positive samples and (b) with other hrHPV positive samples and high-grade cytology are referred urgently we might expect 26 per 1000 patients screened to be referred urgently (18 patients with HPV 16/18 and 8 with other hrHPV). In addition, if all patients with other hrHPV and low-grade cytology are referred semi-urgently to colposcopy, this would be an additional approximately 18 per 1000 patients screened.

The total number of patients referred in this instance will be similar whether based on hrHPV primary screening (44) or on cervical cytology primary screening.(45) However, the number of patients referred urgently would increase from 15 to 26 per 1000 patients screened. If patients with hrHPV 16/18 and normal cytology are referred semi-urgently this may reduce the number referred urgently to 21 per 1000 patients screened.

Therefore, within the context of this pilot study there we expect no appreciable increase in the number of colposcopy referrals in the first round of screening, however it may lead to a higher number of urgent referrals. In each service this is likely to number in the region of 11 patients over 6 months and as such is unlikely to have a significant impact on service provision.

Clearly these numbers are purely estimates, as we have little data from NZ with regard to hrHPV incidence by type. One of the principle aims of this study is to identify, for NZ patients, the relative proportions of hrHPV type and cytology results in order that estimates of colposcopy workloads can be made.

For the national roll out of primary hrHPV screening, the implication of these numbers are more significant. If patients with other hrHPV and low-grade cytology are not referred for colposcopy this will significantly reduce demand for non-urgent colposcopy but not alleviate the demand for urgent colposcopy. An additional cumulative colposcopy load will be created from patients who have persistent hrHPV infection with or without abnormal cytology therefore follow up protocols of this category of require careful monitoring.

Colposcopy management is to a large extent unaltered by hrHPV screening however some patients will present to colposcopy without cytology to guide the colposcopist and the risk of CIN2 or worse will vary by hrHPV type and cytology. Draft guidelines regarding management and follow up of patients referred to colposcopy have been written by the NCSP and will be available to treating colposcopists. In essence as per standard practice patients over 25 with a histologically confirmed high grade will be recommended to undergo treatment. Patients with low grade or normal cytology and no colposcopic evidence or histology of a high-grade abnormality will undergo a repeat hrHPV test (+/- cytology in 12 months). Patients with high grade cytology but no colposcopic evidence of a high-grade abnormality can be reviewed at an MDM if high grade cytology is confirmed treatment is recommended (particularly if type 3 TZ) or alternatively the patient should undergo repeat colposcopy cytology and hrHPV test in 6 months. These recommendations represent little material change from current management.

Appendix 5 Substudies

Study 1

To undertake a structured feedback process with participating GP practices to determine information relevant to the implementation of hrHPV screening.

To describe perceived and experienced primary care related barriers to the implementation of hrHPV screening incorporating self-testing.

Study 2

To undertake a structured feedback process for a proportion of participants undertaking hrHPV screening.

To describe aspects of the patient reported experience of hrHPV screening, particularly participants undergoing vaginal self-test who have a positive test.

