Study protocol for an intervention study investigating the impact of HPV-based cervical screening in New Zealand

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Contents

Abbreviations

AGC: Atypical glandular cells

AIS: Adenocarcinoma-in-situ

ASC-H: Atypical cells of undetermined significance, possible high-grade

ASC-US: Atypical squamous cells of undetermined significance

CI: Confidence interval

HPV: High-risk human papillomavirus

HSIL: High-grade squamous intraepithelial lesion

LBC: Liquid based cytology

LSIL: Low-grade squamous intraepithelial lesion

NCSP: National Cervical Screening Programme

PHO: Primary Health Organisation

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Trial registration and status

The study was prospectively registered on ANZCTR (ACTRN12622000699763) on 16/05/2022. The Universal Trial Number is U1111-1276-2570.

Recruitment for the study started on 19/8/22. At the time of writing, (January 2024) recruitment has been completed. Data analysis is in progress.

Overview

Background

In 2023, the primary cervical screening test in New Zealand changed from cervical cytology to high-risk human papillomavirus (HPV) testing. The purpose of this study is to evaluate the process involved in implementing primary HPV-based cervical cancer screening in primary care, including the option of self-testing. This will generate practical and clinically relevant information for the introduction of primary HPV testing.

Methods

This intervention study offered people the opportunity to undergo HPV testing instead of standard cervical cytology for cervical cancer screening. Over a six-month recruitment period, people who are due or overdue for cervical screening were invited to participate. The study was conducted at general practices in New Zealand. Participants were offered the choice of a vaginal HPV self-test or a clinician-taken cervical HPV test. Data collected included the type of HPV screening test selected, the results of the HPV test, whether a referral was made for cytology and/or colposcopy, whether a cytology and/or colposcopy appointment was attended, and how long it took to complete the screening pathway.

Discussion

This study is designed to provide an evidence-base on which practical recommendations can be developed to guide the introduction of primary HPV testing for cervical screening in New Zealand.

Background

The New Zealand National Cervical Screening Program (NCSP) has successfully reduced incidence of and mortality from cervical cancer.[1] However, cervical cancer incidence has changed little in the last 20 years.[1] Additionally, the outcomes of screening are inequitable, with Māori and Pacific people experiencing higher cervical cancer incidence and mortality.[1] Up until recently, the primary screening test for cervical cancer in New Zealand was cervical cytology. However, in 2023, the NCSP introduced high risk human papillomavirus (HPV) testing as the primary screen, with HPV type and cervical cytology used to triage people to further investigation or repeat screening.

Compared with cervical cytology, HPV testing results in earlier detection of precancerous abnormalities and greater protection against cervical cancer.[2, 3] The HPV test has the option of being performed as a self-test, using a swab to take a sample from the vagina. Alternatively, it can be performed as a clinician-taken test from the cervix, using a cervical sampler and a liquid-based cytology (LBC) medium.

There is evidence that vaginal HPV self-tests are more acceptable to people than cervical cytology or a clinician-taken HPV test.[4-8] HPV self-testing has been demonstrated to improve screening acceptability and uptake in Māori and Pacific people who are overdue for screening.[4-8] As a result, self-testing has the potential to improve cervical screening coverage and to improve health equity.[9]

It is expected that the introduction of HPV screening in New Zealand will increase screening uptake, identify more people with cervical abnormalities, and reduce disparities in cervical cancer incidence and mortality. This study will evaluate the process involved in implementing primary HPV-based cervical cancer screening in primary care.

Methods

Aim

The aim of this study is to evaluate the process involved in implementing primary HPV-based cervical cancer screening in primary care.

Trial design

This single-arm intervention study offers people the opportunity to undergo HPV testing instead of standard cervical cytology. An overview of study procedures in outlined in Figure 1. Study objectives and outcomes are outlined in Figure 2.

STUDY PERIOD	TIME	ACTION			
		Enrol	HPV test	Follow up	Data collected
Enrolment					
Eligibility screen	0	X			X
Informed consent	0	X			
Demographics, screening history & symptom check	0	X			X
Intervention					
Participant selects one of the following HPV tests: - vaginal self-test at home or other location - vaginal self-test at clinic - clinician taken cervical sample#	^		X		X
Follow up					
HPV test completion	^		X	X	
Participant informed of result	^			X	
Cytology and/or colposcopy for positive HPV results	^			X	
Referral back to NCSP	9 months				X

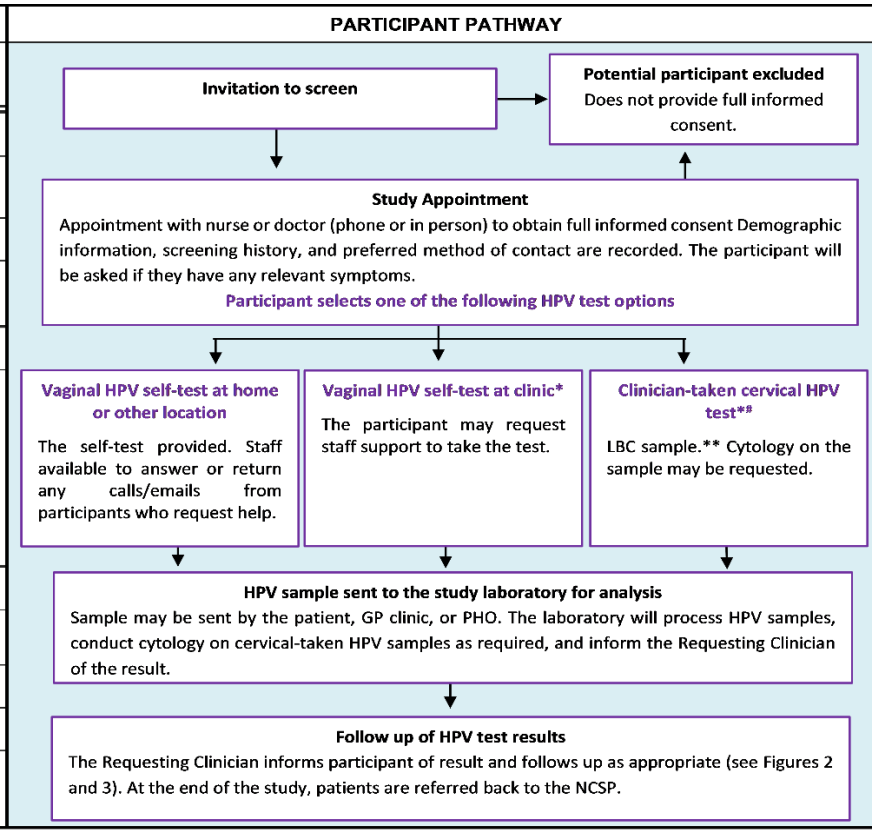

Figure 1. Study recruitment and procedures

GP: General Practitioner, HPV: High risk human papillomavirus, LBC: Liquid based cytology, NCSP: National Cervical Screening Programme, PHO: Primary Healthcare organisation.

Figure 1 details

** Conducted at the study appointment or another time.*

*** Taken under direct visualisation by an accredited cervical screener using a cervibroom™ or equivalent.*

^ Timing is dependent on when the patient and their clinician take action. See safety section regarding time limits to ensure clinical safety with appropriate times for follow up of positive HPV results. Participants will be followed up for 3 months after closure of the 6 month recruitment period.

