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| **Waitemata and Auckland DHB**  **Human Papilloma Virus (HPV) Cervical Screening**  **Self-Sampling Study in Māori Women in West Auckland**  **Short title:**  **HPV-SS**  **Protocol for a feasibility and acceptability research study** |
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**Executive summary**

While overall cervical cancer rates have reduced, Māori women are still twice as likely as non-Māori women to be diagnosed or die from cervical cancer. Auckland and Waitemata DHBs have low Māori cervical screening coverage rates (56.4% and 59.2%, respectively), which remain longstanding despite local and national initiatives to reduce screening barriers. Improving access to cervical screening for Māori women remains a priority for the Ministry of Health and in the Auckland and Waitemata DHBs Māori Health Plans (indicator 5). Innovative ways to address access barriers are required.

In the context of announced changes by the Ministry of Health from the traditional ‘pap smear’ (cytology) to human papilloma virus (HPV) testing to screen women for cervical cancer, there is a window of opportunity to consider the novel technology of self-sampling to improve screening coverage in a New Zealand context relevant for our population. Self-sampling means that women can perform a low vaginal swab themselves (cervical sampling is not required) rather than requiring a speculum examination from a health professional. The sample could be taken at home or in a health care setting, or potentially another appropriate community setting. HPV detection using vaginal self-sampling is as accurate as clinician-sampling, provided that high performing assays are used to test the samples for the presence of HPV.

The objective of this small initial study is to examine the feasibility and acceptability of self-sampling in Māori women as the key audience for this novel technology, and to determine pathway requirements to follow up HPV-positive women. The investigators are committed to Māori health gain and working in partnership with Māori providers, primary care and hospital services. This work purposefully commences with Māori women, to ensure that this novel technology is appropriate and optimised to address inequalities before assessing the technology with other groups of women in our population.

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**List of Abbreviations**

|  |  |
| --- | --- |
| CI | confidence interval |
| CIN2+ | cervical intraepithelial neoplasia grade ≥2 |
| CIN3+ | cervical intraepithelial neoplasia grade ≥3 |
| CRF | case report form |
| DHB | District Health Board |
| GP | general practitioner |
| HPV | human papillomavirus |
| hrHPV | high risk human papillomavirus |
| LBC | liquid-based cytology |
| NCSP | National Cervical Screening Programme |
| PCR | polymerase chain reaction |
| PHO | Primary Health Organisation |
| SAE | serious adverse event |
| STI | sexually transmitted infection |
| WOW | Te Whānau o Waipareira |

## Introduction

### Background Information

The New Zealand National Cervical Screening Programme (NCSP) has been established for 27 years. Although cervical cancer incidence has declined in both Māori and non-Māori, invasive disease persists, predominantly women who are not screened or who are under-screened.[1](#_ENREF_1), [2](#_ENREF_2) Cervical cancer is the fifth most common cancer type in Māori women, and cervical cancer registration and mortality rates in Māori women are two-fold higher than those in non-Māori women.[3](#_ENREF_3)

The cervical screening coverage rate of Māori women in the Auckland and Waitemata District Health Boards (DHBs) is currently the lowest and third lowest of all DHBs in the country, at 56.4% and 59.2%, respectively.[4](#_ENREF_4) This requires 2,373 and 2,673 more Māori women in each respective DHB to be screened to reach the national coverage target of 80%.[4](#_ENREF_4) Large ethnic inequalities in cervical cancer outcomes and in access to cervical screening services (as measured by coverage) are longstanding and unacceptable (see Figure 1).

Figure 1 Cervical screening coverage. Source NCSP.

Reasons for low programme participation include cost, embarrassment, time, inconvenience, and discomfort.[2](#_ENREF_2) Actions to reduce these barriers, including no-cost targeted testing (‘free smears’) and tailored practice-level data-matching with support, have been undertaken in an Auckland regional cervical screening coordination approach since 2012; despite these measures there has been very little change in coverage for Māori women. Novel strategies are required to change the landscape of cervical screening to ensure that Māori women benefit from cervical screening.

The NCSP is currently assessing policy options to transition from traditional cervical screening by cytology (previously a ‘pap smear’, now liquid-based cytology; LBC) to a HPV-based programme. Because persistent cervical infection with high risk HPV (hrHPV) causes virtually all cervical cancers,[5](#_ENREF_5), [6](#_ENREF_6) the World Health Organization[7](#_ENREF_7) recommends primary HPV screening for early detection of cervical cancer. In high resource settings, using HPV testing for primary cervical cancer screening could increase the efficiency of the existing screening programme, more effectively identify women at risk of precancerous changes, and therefore reduce the incidence and mortality from cervical cancer.[6](#_ENREF_6)

New Zealand has an established HPV vaccination programme protecting young women against the two most important hrHPV types, 16 and 18, which are estimated to cause 70% of cases.[8](#_ENREF_8) However, a large proportion (40−46%) of young women are not vaccinated[9](#_ENREF_9) and the vaccine does not protect against other HPV types. HPV of any type was detected in the majority (89%) of New Zealand women with histologically confirmed invasive cervical cancer.[10](#_ENREF_10) Therefore, screening remains important in preventing cervical cancer for the foreseeable future. Of note, the recently published model developed for the NCSP programme change demonstrates that primary HPV screening with partial genotyping would be more cost effective than the current cytology-based screening programme in reducing cervical cancer incidence and mortality in New Zealand.[11](#_ENREF_11)

The Ministry of Health has identified a research gap in New Zealand regarding the use of self-sampling as an adjunctive strategy to improve cervical screening coverage, the pathways of positive hrHPV management, and acceptability in women.