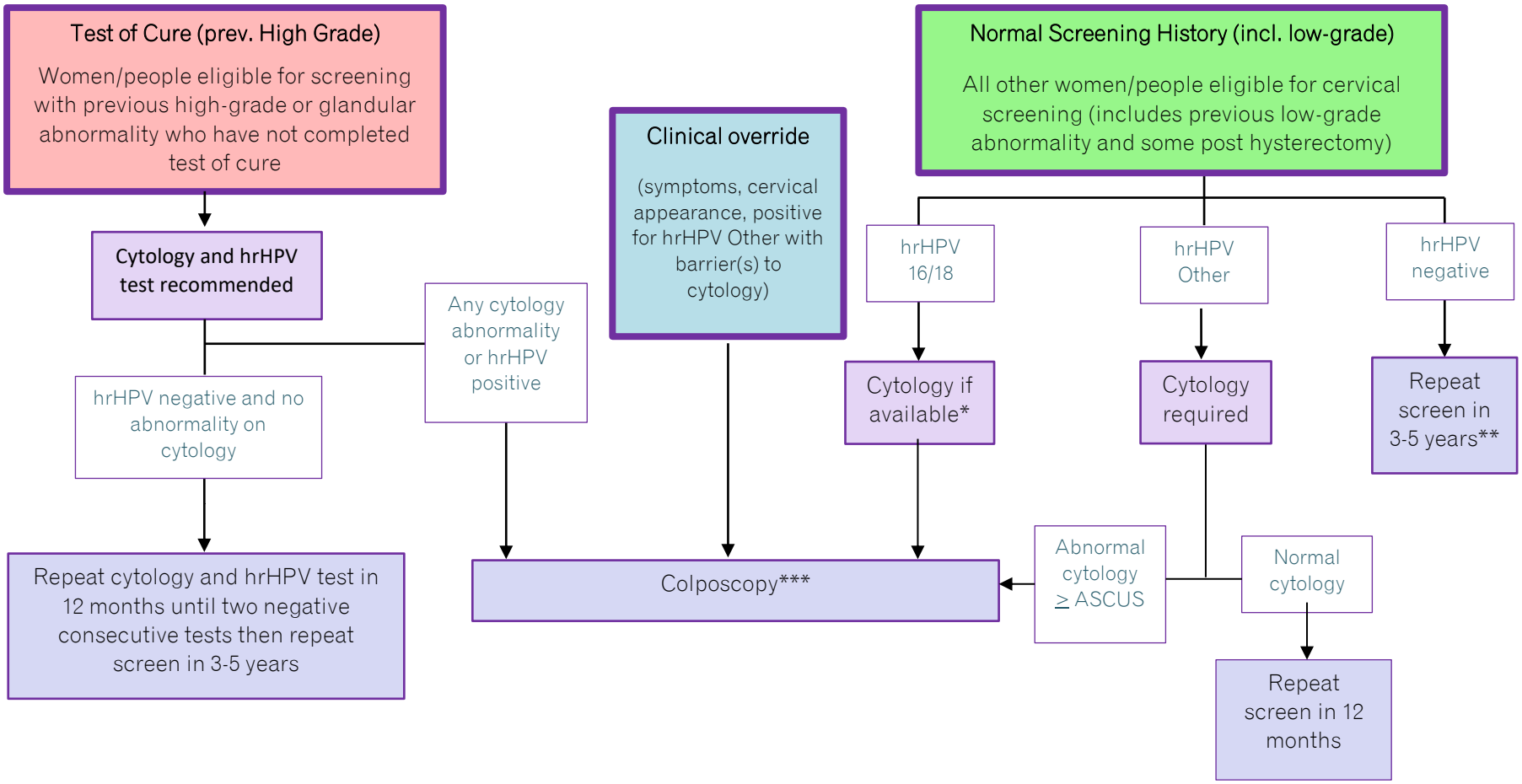
Study 3

Assessment of the educational needs and perceived barriers to hrHPV screening among Primary care practitioners undertaking this pilot study.

In addition to collaborative discussion with primary care practices prior to the commencement of related educational activities all health practitioners who will be undertaking screening activities in the practice will be asked to complete a questionnaire that will help inform this process.

By performing a web-based questionnaire prior to commencing education and recruitment for the study.

Appendix 6 Flowchart for management of hrHPV results either clinician taken or vaginal self-test



*Note if a vaginal self-test is taken and the result is positive a cervical cytology specimen is indicated to stratify risk, however in some circumstances it will not change so is

not required. (i.e. HPV16/18 positive) If a cervical test has been taken this will be performed on the same specimen by the laboratory. It is advised that this test is performed within 2 weeks.

**With the new five yearly screening interval, those coming in for their next screening test (after previous cytology screening) any time in the last five years before age 69, i.e. 65 – 69 years of age (inclusive), can exit the programme if their hrHPV test result is negative. This includes those with normal screening histories, with no screening history and those with previous abnormalities who have already been returned to regular interval (three yearly) screening. Exceptions are:

1. Participants who are still in active surveillance following previous abnormalities need to complete their follow-up. So if a test of cure is indicated and hasn't been successfully completed then they need a test of cure – one negative HPV test is not sufficient in this circumstance.

2. Immune deficient participants with a negative hrHPV test need to return in three years for a repeat hrHPV screen, if this falls before 69 years of age

3. Women who have had a recent hysterectomy will need a test of cure if there is high-grade histology in the hysterectomy specimen, which may or may not have been preceded by high-grade cytology.