 # In some participants a cervical sample for HPV and cytology will be clinically recommended.

Objectives	Outcome measures
To describe the impact of HPV 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** - **Screening outcomes in patients with prior abnormalities in relation to transition guideline recommendations** - **Number of colposcopy referrals, their indication, and outcomes.**	***The number (and percentage) of participants that undertook a: vaginal test at home, vaginal test at their general practice without staff assistance, vaginal test at their general practice with staff assistance, cervical test without concurrent cytology, or cervical test with concurrent cytology.#*** In participants who underwent HPV testing and had an unsatisfactory result, the number (and percentage) that: did have a repeat HPV test or did not have a repeat HPV test. The reason cytology was performed in participants that had cytology results issued from the sample taken during a cervical HPV test. See figure legend for reasons.^ The reason cytology was performed in participants that had cytology performed after an HPV test and before colposcopy: positive for HPV result or other reason.* The reason for no cytology report (prior to colposcopy) in participants positive for HPV and had a vaginal HPV test: cytology not considered feasible by the GP, participant declined, participant unable to be contacted, or other.* The number (and percentage) of participants that had a referral for colposcopy by classification of urgency.* In participants referred for colposcopy, the number (and percentage) that received 1, 2, 3 or >3 invitations for an appointment.*
To describe the impact of HPV testing (by demographics and screening history when numbers permit) in terms of time to completion of the appropriate screening pathway.	***The distribution of times between an HPV test report being issued and GP referral for colposcopy.*#*** The mean and standard deviation or median and interquartile range for time from between various steps of the cleaning pathway, including invitation to screening, the study appointment, HPV testing and receipt of results, referral to follow up, and attendance at follow up. For specific detail on each of the outcome measures, see S Table 1.
To describe the disease burden detected in the study population, in terms of: - **HPV positivity rate by HPV 16/18 or other HPV, by demographics** - **Incidence of CIN2+ in patients with HPV 16/18 by cytology result** - **Incidence of CIN2+ in patients and with other HPV with abnormal cytology.**	***The number (and percentage) of participants who had the following HVP result: HPV 16, HPV 18, other HPV (listed by genotype where available), or HPV not detected.*** In participants that had a cytology test prior to colposcopy, the number (and percentage) with each result. * See Figure legend for result options** In participants that had a cytology test during colposcopy, the number (and percentage) with each result option.* See Figure legend for result options** In participants that had colposcopy, results from the colposcopy, subsequent treatment recommendations and treatments. For further detail on each of these outcomes, see S Table 1.* Incidence of CIN2+ in participants by cytology result.*
To describe uptake of screening by mode of invitation: Centralised 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 HPV screen, and in the event of an abnormal HPV screen, to achieve cervical cytology and/or colposcopy.**	The number (and percentage) of participants with: 1,2,3 or >3 attempts to be contacted prior to their HPV test. The number (and percentage) of participants who were successfully contacted to take part in the study by: letter, text, opportunistic invitation at their general practice, a face to face appointment with a staff member at their general practice, a phone call with a staff member from their general practice, other form of contact. The mean and standard deviation of charges (NZD) for each type of HPV test listed under the outcome above. This will be reported by whether the tests were subsidised or not. The number (and percentage) of participants informed of their HPV result by:* face to face appointment with a staff member at their GP clinic, phone call with a staff member from their general practice, text, other form of contact. 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.* 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 general practice, phone call with a staff member from their general practice, text, other form of contact. The mean and standard deviation for the per participant cost (NZD) to the participant's general practice for each of the following: HPV self-test at home or clinic without support, HPV self-test at clinic with support, HPV cervical test by a nurse, HPV cervical test by a doctor, cytology test as part of HPV cervical test, cytology test performed separately to the HPV test, and colposcopy referral. Of note, deidentified data for non-participating patients will also be collected, including the number and nature of the attempts to invite them to have a cervical screening test during the recruitment period, and whether they opted to have a conventional cytology test.
To report the rate of unsatisfactory HPV samples or documentation.	In participants who underwent HPV testing and had an unsatisfactory result, the reason for that result: incorrect labelling, sample unsatisfactory, or other.

Figure 2. Overview of study objectives and outcome measures

CIN: Cervical Intra-epithelial Neoplasia, GP: General Practitioner, HPV: high risk human papillomavirus.

Figure 2 details

The purpose of this study is to evaluate the process involved in implementing primary HPV-based cervical cancer screening in primary care. The three primary outcomes are italicised. For full outcome details, including the timepoints at which data are collected, see Table 1 in Additional File 3.

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

*** Result options: 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), or unsatisfactory sample.*

^ Reasons: requested by General Practitioner due to previous high-grade lesion (test of cure), requested by General Practitioner due to previous abnormal cytology, requested by General Practitioner due to symptoms, requested by General Practitioner for other reason, performed by laboratory due to detection of HPV (not General Practitioner requested), performed by laboratory due to identification of need to test for cure (not General Practitioner requested), or other reason.

 # The number of patients who have HPV screening will also be presented with the denominator as the number of patients eligible for cervical screening during the study enrolment period, as defined by the reports to primary care organisations as prepared by the NCSP. Non-identifiable demographic data for all patients eligible for screening will be taken from these reports.

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

The full protocol is available on the ANZCTR trial website. Enrolled patients from general practices in New Zealand who are due or overdue for cervical screening were invited to participate. The study aimed to recruit at least 3,000 patients over a six-month period. Study participants could opt for a vaginal HPV self-test or a clinician-taken cervical HPV test. There was no randomisation or blinding. Data were collected throughout the screening pathway.

The study team includes Māori and Pacific steering groups, who were actively involved in the development of the study protocol.

The study was prospectively registered on the ANZCTR (ACTRN12622000699763) on 16/05/2022. The Universal Trial Number is U1111-1276-2570. Ethics approval was granted by the New Zealand Southern Health and Disability Ethics Committee on 1/7/22 (2022 FULL 12546).

Study setting

The study was performed in three regions of New Zealand: Canterbury, Whanganui, and Wellington. To recruit 3,000 people over six months, it was estimated that 15 general practices would be required to participate.

Compared to the other two regions, Whanganui general practices have a relatively high proportion of Māori enrolled. In view of current inequities in cervical cancer outcomes, and the importance of working with local providers to ensure optimal outcomes for Māori, five

general practice clinics in the Whanganui region were selected following the recommendations of a local steering group which included membership drawn from iwi,* health, and research providers. The selection of these clinics ensured access to study participation for all six iwi* in the region.

In the Wellington and Canterbury regions, five general practices in each region were selected for participation using the Microsoft Excel RANDBETWEEN function based on the unique practice identification number. If a selected clinic declined participation in the study, another clinic was randomly selected. If a selected clinic had a small number of enrolled patients, suggesting the study would not reach the recruitment target of 3,000 participants, additional clinics could be randomly selected in the same region.

While general practices in Whanganui have a relatively high proportion of Māori enrolled, the proportion of Pacific patients is comparatively low. To ensure adequate representation of Pacific patients, one practice in each of the Wellington and Canterbury regions was randomly selected from practices that have a comparatively high proportion of Pacific patients enrolled (>8.1%, which is the proportion of the overall New Zealand population that identify as Pacific).[10]

** Iwi is the Māori term to describe a kinship group or tribe.*

Participant inclusion/exclusion criteria

People were eligible to take part in the study if they were enrolled as a patient in a participating general practice, eligible for cervical screening as part of the NCSP, and due or overdue for a cervical screening test within the study enrolment period.

Patients who were invited to take part in the study could participate within three months of the completion of the six-month recruitment period. Patients were excluded if they were unable or unwilling to provide informed consent.

Study recruitment

The study recruitment process is outlined in Figure 1. Whanganui utilised centralised recruitment through their Primary Health Organisation (PHO), while the Wellington and Canterbury regions recruited directly from the participating general practices. PHOs are regional organisations funded by the New Zealand Ministry of Health to ensure the provision of essential primary health care services (mostly through general practices) to people who are enrolled with the PHO.