The goal of this study is to evaluate the acceptability and feasibility of HPV self-sampling in the high priority population of Māori women. Findings from this study are anticipated to inform further studies. Our group is involved in a proposal for a larger, randomised controlled trial to examine two invitation approaches for HPV self-sampling in New Zealand Māori, Pacific and Asian women (Health Research Council (HRC) funded study, Prof John Potter Massey University Principal Investigator). Ultimately, these studies will assist in the Ministry of Health’s policy decisions on cervical screening.

**The novel technology of HPV self-sampling**

Unlike cytology assessment, HPV testing is DNA based and does not require intact cells. Therefore, a less invasive method of sampling may be used, such as self-sampling. In New Zealand, vaginal self-sampling is a technology already used to test for Sexually Transmitted Diseases (STIs) such as chlamydia and gonorrhoea.[12](#_ENREF_12) Self-sampling for chlamydia is associated with high accuracy relative to clinician sampling,[13](#_ENREF_13) and is preferred by Māori women.[14](#_ENREF_14)

Vaginal HPV self-sampling is an intervention aimed to simplify the screening encounter and reduce barriers to programme participation.[15](#_ENREF_15) The self-sampling approach has been used in international studies targeting underserved populations who bear the disproportionate burden of cervical cancer.[16-18](#_ENREF_16) Self-sampling approaches are popular, research studies consistently showing improved participation in cervical screening, including the hardest-to-reach women who have never been screened.[15](#_ENREF_15), [19-23](#_ENREF_19) The iPAP trial in Australia, where HPV self-sampling kits were posted to underscreened women demonstrated 20.3% uptake compared with 6% usual care.[21](#_ENREF_21) Underserved women not only lack access to screening, they have a greater prevalence of hrHPV infection and a higher risk of developing cervical cancer than the general population.[24](#_ENREF_24), [25](#_ENREF_25) HPV self-sampling is being considered as a policy option in the Australian Renewal primary HPV screening process [26](#_ENREF_26) and has been incorporated into the cervical screening programme in the Netherlands for some time.[27](#_ENREF_27)

The accuracy of self-sampling versus clinician sampling in detecting high grade precancerous cervical changes (cervical intraepithelial neoplasia grade two or higher; CIN2+) is variable, as studies evaluating self-sampling differ in terms of sampling device, sample site (e.g. cervicovaginal vs. vaginal) and HPV assay type.[20](#_ENREF_20) A recent meta-analysis reported that, provided a high performing HPV polymerase chain reaction (PCR) assay is used, different HPV self-sampling device types detect CIN2+ with the same accuracy as a clinician-collected sample.[28](#_ENREF_28) More recent studies confirm these findings (relative sensitivity 0.98 [95% CI 0.93−0.98], relative specificity 1.02 [95% CI 0.94−1.09]).[27](#_ENREF_27) A subsequent study of >5,000 women in Scotland (not included in the meta-analyses) was conducted in the in the routine cervical screening setting rather than in under-screened populations. In this study (called the PaVDaG study) the accuracy of vaginal self-sampling was similar to cervical clinician-sampling as detected using the cobas 4800 HPV assay (CIN2+ sensitivity 94.6 [95% CI 90.7−98.5], specificity 85·4 [95% CI 84·4-86·3]; relative sensitivity and specificity of hrHPV positivity for the detection of CIN2+ in vaginal vs. cervical samples were 0·97 [95% CI 0·94-1·00] and 0·98 [95% CI 0·97-0·99]).[29](#_ENREF_29)

Most studies did not compare different sampling devices, However, no significant difference was reported between a brush-based and a lavage-based device in terms of CIN2+ and CIN3+ detection rates (when using a high performing PCR DNA assay)and user comfort.[30](#_ENREF_30) An inexpensive and low technology device, the dry flock swab, has the same accuracy when used for wet or dry self-sampling in Australia.[31](#_ENREF_31)

Internationally, HPV self-sampling has been utilised with a range of invitation approaches, including in general practice clinics,[18](#_ENREF_18) community health worker delivery[19](#_ENREF_19) and by mail.[31](#_ENREF_31), [32](#_ENREF_32) A meta-analysis confirmed that a range of delivery approaches are acceptable to and improved participation in under-screened women, and should be tailored to local populations.[33](#_ENREF_33)