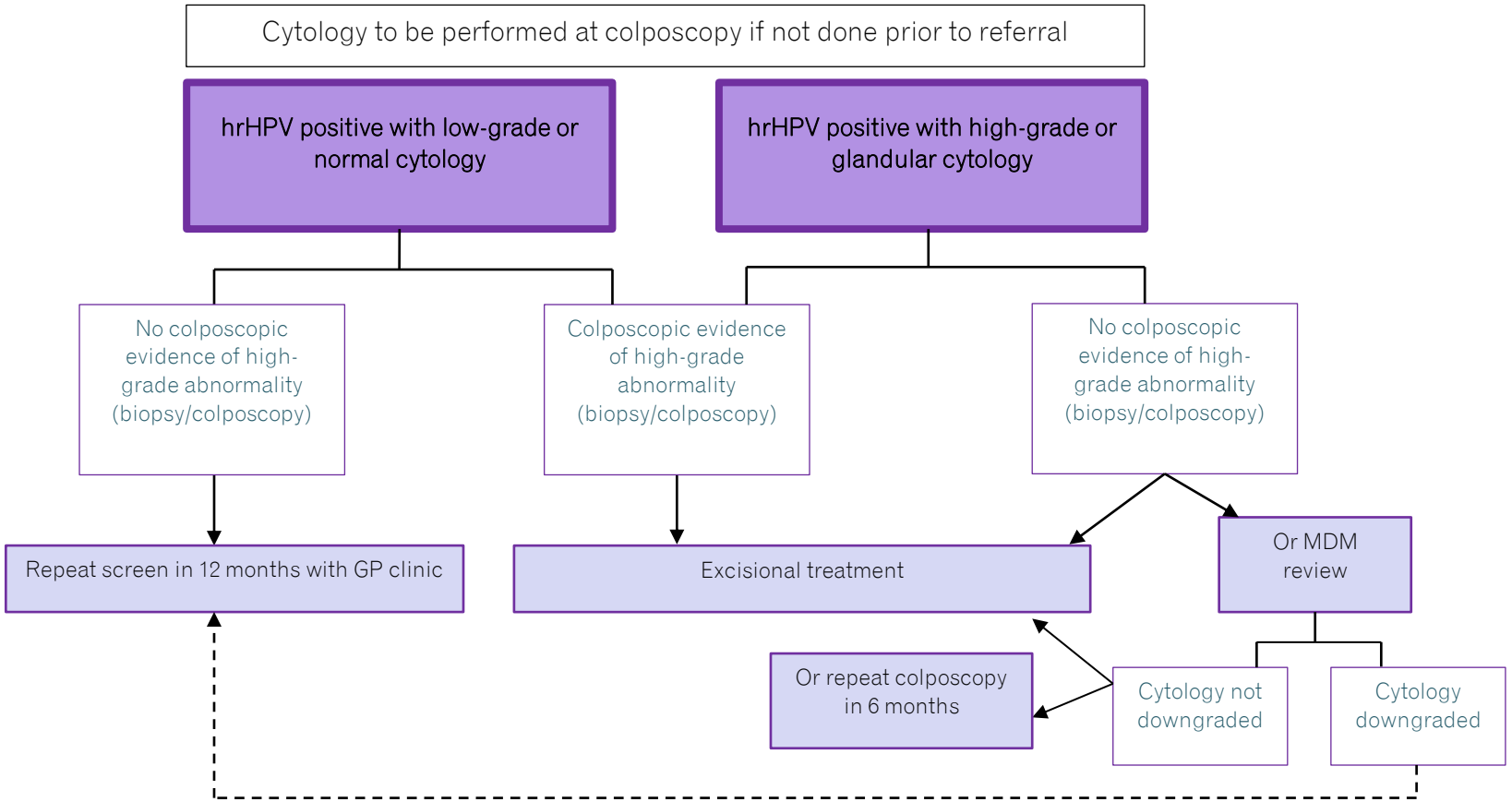
Those who would normally exit the NCSP under the current NCSP exit requirements i.e. have had two normal screening cytology samples between ages 62 and 69 years of age, can exit at 69 years of age without HPV testing (providing not immune deficient or requiring further follow-up because of abnormal results).

***Urgency of referrals to Colposcopy are as follows;

- **Very Urgent** – Suspicion of Malignancy (10 working days)
- **Urgent** – High-grade cytology and/or HPV 16 or 18 positive (20 working days)
- **Semi-Urgent** – other high-risk HPV and low-grade/ASCUS cytology (3 months)
- Colposcopy can be referred as a clinical override e.g. hrHPV other and patient declining cytology triage.

ASCUS: Atypical Squamous Cells of Undetermined Significance hrHPV: high risk human papillomavirus NCSP: National Cervical Screening Programme

Appendix 7 Flowchart recommendations for colposcopy management



hrHPV: high risk human papillomavirus MDM: Multidisciplinary Meeting