Eligible patients were identified using NCSP recall reports, general practice recall registries, and general practice patient information systems. Eligible patients were sent a written invitation (letter or email) and/or text invitation to undergo cervical screening, which included an invitation to opt for HPV testing as part of this study. If a patient did not respond, a second and third invitation could be made by letter, email, text, or direct contact. Patients

could also be recruited when they attend their general practice if they were identified as being due or overdue for cervical screening. In addition to the Participant Information Sheet (Appendix Figure A1), engagement material (such as the study poster and the study engagement brochure (Appendix Figures A2 and A3)) were available to assist in recruitment and/or education. These documents were developed in conjunction with the study Māori and Pacific Steering groups. The Māori engagement brochure was specifically recommended and developed by the Māori steering group. The Pacific steering group subsequently developed the Pacific engagement brochure. The Participant Information Sheet was developed based on materials developed by Te Tātai Hauora o Hine – The National Centre for Women's Health Research Aotearoa and the findings of New Zealand based studies that specifically investigated acceptability of patient information material about HPV screening.[7, 11] Screening support services could be utilised with other methods of recruitment, as per standard clinical practice for cervical screening in each practice and region.

Study appointment

As outlined in Figure 1, a phone or in-person study appointment took place with a doctor or nurse who was working on behalf of the PHO or was a staff member at a participating general practice. Written or verbal consent was obtained. If verbal consent was obtained, this was formally documented. Demographic information, screening history, and preferred method of contact for results (letter, phone call, or text) were recorded. The participant was asked if they have any symptoms (including abnormal vaginal bleeding, persistent vaginal discharge,

or pain). Participants with relevant symptoms were strongly advised to book an appointment with their doctor or nurse for further review and a cervical HPV test with cytology.

HPV testing

The advantages and disadvantages of each type of test were discussed with participants.

Participants then selected one of the following:

- Vaginal HPV self-test performed at home or other suitable location.
- Vaginal HPV self-test performed at the general practice with or without support/assistance from a nurse or doctor.
- Clinician-taken cervical HPV test using a cervibroom^{TM} or equivalent.

A clinician-taken cervical HPV test was recommended in people who were symptomatic and people that had a prior high-grade lesion or glandular abnormality and had not returned to three yearly screening (i.e., eligible for a cervical HPV and cytology test, also known as a test of cure). If a cervical HPV sample was recommended, a participant was only offered a vaginal HPV self-test if they declined a cervical test. A nominated requesting clinician was responsible for ordering the HPV test and follow up of the result. A patient could choose not to take part in the study and instead have a conventional cytology test at their general practice or elsewhere.

Participants who opted for a vaginal HPV self-test were given verbal instructions and supplied with a screening kit which included a dry FLOQswab^{R}, sterile container, and written self-test instructions (Appendix Figure A4). If the participant opted to have a vaginal HPV self-test at their general practice, they were provided with a private space to perform the test. They could request a staff member provide assistance or take the sample for them. If the participant opted to have a vaginal HPV self-test at a location other than their general practice (e.g., at home), this ideally would have been performed in conjunction with a telehealth appointment, otherwise participants were provided with contact details to ask for advice or assistance. Participants could send their HPV sample to the study laboratory directly (using a prepaid courier bag) or they could drop it to their general practice.

Clinician-taken cervical HPV tests were taken at the participant's general practice. They were performed under direct visualisation of the cervix by an accredited cervical screener (smear-taker) using a cervibroom^{TM} or equivalent and placed in an LBC medium (Surepath®).

All study samples were sent to an accredited medical laboratory (Canterbury Health Laboratories, Christchurch NZ), which uses the BD Onclarity™ HPV Assay. This is validated and approved in New Zealand for HPV testing of vaginal swabs for self-testing, as well as for HPV testing of LBC samples. The samples were transported as either a dry FLOQswab^{R} or an LBC vial. Samples were processed as per manufacturer's instructions. The laboratory sent results to the requesting clinician via normal clinical information systems and to the study

team. For those LBC samples which included cytology, the results were also directly reported to the NCSP.

HPV test result follow up

The requesting clinician was responsible for the follow up of HPV results and ensuring participants received their test result. Where appropriate, participants were informed using their preferred method of contact. Participants who received an unsatisfactory or invalid result were asked to repeat their HPV test.

Guidance for the follow up of HPV test results in this study is outlined in Figure 3.

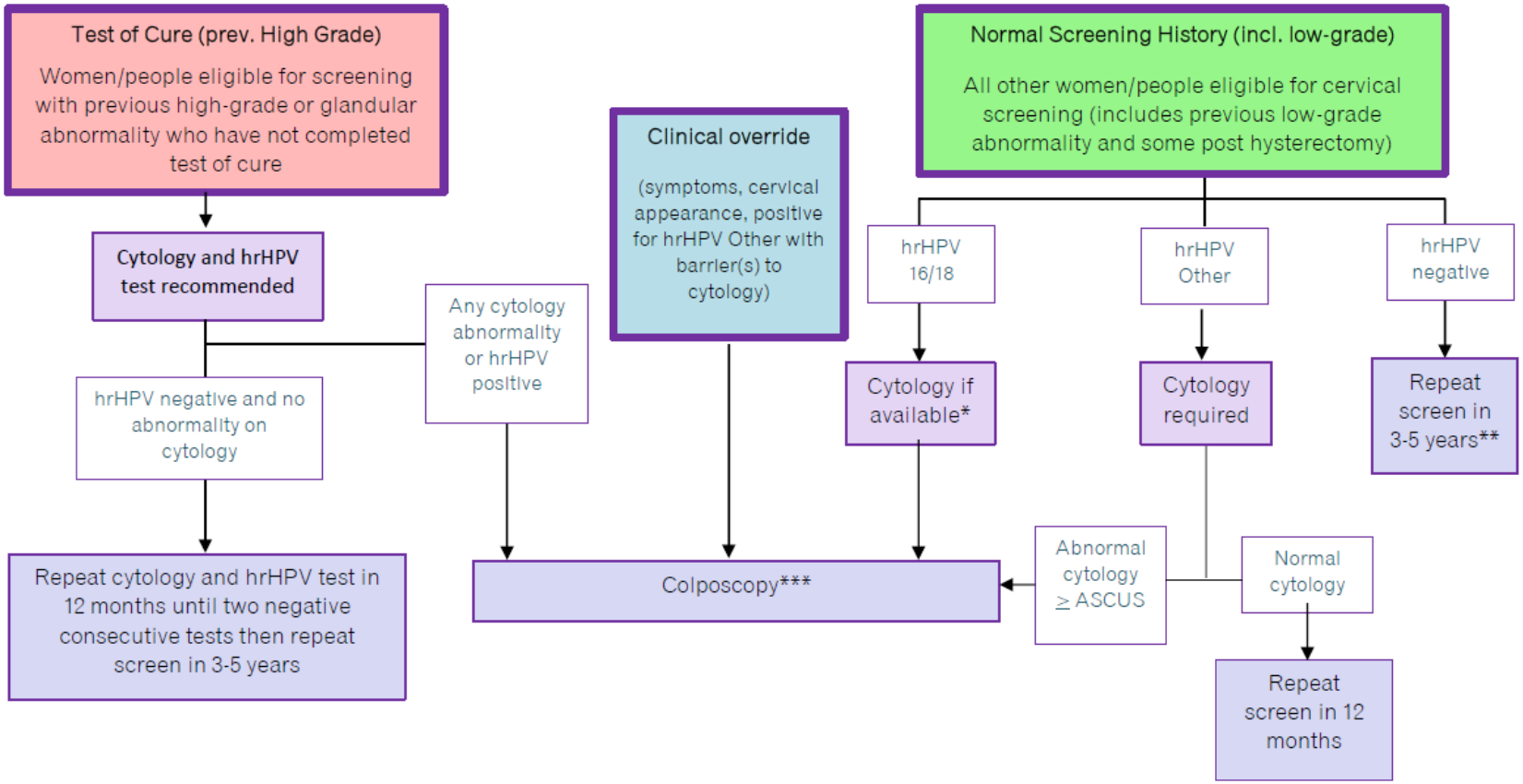

Figure 3. Study guidelines for the management of HPV results

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

Figure 3 details

**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 HPV 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. See protocol for details of exceptions.*

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., HPV other and patient declining cytology triage.*

Positive clinician-taken LBC cervical HPV samples had cytology performed by the laboratory. The result was sent to the requesting clinician and study staff, as well as directly to the NCSP by the laboratory. Positive HPV vaginal self-test samples cannot have cytology performed on them, so a separate clinician-taken cytology test at the participant's general practice was recommended.