There has been international discussion about whether self-sampling is a technology that should be offered to any women who wishes to take it up or be limited to under-served women. In the Australian Renewal programme there has been policy discussion on the pragmatic aspects of limiting the offer of self-sampling at a general practice or invitation level. Of note, Dutch[34](#_ENREF_34) and Australian[35](#_ENREF_35) models suggest that some of the benefits anticipated with HPV self-sampling in reducing cervical cancer diagnosis and mortality rates would be lost if large numbers of women who are currently regularly screened (and would be clinician-screened with the newer HPV test rather than pap smear in the new Programme) switch from regular screening to self-screening. The Dutch analysis, where self-sampling is already offered, reported that self-sampling will generate gain if the relative CIN2+ sensitivity is ≥0.95, unscreened attendees are recruited, and the total attendance increases by ≥6 percentage points.[34](#_ENREF_34) In the Australian modelling of 100,000 under-screened women aged 30-84 they found 908 cancer diagnoses and 364 cancer deaths averted with self-sampling; but that potentially twice that many could have been prevented if the same women joined the mainstream primary HPV programme.[35](#_ENREF_35) It is unknown what proportion of women might join the mainstream programme from this hard-to-reach population, and therefore whether this comparison is valid (it may be self-sampling vs no participation for a large proportion of this group). From this overall modelling self-sampling is considered to be the most efficient and cost-effective if it is used to specifically target under-served women rather than the general population.[27](#_ENREF_27)

In high resource settings, such as New Zealand, self-sampling is a valid option for consideration, with particular focus on feasibility assessment, logistics, effectiveness in improving coverage (particularly for currently underserved populations such as Māori women), and costs.[28](#_ENREF_28) How best to ensure that there is appropriate management of women with positive HPV results needs to be determined, as follow-up with a clinician is required to identify precancerous lesions and to provide treatment.[27](#_ENREF_27) While women in international studies prefer self-sampling over clinician-sampling, some women lack the confidence to perform the procedure correctly; appropriate and adequate education and support will be needed to address this concern.[36](#_ENREF_36), [37](#_ENREF_37)

### 1.2 Hypothesis

In addition to cost, there are many barriers to cervical screening for Māori women. We hypothesise that access to self-sampling will reduce barriers to cervical screening, such as cost, primary care access and whakamā (shame/shyness/embarrassment), thereby increasing programme participation in never- and under-screened Māori women.

### 1.3 Aim

In this feasibility study, our aim is to evaluate participation (proportion uptake) and acceptability of HPV self-sampling in Māori women, prior to conducting a larger, randomised controlled trial to compare two invitation methods with usual care in Māori, Pacific and Asian women.

### 1.4 Justification for the study

In Māori women, along with high HPV vaccination coverage, early detection is a key intervention to reduce cervical cancer inequalities.[38](#_ENREF_38) [20](#_ENREF_20), [23](#_ENREF_23) In a qualitative study,[39](#_ENREF_39) Māori women indicated a preference for self-sampling. The use of a novel HPV self-sampling technology in never- or under-screened Māori women may improve participation (as observed in international studies discussed above) to address the burden of cervical cancer in Māori women. In addition the development of targeted resources (for women and for healthcare providers), based on a health literacy and culturally appropriate approach, will address knowledge gaps about HPV.

## Study Objectives and Purpose

**Primary objectives**

1. To determine the self-sampling participation rate in Māori women.
2. To determine the follow-up rate for hrHPV-positive women.
3. To determine the prevalence of hrHPV positivity (including genotype) and the associated colposcopic findings.

**Secondary objectives**

1. To determine the level of support needed to achieve at least 90% follow-up of hrHPV-positive women to attend a primary care smear taker or colposcopy.
2. To determine the knowledge and attitudes to HPV for Māori women and healthcare providers.
3. To determine various feasibility issues, including:

* What preference women have for invitation, sample return and follow-up methods.
* What are the education needs of health professionals regarding HPV, self-sampling and results management.
* Are the level of information in the printed material appropriate and acceptable to Māori women, and are further localisation or refinement required.
* What are the provider perspectives on self-sampling, discussing HPV with women, and managing samples and results.
* What invitation approaches are available and which are most successful and preferred by women.

### Study Design AND PROCEDURES

This is a single-arm feasibility study design screening 200 Māori women in West Auckland.

* + 1. **Partnership**

We will further develop existing relationships between study investigators, staff, Te Whānau o Waipariera (WOW), the relevant general practices in West Auckland, and the colposcopy service at Auckland City and Waitakere Hospitals.

* + 1. **Provider education**

Health Literacy New Zealand has been contracted to develop a healthcare provider education session for participating general practices and WOW community health worker and nursing staff. The educational model is based on a successful train-the-trainer model developed for a recent cervical screening initiative designed to safely involve administrative staff in invitation and recall activities. The education package will be delivered with clinical oversight from the study research nurse.