Indications for colposcopy are outlined in Figure 4. Colposcopy was performed as per standard practice guidelines.

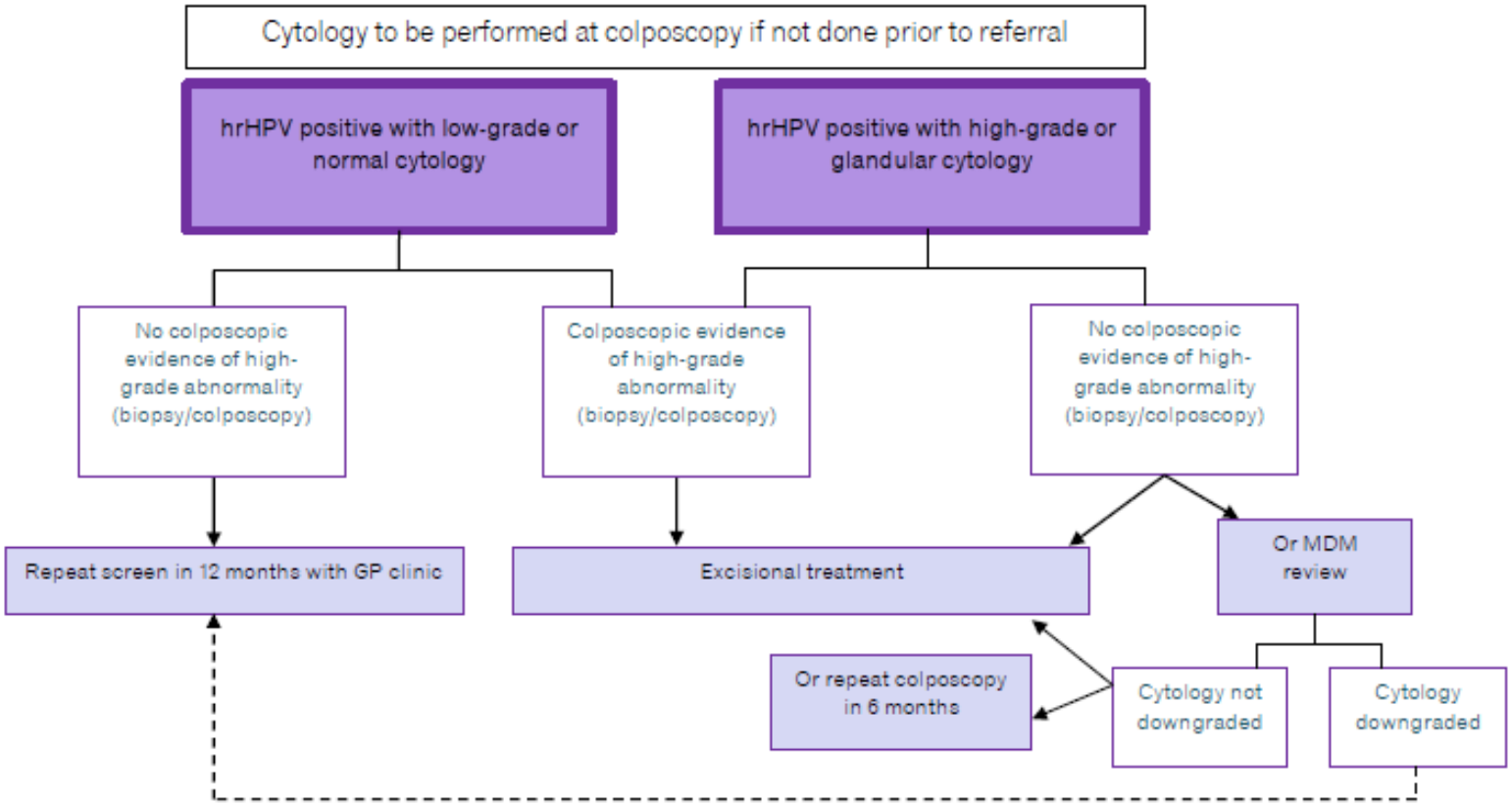

Figure 4. Recommendations for colposcopy management

GP: General Practitioner, HPV: high risk human papillomavirus, MDM: Multidisciplinary Meeting.

On completion of the study, participants were referred back to the NCSP for ongoing follow up. Enrolled patients who were due or overdue for screening and were not screened by the end of the study were referred to the NCSP and screening support services as per standard regional practices.

Participant support and education

Throughout the study, participants could access information on the study website, including the text and audio of the Participant Information Sheet and self-test instructions (Figure 1 and Appendix Figure A4). Additionally, contact details were provided for an independent disability advocate, cultural support, the study nurse, and the study clinical lead.

Costs to participants

Participants could be charged by their general practice for their HPV test and, if required, a subsequent cytology test. As is standard practice in New Zealand, cervical screening is not fully funded. Participants could be charged for their testing at a fee no more than the usual practice fee for cervical cytology. Regional 'support to screen' funding could be utilised to subsidise or cover the cost to patients. Taking part in this study did not interfere with access to this support.

Study funding was provided to participating GP clinics and PHOs to cover the time and resources required to provide study information for full informed consent and to perform

data entry. This cost was not passed on to patients. Patients are not charged for colposcopy in the New Zealand public health system.

Safety processes

The study team provided reminders to general practices and/or PHOs when participants had returned an HPV sample and were overdue for further investigations or repeat testing during the study period (Figure 3). They also checked results to ensure management recommendations are correct. Authors PS, CI, AM, and RB had access to identifiable participant data.

Sample size

It was estimated that the average New Zealand general practice would have 266 patients due for cervical screening over a six-month period and 25% of patients would decline participation in this study. As a result, approximately 15 general practices would be required to recruit 3,000 patients over a six-month screening period. Based on studies investigating the acceptability of vaginal HPV self-testing,[5, 12-14] it was estimated that 60-70% of participants would opt for a vaginal HPV self-test (1,800-2,100 participants). Results from a previous study[3] suggested that approximately 12% of HPV self-tests would be positive, which could result in an estimated 216-252 participants being invited to return to their general practice for cervical cytology. With a sample size of 216 participants with a positive HPV result, there was 95% power to observe a failure to return rate of 2% or more. This is one of multiple clinically meaningful outcomes measured in this study (Figure 2). As this outcome

requires the largest sample size, it was used to determine that recruitment of 3,000 participants would be required.

Outcome measures and data management

The study outcome measures are presented in Figure 2. For further details, see Appendix Table A1.

Staff from participating general practices and PHOs entered data from participants into a secure REDcap database. Study staff also collected:

- Screening data from the NCSP.
- HPV and cytology results from the study laboratory.
- Colposcopy results from hospital records.
- Human papillomavirus vaccination status from the Ministry of Health National Immunisation Register, for participants who specifically consented to have this data collected.
- Socioeconomic status (though coding of street addresses to the New Zealand Index of Deprivation).[15]
- Proximity to health services (through coding of street addresses to Statistics New Zealand's urban accessibility classification[16] and the Geographic Classification of Health).[17]

Participants could opt to withdraw from the study at any time. Data collected up to the point of withdrawal was kept and processed. Data was anonymised prior to analysis.

At the completion of the study, participating general practices and/or PHOs were to provide the total number of their patients identified as being due or overdue for screening during the study period. Deidentified data from patients that did not take part in the study was also collected, including detail on attempts to invite them for screening, demographics, screening history, and whether they had cervical cytology during the study period. For further detail see Appendix Table A1.

Statistical analysis

Statistical analyses will be performed using R[18] and STATA.[19] Discrete endpoints will be summarised as counts and percentages with 95% binomial confidence intervals (CI). Continuous variables will be displayed graphically, and summarised as means with 95% CI and standard deviations or medians and interquartile ranges as appropriate. Time to event data with censoring will be displayed using Kaplan-Meier or cumulative density plots. Outcomes will be stratified by participants' choice of self-taken vaginal HPV or clinician-taken cervical HPV test and/or other variables of interest such as screening history, age, self-reported ethnicity, socioeconomic status, and region (further details are available in Table A1 of the Appendix).

Results dissemination

Results will be deidentified prior to dissemination. A report will be forwarded directly to the NCSP. Results will be disseminated to cultural consultation groups and to groups involved in locality approval, trial registration, and ethical approval of the study. Importance will be placed on communicating results to local iwi and community groups supporting the study. Participants and study sites will be sent a summary of the overall results if they opt for this. Results will be submitted for publication in a peer reviewed journal and may be presented at academic conferences.

Discussion

This study will evaluate the impacts of implementing primary HPV-based cervical cancer screening, including the option of a self-test, in the New Zealand primary care setting. It is designed to give pragmatic and detailed information regarding screening participation and the impact on services that will occur with the introduction of HPV testing. It provides a unique opportunity to directly inform nationwide recommendations and practice.

It is well established that screening with primary HPV testing is more sensitive than primary screening with cervical cytology, and that self-testing offers opportunities to reduce barriers and improve participation in cervical screening.[2-7] However, the introduction of primary HPV testing is a significant change to the prior cervical screening process in New Zealand. Therefore, in this implementation study, we enable a range of primary care organisations to

offer eligible people the choice of a vaginal HPV self-test or a clinician-taken HPV sample. We collected data to observe which tests were selected, the resources required to complete the screening and diagnostic pathway, HPV test results, and engagement with the triage and diagnostic pathway.

Measures to ensure the engagement of local populations need to be individualised and tailored to the resourcing and health systems where the HPV screening program takes place. In New Zealand, most cervical cancer screening is delivered by primary care practices and people pay for their screening, although funding to support some priority groups is available. Laboratory tests and specialist gynaecology care are provided for free. General practices participating in this study may opt to charge their patients for cervical screening as part of their standard practice, reflecting what occurs in the clinical setting.

While New Zealand had a well-established and successful cervical cytology-based screening program, outcomes were inequitable.[1] In recognition of this, the study team includes Māori and Pacific steering groups, who have worked to ensure that the study is as equitable as possible, cultural safety is upheld, and recruitment is representative of Māori and Pacific people in New Zealand. Additionally, the selection of participating general practices has been designed to maximise adequate representation of Māori and Pacific people.

In this study, tests can only be ordered by accredited smeartakers. This is to ensure the clinical safety of participants. In order to take full advantage of the portability of the self-test,

community health workers (and kaiāwhina) and other health professionals may need to have the option to arrange screening tests themselves, however this is beyond the scope of the current study.

This research does not sit in isolation; there were two other implementation studies running concurrently in New Zealand, focussing on different demographics and methodologies.[20] All three studies will provide a collective evidence base to inform the practical aspects of the national roll out of HPV testing. In addition, multiple international screening programs utilise HPV testing including the option of a self-test. This study is unique with regards to participant population, the context of the New Zealand health system, the requirement for most participants to pay to access their screening test, and the ability for participants to choose a clinician-taken cervical HPV test or a vaginal HPV self-test. Information from this study, along with data from other local studies and international cervical screening programs will inform the NCSP of the important issues that can be anticipated with the introduction of their HPV screening program.

Conclusions

This study is designed to provide a clinically relevant evidence-base from which practical recommendations can be made to optimise the introduction of primary HPV testing for cervical screening in New Zealand. These recommendations have the potential to improve

health outcomes, guide resource allocation, and identify factors that could reduce inequities in the cervical screening programme.

Competing interests

Funding was provided by the Ministry of Health National Screening Unit, which included salaries for the authors on this submission.

PS has done other funded work for the National Screening Unit. JN has had salary funding from the Health Research Council of New Zealand. CI received grants from the New Zealand Ministry of Health during the conduct of the study. JM is General Practice/Primary lead for the National Screening Unit. BL received grants from the New Zealand Health Research Council and the Ministry of Health New Zealand, she is a member of the New Zealand National Screening Unit HPV Programme Action and Advisory Group. AT has worked for Christchurch Heart Institute, Omics and Pacific Heart Health Laboratories, University of Otago, Christchurch, Canterbury Clinical Network Pasifika Caucus, and Pacific Peoples Advisory Committee, University of Canterbury. AT also has a voluntary role with P.A.C.I.F.I.C.A. Inc. JW has done other funded work for the National Screening Unit. AM was on the NCSP Advisory Group for many years until 2021 and has non-financial competing interests that include but are not limited to membership in a government or other advisory board. LM, BH, STW, MG, RB and DS have nothing further to declare.

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Appendix

Supporting Tables and Figures:

- Figure A1. Example of Participant Information Sheet
- Figure A2. Study Poster
- Figure A3. Study Brochure
- Figure A4. Self-test Instructions
- Table A1. Full list of study outcomes

Figure A1. Example of Participant Information Sheet

Privacy and confidentiality

Staff at your GP clinic will record information about you, your results, and journey through the screening programme. The Research Team at Otago University will collect information from your National Screening Unit record and, if needed, your hospital clinical records. This information, including your name, date of birth, and National Health Index (NHI) number, will be entered onto a secure database located on the University of Otago. After the study, this data will be transferred to an Otago University secure archiving site and stored for at least 10 years. The number of patients who are due for screening and the number of patients who had smear tests during the study period at your GP clinic will be recorded.

The Research Team at Otago University will have access to all data on a database. This will allow a safety review by a Senior Gynaecologist who can support your GP clinic if you need further care. Your HPV test will be sent to a laboratory that is accredited to analyse HPV tests. Your HPV test sample will be stored by the laboratory for the usual amount of time (for quality checking). Your data will be provided to the Ministry of Health National Screening Unit to ensure that you are adequately followed up by the screening programme in the future.

Study data will be de-identified before analysis. The results of the study may be published or presented, but not in a form that would reasonably be expected to identify you. You have the option to receive a summary of the overall study results when available (there may be a delay between your participation in the study and delivery of the summary). You have the right to request access to your information held by the Research Team. You also have the right to request that any information you disagree with is corrected.

Consent for further testing and contact

We will ask you whether you would be interested in being contacted by the Research Team at Otago University for another study to ask some questions about your HPV testing experience. This is voluntary and your care will not be affected if you do not wish to be contacted.