* + 1. **Materials development and Focus Group testing**

With permission from the iPAP investigators, iPAP materials for women have been localised and redeveloped into a brochure Participant Information Sheet. Health Literacy NZ has been contracted to perform this localisation which includes review for health literacy and cultural appropriateness, and inclusion of key messages related to iPAP and other qualitative research on self-sampling (e.g. addressing women’s concerns of not performing the test correctly and highlighting that HPV testing is not a test of fidelity). The test kit instructions are also being localised. The brochure (including different options for graphical design) and instructions will be focus group tested with 24 under-screened or unscreened Māori women (who will also be offered participation in this research study or usual care screening if they would like to), and the materials revised based on this feedback.

* + 1. **Focus group process**

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| Karakia/welcome | Explanation of the HPV self-testing research and the focus group process. |
| Consent to the focus group | Go through this information sheet with the research team and answer any questions. Ask for your verbal consent to participate in the focus group. |
| Looking at the self-test research study information | The research team will show the information we plan to give to women for the self-testing study and will ask questions on this information. |
| Looking at the self-test kit | The research team will show the self-test kit and the instructions and ask questions on these. |
| Offer of cervical screening  OPTIONAL | At the focus group women can choose:   1. To do a self-test at the focus group 2. To do a usual cervical screening test (also called a *smear* or *pap* test) at the focus group with one of the research nurses 3. To do either a self-test or have a cervical screen at a future date with the research nurse or your usual nurse or GP 4. Have no cervical screening test done   There will be private rooms or bathrooms available at the focus groups for this purpose.  This is completely voluntary and women do not have to have any testing done at the focus group. Women can still to be part of the focus group and not do any kind of tests. |
| Kai |  |
| Questionnaire | Completion of the questionnaire. This is the same questionnaire that will be part of the self-test research and we hope to find out if Māori women find the test acceptable, and how they might prefer to be tested in the future. Questions about the questionnaire (understanding, readability). |
| Come back to focus group hui | For further discussion and feedback |
| Karakia / koha | Women are offered a $50 voucher for their time and sharing their experience. |

Approximately time commitment is 1.5 hours, with the addition of any appropriate follow-up.

The research nurse (registered smear-taker) will be responsible for the management of results for the focus group women rather than the GPs in the main study, this will be facilitated through the Independent Service Provider (ISP) Well Women and Families Trust (WWFT).

* + 1. **Questionnaires**

We have obtained permission from the Australian iPap study investigators[37](#_ENREF_37) and the investigators of a validated knowledge and attitudes questionnaire (for providers[40](#_ENREF_40) and for women[41](#_ENREF_41)) to localise the material into a knowledge and acceptability questionnaire for women. This will be focus group tested as part of the materials testing above. The provider’s knowledge questionnaire (which already has ethical approval from Massey University Institutional Committee, and is already in use with providers in the Auckland and Wellington regions) will be completed with different health disciplines within Primary care before the recruitment of women commences.

* + 1. **Invitation**

Permission by three local Primary Health Organisation (PHOs) has been granted for study participation to recruit women. The PHOs have each identified three practices each in the West Auckland area with high Māori enrolment, low cervical screening coverage/high numbers of under-screened or unscreened Māori women. Further collaborative work will be undertaken with the individual general practices involved in terms of current cervical screening invitation and recall activities, and a flexible approach to working with each practice will be negotiated.

In partnership with the nominated general practices, we will identify eligible Māori women who have never been screened or are overdue for a screen (according to NCSP guidelines[42](#_ENREF_42)). Because of the high prevalence of transient HPV infection in women aged <30 years (e.g. 69% in New Zealand women aged <30 years),[10](#_ENREF_10) the age range for our study is set at 30−69 years, to minimise unnecessary colposcopy procedures in younger women and to avoid self-sampling being the first contact for cervical screening. A considerable number of Māori women aged ≥30 years are never- or under-screened, and our inclusion age range is not expected to impact recruitment.

Women will be identified through a routinely available national data-match process between PHOs and the NCSP, where enrolled and eligible women’s screening status is updated monthly. All PHOs have access to this data, and some use it regularly. Recruitment from these lists is highly preferred for participation in this research project, however if recruitment is slow then the investigators will consider approaches for women not currently enrolled with a PHO or who may be recruited via Māori Providers or Independent Service Providers (ISPs) eg Well Women and Families Trust (WWFT).

Those PHOs that do not currently use the lists will be supported to access the lists to have a standardised tool (based on the NCSP-register as the ‘source of truth’) for identification of appropriate women. The invitation process will be managed by the general practice with support from the research nurse or ISP (ISPs are contracted to provider outreach support to service (invitation, screening or colposcopy)).

General practices have indicated that they would like the offer of the research nurse to contact women. This would allow standardised high quality information for women to make the decision to attend clinic and talk through the study further and participate or not. It would also allow sufficient time to answer women’s questions if she has any. Practices nurses and General Practitioners (GPs), even though they will be trained via this project, may not have the capacity, time or ability to engage women at this critical early stage. The co-investigators for the project consider informed consent to be fundamental, and would like to invest time early in the research pathway to ensure this.

Approval from the Health and Disability Ethics Committee (HDEC) will be sought for the research nurse to contact participants because this is technically considered to be un-consented release of contact information. Standard management would be to ask practices to invite women, and for women to contact the researchers directly or to get permission to pass contact details on to the researchers. As this study is about an approach reduce participation barriers for cervical screening, the co-investigators believe that these additional steps would create barriers, and are therefore seeking approval for the release of this information.

* + 1. **Consenting and test kit**

Women will be invited to participate in the study and attend a clinic. It is estimated to be approximately a 30 minute time commitment (plus follow-up if required). In a private space the research nurse will explain *kanohi ki te kanohi* (face to face) the study and discuss the Participant Information Sheet (brochure) and consent form, and answer any questions. If the woman consents the research nurse will explain the test kit and pictorial instructions, and note that there is a questionnaire to go through afterwards. A study number will be assigned and study testing barcodes and forms prepared.

The woman will have the option of taking the test kit home (and returning it to the clinic) or performing the test at the general practice rooms (e.g. in the bathroom or private room) and return the kit to the research nurse.

The research nurse will then read the acceptability questionnaire and record the answers, or alternatively the woman can complete the questionnaire on paper or take it home.

* + 1. **Test device**

The study will use the Roche CTNG test kits together with a single sterile Copan flocked swab (511CS01). The liquid in the Roche tubes is a lytic guanadinium hydrochloride saturated buffer (hazardous) which stabilises the sample and allows storage at room temperature for up to 6 months.

This test kit is compatible with the cobas 4800 instrument for running the cobas HPV Test and has been validated by the large PAVDAG study in Scotland**.**[**29**](#_ENREF_29)

The usual swab provided is a Dacron tipped wound swab and this will be replaced by the copan flocked swab, which has been shown to increase both the pick up and release of cellular material.

Together the Roche CTNG tube and the copan flocked swab will be placed in a study specific specimen bag labelled clearly for the study.

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* + 1. **Sample Collection**

Women should be advised to follow instructions provided which are as for the Roche protocol for obtaining a self taken vaginal sample using the CTNG kit. The formal test kit instructions are below. These are being formulated into a visual pictoral instruction set, localising similar instructions from chlamydia self-sampling research and the iPAP study test instructions. These will be focus group tested as per the other study materials.

**VAGINAL SWAB SPECIMEN- SELF-COLLECTION TEST KIT FORMAL INSTRUCTIONS**

**These will not be used in the study but are the basis for the pictorial instruction card**

Preparing for Sample collection:

* Undress to expose the vaginal area
* Put yourself in a comfortable position
* Remove the collection tube and one swab from the collection kit, discard the second swab.

How to self-collect a vaginal swab sample:

1. Position: Hold the swab in one hand and with the other hand separate the folds of skin around the vaginal opening (labia).

2. Collect: Insert the swab about 5cm into the vaginal opening. Gently turn the swab for about 30 seconds while the rubbing the swab against the wall of the vagina. Remove the swab carefully. Do not touch the swab to any surface before placing it into the collection tube.

3. Open tube: While the holding the swab in the same hand remove the cap from the tube as shown in the diagram.

4. Align: Lower the swab into the tube until the visible dark line on the swab shaft is lined up with the tube rim. The tip of the swab should be just above the liquid in the tube.

5. Break: Carefully lean the swab against the tube rim to break the swab shaft at the dark line; discard the top portion of the swab.

6. Close: Tightly close the cobas PCR Media tube. Return the sample to your healthcare provider.

CAUTION: The collection tube media can cause irritation if contacted with skin or other body parts. Handle the collection tube carefully. Do NOT pre-wet the collection swab with the media or any other liquid before obtaining the vaginal sample. Use care to avoid splashing contents of the tube. If the contents of the tube are spilled on your skin, wash the affected area with soap and water. In case of eye contact, flush with water immediately. Notify your healthcare provider.

Once samples are collected, the tubes will be checked by the research nurse for correct labelling and then placed in a biohazard bag together with a laboratory test request form and be placed in the courier pickup area. Samples can be stored and transported at room temperature.

* + 1. **Laboratory testing**

**Test Request Forms**

Auckland Pathology Services will develop a specific request form that is clearly labelled as belonging to the HPVSS study. Information required on this form includes:

* at least 3 identifiers: first name, last name, DOB and NHI
* Name of nominated primary carer and address for results
* Instructions to test the yellow capped tubes for HPV ONLY, DO NOT TEST FOR CHLAMYDIA OR GONORRHOEA

On arrival in the laboratory, the study samples should be entered in the LIMS and go on the next available batch of HPV testing on the cobas 4800. Samples can be stored at room temperature up to 25C for up to 6 months.