ACC statement

If you were injured in this study, you would be eligible to apply for compensation from ACC just as you would be if you were injured in an accident at work or at home. This does not mean that your claim will automatically be accepted. You will have to lodge a claim with ACC, which may take some time to assess. If your claim is accepted, you will receive funding to assist in your recovery. If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

Further information

If you have any further questions, or complaints about the study, you can contact our study nurse, [redacted] You can also contact the clinical lead of the study, Dr Peter Sykes, at the University of Otago, on [redacted] or [redacted]

You can contact your GP practice to request cultural support. To access Māori cultural support, you can also contact [redacted]

The study was approved on 1/7/2022 by the Southern Health and Disability Ethics Committee (Ethics reference: 2022 FULL 12546), and has site-specific local authorization. This study is registered at www.anzctr.org.au (ACTRN12622000699763). This study is funded by the Ministry of Health. If you participate in this study, your medical practice may receive a fee from the research grant to cover administrative costs of the study. If you have any concerns about trial participation, please feel free to access independent medical advice. If you want to talk to someone who isn't involved in the study, you can contact an independent health and disability advocate on: 0800 555 050 or advocacy@hdc.org.nz

Let's test for HPV

...and prevent Cervical Cancer

UNIVERSITY of OTAGO
Te Whare Wānanga o Otāgo
NEW ZEALAND

Participant Information Sheet

Research about giving the choice of an HPV self-test for Cervical cancer screening

What is this study about?

The primary screening test for cervical cancer in New Zealand is a cervical screening test otherwise known as a smear. In 2023 this will change to the human papillomavirus (HPV) test. The HPV test is a better screening test than the usual cervical screening test. It is already offered in other countries, including Australia.

The HPV test gives you a choice– you can do the test yourself or have a doctor or nurse do it. A self-test is done by putting a small swab into the vagina, this swab is tested for HPV. Alternatively, a doctor or nurse can take a sample from your cervix, like a regular cervical screen. This sample is tested for HPV. The self-test is just as accurate as the cervical test, but further tests can be done on the cervical test if they are needed. It is your choice which test you take.

Your GP clinic is part of a study looking at the best way to introduce the HPV test and you are invited to take part. The study will look at all parts of the screening pathway, from the invitation to have an HPV test through to the test result, and whether any further tests or treatments are required. It will investigate which parts of the screening pathway work well and which parts need to be improved.

It is important to be aware that neither the HPV test or the usual cervical screening test detect other diseases, so if you have abnormal bleeding or discharge or bleeding after sex you must tell your health professional.

What am I being asked to do?

Approximately 3,000 people are expected to take part in the study.

This study offers you a choice about what sort of test you wish to have for cervical screening. An HPV test or a usual cervical screen. The choice is up to you. You are welcome to discuss this study with your friends and/or family/whānau/aiga.

If you agree to take part in the study, you will be offered the HPV test. You will be invited to a Study Appointment with your GP clinic (phone call or face-to-face). Appointments are available up until March 2023.

A nurse or doctor will discuss the advantages and disadvantages of having an HPV test instead of a usual cervical screening test. They will also explain the types of HPV test available: a self-test from the vagina (completed at home, or at your GP clinic) or a test from the cervix taken by a nurse or doctor.

It is your choice as to which type of HPV test you have. However, some people may be recommended to have a cervical test instead of a self-test. Your nurse or doctor will let you know if this applies to you.

If you opt for a self-test, you will be able to take the test at your GP clinic or at home. The cost of your appointment will be the same or less than what you would pay for your usual cervical screening test. Many patients are eligible for a subsidised screening test. You are welcome to check the cost with your GP clinic prior to taking part. You may need a follow up appointment to discuss your results or to have a cervical screen. If so, the total cost of these visits should not exceed what you would normally pay for your cervical screen.

Your HPV test will be taken to a laboratory for analysis. Test results are usually available within two weeks. You will get the result by text or an appointment (phone or face-to-face). Most HPV test results are negative. A negative result means you are unlikely to need another cervical screening test for at least three years.

A positive HPV test result does NOT mean that you have cancer. Some types of HPV indicate that you could have cell changes that could lead to cancer, and you need a specialist appointment for assessment in the hospital. Other types are less likely to cause these cell changes. If you opted for an HPV self-test, your GP or nurse may recommend you have a cervical screen prior to hospital assessment. You will have an appointment with your GP to explain which follow up is right for you.

Your medical care will continue to be managed by your GP clinic during and after the study. Responsibility for your screening information will be held by the Study Team for the duration of the study. At the end of the study your HPV test results will be given to the National Cervical Screening Programme to ensure that you are adequately followed up in the future.

Who is doing this study?

The University of Otago, Christchurch, is leading this study. Participating GP clinics and Hospitals are in Christchurch, Whanganui and Wellington. The study is funded by the New Zealand Ministry of Health National Screening Programme.

Withdrawing from this study

Being part of this study is your choice. You can choose not to take part, or to withdraw from the study at any time. Your care won't be affected in any way. If you withdraw from this study, we will keep and process the information collected up to the date you withdraw. We will not collect any new information after that.

What are the possible benefits and risks of this study?

While the HPV test is a more sensitive screening test than the usual cervical screening test, there is still a very small risk that an abnormality may be missed. The HPV test does not detect abnormalities that relate to conditions other than cervical cancer. The HPV test has the advantage of a self-test option, which may be more comfortable than having a cervical screening test.

Having an HPV test, rather than the usual cervical screening test, may make it slightly more likely to require further assessment. If your HPV test result is positive you will need further tests, this may include a cervical screening test if you opt for an HPV self-test.

Information about you is collected as part of this study. Although every effort will be made to protect your privacy, absolute confidentiality of your information cannot be guaranteed. The risk of people accessing and misusing your information is very small, but may increase in the future as people find new ways of tracing information.

More information about HPV tests

HPV stands for "human papillomavirus". Most people will have HPV at some time in their lives and it usually clears up by itself. However, some types of HPV are associated with increased risk of cancer and precancerous changes in the cervix. The HPV test is designed to detect these types of HPV. The HPV test can be taken from the vagina or cervix. Both types of HPV test are very effective screens for cervical cancer. It is your choice as to which type of HPV test you have.

The HPV test taken from the vagina

Unlike a cervical screening test, an HPV test taken from the vagina does not require a speculum. A nurse, doctor or kaiāwhina (community health worker) will explain how to use a swab to take a sample from your vagina. There will be written information to assist you. You can choose to do the test at the GP clinic, with or without help from a staff member. Alternatively you can choose to do the test by yourself at home or somewhere you feel comfortable (e.g. marae or community centre).

The HPV test taken from the cervix

This is performed by a nurse or doctor at your GP clinic. They will use a speculum to take a sample from the cervix. In some patients this method will be recommended so that the cervical screener can take a look at your cervix and take a sample of cells for testing (just like the usual cervical screen).

Follow up for a positive HPV result

If you had an HPV self-test, you may need a cervical screening test taken by a nurse or doctor at your GP clinic. This will allow the cervical screener to look at your cervix and take a sample of cells for testing. You may also require an assessment at the hospital, this is called a colposcopy test. They will look at your cervix with a microscope to check for cell changes. If there are precancerous changes on your cervix they can normally be easily treated.