**Testing**

All samples will be tested for the presence of hrHPV using the clinically validated cobas 4800 HPV assay[43](#_ENREF_43) (Roche Molecular Systems, Pleasanton, CA, USA) at LabPlus, Auckland City Hospital. LabPlus performs cytological services within the current NCSP programme under the NCSP quality assurance parameters and usual laboratory results reporting mechanisms. The cobas 4800 HPV assay is approved by the US FDA for primary HPV screening (other HPV DNA assays are approved for use in conjunction with cytology),[44](#_ENREF_44) fulfils the NSCP criteria for HPV testing,[45](#_ENREF_45) and has been selected by the Netherlands for primary HPV testing.[46](#_ENREF_46) This assay specifically detects HPV types 16 and 18, and 12 other hrHPV types concurrently as a group.[44](#_ENREF_44) The protocol for testing self-taken swabs on the cobas HPV test is not validated by the manufacturer (Roche) and is based on the findings of the PAVDAG study (see above for reference). On receipt in the laboratory, samples should be vortexed for at least 30 seconds prior to decapping and loading in swab sample carriers on the cobas 4800. Samples will require batching as it is not possible to use both swab and liquid based cytology vial carriers in the same run. The cobas HPV test is then run according to the manufacturer’s instructions. Testing will be timely, and in accordance with the turnaround times specified by the NCSP OPQS. Results will be reported to both the study coordinator and the nominated primary care giver with a copy to the NCSP register.

Samples will be stored for the required length of time as per quality assurance requirements by the laboratory. They will then be destroyed as per usual laboratory processes.

* + 1. **Results management**

*Negative results* will be provided to women even if the routine practice approach is not to provide negative results. Women will be asked their preference for receiving this result (e.g. a letter or phone call). Negative result communication will be provided with advice to return for a routine cervical screen at the appropriate clinical interval, according to NCSP guidelines and proposed HPV primary screening algorithm.[42](#_ENREF_42)

*Positive results* will be provided to women *kanohi ki te kanohi* (face-to-face) by their usual primary care/provider or the research nurse. Positive results management indicated in the proposed HPV primary screening algorithm (below, similar to the management approach in the iPap study[47](#_ENREF_47)) will be used. Approval for this approach has been indicated verbally from the NCSP, however approval will be sought formally.

* Women who are positive for HPV 16 or 18 will be referred directly to colposcopy.
* Women who test positive for the group of 12 other hrHPV types will be triaged (at no cost to the woman) in the current standard process (i.e. with speculum examination and cervical sampling, with cells assessed by Liquid Based Cytology (LBC)) by the women’s usual smeartaker or an alternative smeartaker if she prefers (for example an ISP or Family Planning). Women with positive LBC results will be referred for colposcopy; women with negative LBC results will be referred for management by their usual primary care/provider team for a repeat test in 12 months (see NCSP algorithm overleaf).

Support to screening and support to colposcopy will be provided.

**Figure 2. Proposed NCSP Primary HPV Screening algorithm**

Women’s participation in this feasibility study will be recorded on the NCSP register (research flag) for additional safety and follow-up, as per the Compass study protocol.[48](#_ENREF_48) Women will be advised of this in the Participant Information Sheet (brochure) and this will also be discussed verbally by the research nurse.

Although test results will be managed by the women’s usual care provider, our research nurse will monitor positive results and provide a failsafe follow-up process. If follow-up with a primary care/provider visit does not occur within ten days (the interval selected in the bowel screening pilot currently being conducted at Waitemata DHB), the research nurse will work with the general practice and the ISP to ensure that women are notified and offered support to attend appropriate follow-up.

* + 1. **Follow-up committment**

Our study is committed to follow-up ≥90% of women who test positive for HPV. Our study cohort is expected to comprise hard-to-reach women, who are at greater risk of developing cervical cancer. In partnership with the colposcopy service, ISPs, and community health workers, we will provide all appropriate support (e.g. assistance with transport, child care, visit attendance support) to ensure that women with a positive HPV result will be followed-up.

Having received information that HPV increases the risk of cervical cancer as part of the informed recruitment process, women with a positive HPV result have been demonstrated to have high rates of follow-up (as observed in the iPap study).[49](#_ENREF_49) A 100% follow-up rate may not be achievable as we respect a woman’s right to make an informed choice to refuse a follow-up speculum examination.

We will resource and measure the support-to-service requirements (type of support and resource needed) for positive results management as part of the study to inform resource requirements for any future programme. There will be no charge to women for support-to-services.

* + 1. **Colposcopy management**

*Reimbursement:* The study will fund $272.30 current price for colposcopy visit for any colposcopy attendances. Although any work that aims to increase coverage, particularly for NCSP priority women, will be likely to increase colposcopies and would not be expected to pay for those colposcopies. However the co-investigators recognise that this research is outside of the NCSP current programme and that there will be additional paperwork required (Case Report Form) by colposcopists for the small number of women expected (positivity rate 6-8%, with 2% 16/18 positive in the iPAP study, therefore estimate 6-8 women in each DHB requiring colposcopy).

*Referral Process:* Referral to the colposcopy clinic will occur through the usual referral process either electronically or via paper referral. The research nurse can advise the colposcopy clinic of any new referrals coming through. Referrals will be entered into the colposcopy database to ensure the referral data is electronically messaged to the NCSP register as per the current referral process.

*Timeliness of Assessment:* Women referred to the colposcopy clinic that are positive for HPV 16 or 18 will be seen within 20 working days. Women with a positive other hrHPV and cytology >ASC-H/HSIL will be seen within 20 days of receipt of referral as per the current NCSP guidelines. Women who have a positive hrHPV following follow up of hrHPV other and ASCUS/LSIL cytology will be seen within 20 working days.

*Colposcopy Management:* Women referred with a positive HPV for 16 or 18 will have cervical smear taken at the time of their colposcopy visit to avoid the requirement of a cervical smear in primary care prior to referral. Case report forms will be developed to capture clinical history, colposcopy findings and results and any subsequent treatment / follow up visits. Each case will be entered into the colposcopy database so the NCSP register receive HL7 messages relating to the woman’s care and ensure appropriate follow up mechanisms. Dependent on the results women will be managed as per the draft NCSP guidelines. In any instances where there is a discrepancy with results the case will be reviewed at the colposcopy multidisciplinary meeting.

*Management of Non-Attendance:* If women do not attend their colposcopy appointment the research nurse will be notified of the non-attendance and will arrange follow up with the project support to service provider. As per usual care hospital processes women will be sent a text reminder and a letter explaining the importance of attendance as per current colposcopy clinic practices. If the woman does not attend her second appointment the colposcopist will write to the woman (with a copy to referring practitioner) advising of the importance of attendance and the recommendation of being re-referred to the service for assessment as per current clinic process. Non-attendance will be documented in the colposcopy databases so the NCSP register receive HL7 messages relating to the woman’s care and ensure appropriate follow up mechanisms. A study completion form will be developed to capture women who do not attend and discharged back to their primary care provider and provided to the research nurse.

* + 1. **Evaluation**

Our partner organisation Te Whānau o Waipareira has been contracted to conduct the evaluation of this study. A process and short term impact evaluation will be conducted, focusing on improvements and key learnings to inform the HRC funded study and policy implications. An evaluation framework is being developed and key performance indicators.

The evaluation will include document review, analysis of de-identified quantitative data, questionnaire data and further qualitative analysis. This will include key informant interviews and/or small focus groups with health professionals and Māori provider(s), and may involve a small number of interviews or focus groups with study participants. This will be an optional component of study consent (re-contact for evaluation).

* + 1. **Sample size**

There are just over 5,000 Māori women in Auckland DHB and Waitemata DHB combined who have never been screened or who are overdue for screening.[4](#_ENREF_4) Many of these women reside in West Auckland. This feasibility study requires a sample size that is practical to recruit and sufficient to inform the feasibility issues. We have selected 200 women screened for pragmatic reasons – this would allow a sufficient sample to test positive results management at each DHB. We anticipate that recruiting 200 Māori women (across both Auckland and Waitemata DHBs) would achieve this and contribute to improving cervical screening coverage. Part of the study question is how many women we will need to invite to achieve 200 women screened; based on iPAP experience (20.3% for a mail out kit) we anticipate that we might need to invite approximately 1,000 women from 3-9 general practices.

* + 1. **Data analysis**

All women will be given a study identification code and all data will be deidentified for analysis. Test results will be provided to the NCSP register as per usual laboratory reporting and this will be maintained in an identifiable manner as all research involving NCSP participants is required to do (and women will be notified of this as above). We will report the percentage and genotype of hrHPV positive samples detected in the feasibility study, and document the pathway to follow up for hrHPV positive women. We will report the questionnaire findings with descriptive statistics, and the interviews/focus groups with thematic analysis. Time for return of sample will be recorded at the laboratory as an indicator of sample integrity (samples are stable at room temperature for up to seven days).

* + 1. **Procedures table**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Pre study** | **Initial visit** | **Results** | **Follow up of positive results** | **Evaluation** |
| Initial contact and invitation by the practice | **X** |  |  |  |  |
| Clinic visit and consent |  | **X** |  |  |  |
| Perform self sample test |  | **X** |  |  |  |
| Post-test questionnaire |  | **X** |  |  |  |
| Return of results |  |  | **X** |  |  |
| Smear or colposcopy |  |  |  | **X** |  |
| Support to service |  |  |  | **Optional** |  |
| Further qualitative research |  |  |  |  | **Optional re-contact if required** |

* + 1. **Criteria for discontinuation of the study**

This is a low risk intervention therefore discontinuation is not anticipated. However if a serious adverse event was recorded this would immediately be investigated and the decision for termination taken by the co-investigators.