You can find out more about cervical screening at www.timetoscreen.nz

Figure A2. Study Poster

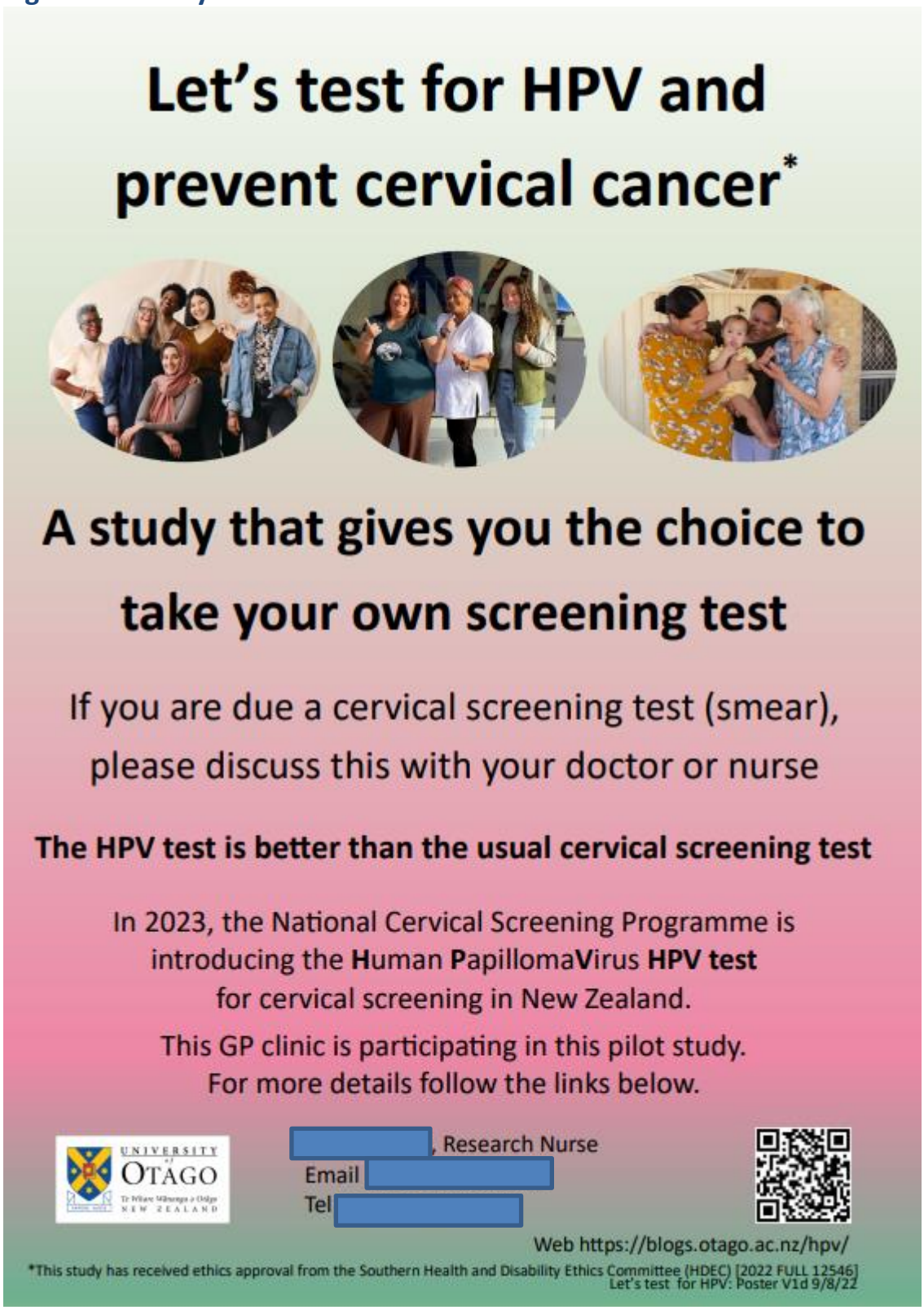


Figure A3. Study Brochure (Pacific Brochure)

What is HPV?

Human papillomavirus (HPV) is a virus spread through skin to skin contact. Certain types of HPV cause the majority of cervical cancers.

Why should I self-test for HPV?

It is an opportunity for you to test yourself for HPV linked to cervical cancer. The HPV test is better than the usual cervical screening test. You can take this test wherever you feel most comfortable.

Why should I be involved in this research?

This study will look at all parts of the screening pathway, and find out which parts of the pathway work well and which parts need to be improved. So, by taking part you will find out if you are at risk of developing cervical cancer and help improve cervical screening in the future.

What do I have to do?

If you choose to take part, a nurse or doctor will discuss the advantages and disadvantages of having an HPV test and how to take it.

Your choices are either a self-test from the vagina (completed where you choose) or a test from the cervix taken by a nurse or doctor.

The HPV self-test is a simple process and you will be given step by step instructions on how to take it.

If you choose not to be in the study, that's okay. You can have your health professional take your cervical screen (smear) as usual.

What does this mean for me and my aiga/fanau/family?

You are a role model to your daughters, nieces, and grandchildren. We recognise an HPV test affirms your ability to take care of yourself and make decisions for your body. This study provides a test that is easier and less invasive. Your partnership in this will refine the screening process for the future and your feedback is welcome.

What if I get the self-test wrong?

No problem. There will be people to help you talk through what happened and take another test.

What happens when the results come back from my test?

The results will take two weeks and you will get the result back from your GP practice.

If the HPV *test is positive*, you have a choice as to what your next step will be. You may be offered a regular cervical screening test (smear) if you have had a self-test. You could choose to do this or you could choose to be referred onto colposcopy without the cervical screening test.

If the HPV test is negative, you will be advised when your next screening test is due.

Figure A4. Self-test Instructions

Prevent Cervical Cancer: Let's Self-Test For HPV

How to Self-Test

1 We recommend you complete this test with your Telehealth/clinic appointment.

Please read the patient information brochure.

Read and sign the consent form.

Follow the instructions on the right side of this leaflet to take the self-test.

3 Complete the lab form by writing the **DATE** your sample was taken and **check your details** are correct – TICK the box

Place the self-test sample in the zip-lock bag provided.

Place the consent form, lab form, and self-test sample in the free courier bag provided and seal it.

Either return this to your healthcare practice, or send it via mail within 48 hours of taking the test.

Your sample will be sent to a lab for HPV testing. Your healthcare provider will notify you of your result.

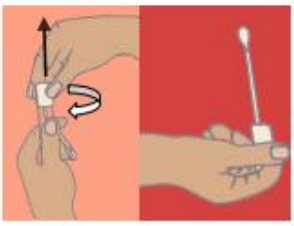
It is important you **tell your healthcare provider** if you are experiencing **abnormal vaginal bleeding or discharge, or bleeding after sex.**

If You Need Help

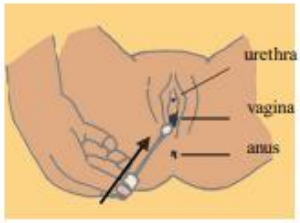
Please talk to **your GP practice nurse**, or call the research nurse on [redacted] and your call will be returned as soon as possible.

2

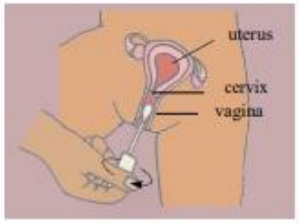
Ensure your hands are clean and dry before you **get into a comfortable position** with underwear lowered that will allow you to take a sample from your vagina.



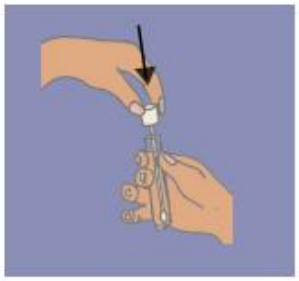
Open the swab by holding and twisting the plastic end firmly to break the swab label. Then pull the swab out. Avoid any contact with the cotton bud end, which is for the sample. If it touches a wet surface, please ask for a new kit.



Similar to inserting a tampon, use your free hand to find the entrance of your vagina so the other can then **gently insert the cotton bud end of the swab** about 2-3cm inside.



Take the sample by rotating the swab for 10-30 seconds inside your vagina. This should not cause any more than mild discomfort.



Carefully remove the swab from your vagina and return it to its plastic tube. **Close it securely**. Write your **FULL name and your date of birth** on the tube. If you have been provided a label with these details you can use this instead. **Write the date the sample is taken on the tube.** Return your sample for testing using the instructions on the left.

2022_09_01 Let's test for HPV Self-test instruction sheet V2c

Table A1. Full list of study outcomes

Please note, as appropriate, data will be presented separately by whether the participant opted for:

- Vaginal high risk human papillomavirus (hrHPV) self-test performed at home or other suitable location
- Vaginal HPV self-test performed at the general practice with or without support/assistance from a nurse or doctor.
- Clinician-taken cervical HPV test.

Outcomes relate to all participants unless otherwise stated.

Primary outcome 1
The number (and percentage) of participants that undertook a:
- Vaginal test at home
- Vaginal test at their General Practice (GP) clinic without staff assistance
- Vaginal test at their GP clinic with staff assistance
- Cervical test without concurrent cytology
- Cervical test with concurrent cytology.

Data obtained from participating GP clinics.

Timepoint:
By the end of screening period.

Primary outcome 2
The number (and percentage) of participants who had the following high risk human papillomavirus (hrHPV) result:
- HPV 16
- HPV 18
- Other hrHPV (listed by genotype where available)
- hrHPV not detected.

Data obtained from participating GP clinics and laboratories.

Timepoint:
By six months after the end of the screening period.

Primary outcome 3
The mean, median and range for the time between an hrHPV test report being issued and GP referral for colposcopy in all participants that had an hrHPV result that indicated requirement for referral to colposcopy.

Data to be presented separately by whether participants had a cervical or vaginal hrHPV test, and whether the referral was made with or without cytology results.

Data to also be presented separately for participants negative for hrHPV, participants positive for human papillomavirus (HPV) 16 and/or 18, and participants positive for hrHPV other than 16 or 18.

Data obtained from participating GP clinics and laboratories.

Timepoint:
By six months after the end of the screening period.

Secondary outcome 1
The number (and percentage) of participants with: 1,2,3 or >3 attempts to be contacted prior to their hrHPV test.

Data obtained from participating GP clinics.

Timepoint:
By the end of screening period.

Secondary outcome 2
The mean, median and range for time from the first study appointment to an hrHPV test being conducted, for each participant.

Data obtained from participating GP clinics.

Timepoint:
By the end of screening period.

Secondary outcome 3
The mean, median and range for time from first the contact attempt to an hrHPV test being conducted, for each participant.

Data obtained from participating GP clinics.

Timepoint:
By the end of screening period.

Secondary outcome 4

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 phonecall with a staff member from their GP clinic
- Other form of contact.

Data obtained from participating GP clinics.

Timepoint:
By the end of screening period.

Secondary outcome 5
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.

Data to be presented separately by whether participants had an hrHPV test at home or at their GP clinic.

Data obtained from participating GP clinics and laboratories.

Timepoint:
By six months after the end of the screening period.

Secondary outcome 6
The mean, median and range of charges (NZD) for each type of hrHPV test listed under Primary Outcome 1 above.

This will be reported by whether the tests were subsidised or not.

Data obtained from participating GP clinics.

Timepoint:
By the end of screening period

Secondary outcome 7
The mean, median and range for the time from an hrHPV test to the results report being issued.

Data obtained from participating GP clinics and laboratories.

Timepoint:

By six months after the end of the screening period.

Secondary outcome 8
In participants who underwent hrHPV testing and had an unsatisfactory result, the reason for that result:
- Incorrect labelling
- Sample unsatisfactory
- Other.

Data obtained from participating GP clinics and laboratories.

Timepoint:
By six months after the end of the screening period.

Secondary outcome 9
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.

Data obtained from participating GP clinics and laboratories.

Timepoint:
By six months after the end of the screening period.

Secondary outcome 10
In participants who underwent hrHPV testing and had a repeat test, the mean, median and range for the time from the first hrHPV test to the repeat hrHPV test.

Data obtained from participating GP clinics and laboratories.

Timepoint:
By six months after the end of the screening period.

Secondary outcome 11
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.

Data obtained from participating GP clinics and laboratories.

Timepoint:
By six months after the end of the screening period.

Secondary outcome 12
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.

Data obtained from participating GP clinics.

Timepoint:
By six months after the end of the screening period.

Secondary outcome 13
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 lab due to detection of hrHPV (not GP requested)
- Performed by lab due to identification of need to test for cure (not GP requested),
- Other reason.

Data obtained from participating GP clinics and laboratories.

Timepoint:
By six months after the end of the screening period.

Secondary outcome 14
The reason cytology was performed in participants that had cytology test* performed after an hrHPV test and before colposcopy:
- Positive for hrHPV result
- Other reason.

*Please note for this and subsequent outcomes the term “cytology test” refers to a cytology sample taken at a GP clinic after an hrHPV test and before 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.

Data obtained from participating GP clinics.

Timepoint:
By six months after the end of the screening period.

Secondary outcome 15
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.

Data obtained from participating GP clinics.

Timepoint:
By six months after the end of the screening period.

Secondary outcome 16
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.

Data obtained from participating GP clinics.

Timepoint:
By six months after the end of the screening period.

Secondary outcome 17
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.

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.

Data obtained from participating GP clinics and laboratories.

Timepoint:
By six months after the end of the screening period.

Secondary outcome 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.

Data obtained from participating GP clinics and laboratories.

Timepoint:
By six months after the end of the screening period.

Secondary outcome 19
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.

Data obtained from participating GP clinics and laboratories.

Timepoint:
By six months after the end of the screening period.

Secondary outcome 20
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.

Data obtained from participating GP clinics.

Timepoint:
By six months after the end of the screening period.

Secondary outcome 21
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
- 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.

Data obtained from participating GP clinics.

Timepoint:
By six months after the end of the screening period.

Secondary outcome 22
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.

Data obtained from participating GP clinics and laboratories.

Timepoint:
By six months after the end of the screening period.

Secondary outcome 23
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.

Data obtained from participating GP clinics.

Timepoint:
By six months after the end of the screening period.

Secondary outcome 24
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.

Data obtained from colposcopy clinics.

Timepoint:
By six months after the end of the screening period.

Secondary outcome 25
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.

Data obtained from participating GP clinics and colposcopy clinics.

Timepoint:
By six months after the end of the screening period.

Secondary outcome 26
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.

Data obtained from participating GP clinics, laboratories and/or colposcopy clinics.

Timepoint:
By six months after the end of the screening period.

Secondary outcome 27
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.

Data obtained from participating GP clinics or colposcopy clinics.

Timepoint:
By six months after the end of the screening period.

Secondary outcome 28
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.

Data obtained from participating GP clinics or colposcopy clinics.

Timepoint:
By six months after the end of the screening period.

Secondary outcome 29
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.

Data obtained from participating GP clinics or colposcopy clinics.

Timepoint:
By six months after the end of the screening period.

Secondary outcome 30
In participants that had colposcopy with a biopsy, the number (and percentage) that had a 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.

Data obtained from participating GP clinics, laboratories or colposcopy clinics.

Timepoint:
By six months after the end of the screening period.

Secondary outcome 31
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.

Data obtained from participating GP clinics or colposcopy clinics.

Timepoint:

By six months after the end of the screening period.

Secondary outcome 32
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.

Data obtained from participating GP clinics or colposcopy clinics.

Timepoint:
By six months after the end of the screening period.

Secondary outcome 33
The mean, median and range for times from colposcopy to initiation of each of the treatments in outcome 32 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.

Data obtained from participating GP clinics or colposcopy clinics.

Timepoint:
By six months after the end of the screening period.

Secondary outcome 34
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.

Data obtained from participating GP clinics, laboratories and colposcopy clinics.

Timepoint:
By six months after the end of the screening period.

Secondary outcome 35
Where numbers permit, all outcomes will be presented by:
- Screening history (previously undergone cervical treatment/had an abnormal smear, or not)
- Age band (<25, 25 to 34 years, 35 to 54 years, 55 to 69 years, >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).

Secondary outcome 36

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.

Data obtained from participating GP clinics.

Timepoint:
By six months after the end of the screening period.

Secondary outcome 37

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.

Data obtained from participating GP clinics.

Timepoint:
By the end of the screening period.