### 2.2 Definition of End of Project

When 200 participants are recruited.

## SELECTIon AND withdrawal of participants

### Participant Selection and ELIGIBILITY

1. Participants will be recruited from the following general practice clinic populations in West Auckland:

* East Tamaki Healthcare PHO
* National Hauora Coalition PHO
* ProCare PHO (if required)

1. Participants will be Māori as identified by the PHO age-sex register (ethnicity will not be sought from the NCSP-Register) on the routine datamatched lists.
2. Participants will be under-screened (overdue for screening) or never-screened, as determined by the NCSP-Register identified on the routine datamatch lists.
3. Participants will be Waitemata DHB or Auckland DHB residents (domicile code).
4. Participants will be aged 30-69 years.

### ExclusionS

1. Women who have had a benign total hysterectomy will be excluded as per NCSP guidelines.
2. Women who are pregnant.

### Withdrawal

Women are able to withdraw from the study at any time for any reason without impacting on medical care. If a woman tests positive for hrHPV and then elects to withdraw, the potential risk of this will be discussed with her by the research nurse, and she will be strongly encouraged to see a health professional and attend follow-up outside of the study. Withdrawal can be verbal, by phone or in writing. The woman will be notified that her data up to that point in time will continue to be processed, but no new data will be collected. Data cannot be removed from the NCSP register unless the woman elects to withdraw from the NCSP programme.

## ethical and Cultural considerationS

There are a range of ethical cultural issues, including informed consent, tapu, privacy and confidentially, sampling and storage of tissue, and data ownership involved in this study. Our research group contains significant research expertise with Māori health, kaupapa Māori methodology, research with women and in cervical screening specifically. These issues have been discussed within the research group and with our Māori advisors as part of our peer review process.

Although a range of views is held by Māori regarding te whare o te tangata (reproductive organs) in contemporary Aotearoa New Zealand, in general, te whare o te tangata is considered to be tapu. Training will be required for all staff involved in discussion with Māori women. Women’s information will be protected (each will be assigned a study identification code and deidentified in the study records) and the information held on the NCSP register will be cared for under the usual protections (the National Kaitiaki Group is responsible for approving the release of aggregate Māori data from the NCSP register).

Whakamā may be an issue for some women in this study, and appropriate ways to approach women will be co-designed with each provider; a range of strategies are likely to be required.

There is also the issue of stigmatisation (e.g. a deficit focus for never-screened/under-screened women); however, this study seeks a strength-based approach of enabling women access to novel technologies to enhance their wellbeing.

The request for HDEC approval of the disclosure of non-consented contact details for invitation by the research nurse has been noted above, and is discussed specifically in the HDEC application form and cover letter.

## Clinical Safety

All adverse events will be assessed for seriousness by the research nurse or GP immediately.

A serious adverse event (SAE) is any adverse event that occurs, having received the study invention that results in any of the following outcomes:

* Death
* A life-threatening adverse event
* Inpatient hospitalisation or prolongation of existing hospitalisation (with the exception of being in hospital when giving birth)
* A disability/incapacity
* A congenital anomaly in the offspring of a participant

No serious adverse events directly attributable to the HPV self-sampling are anticipated.

### Potential risk with exposure to liquid sample medium

There is a small risk of skin/mucosal irritation from the liquid sample medium if a women dips the swab into the medium before self-sampling. This is emphasised in the visual material and verbal instructions to women before testing.

Risk of spill and cleanup. Provider education package will identify this risk.

The buffer in the cobas sample tube is classed as an irritant hazard as it contains a high concentration of the salt guanidinium hydrochloride. Therefore it should not be allowed to contact skin or mucous membranes and in the event of that happening the area should immediately be flushed with clean water to remove the contamination. It is important that any spills should be first soaked up with paper towel or other absorbed material before applying a NON-BLEACH disinfectant (such as Trigene, Virkon or ethanol) to the surface.

IMPORTANT

Combining bleach with the sample buffer will cause release of toxic chlorine gas which is a hazardous respiratory irritant. Avoid the use of bleach or other hypochlorite based cleaning products. These instructions will be a specific part of the provider education package, and women will also be told.

## 6. confidentiality

Each participant will be assigned study identification code number, for use on questionnaires and other study documents and in the electronic database.

Results will be kept in an electronic database on the Waitemata DHB hospital server protected by DHB firewalls and password protected. Only the research nurse, research coordinator and study clinicians (GP, smeartaker, colposcopists) will see identifiable results, all other study data will be deidentified for reporting.

As noted previously identifiable trial results (HPV, colposcopy, histology) will be kept on the NCSP-Register indefinitely as is required for all research in NCSP enrolled women, for their clinical safety and follow up. This is appropriate and required as women will be returned to usual care after the study is completed.

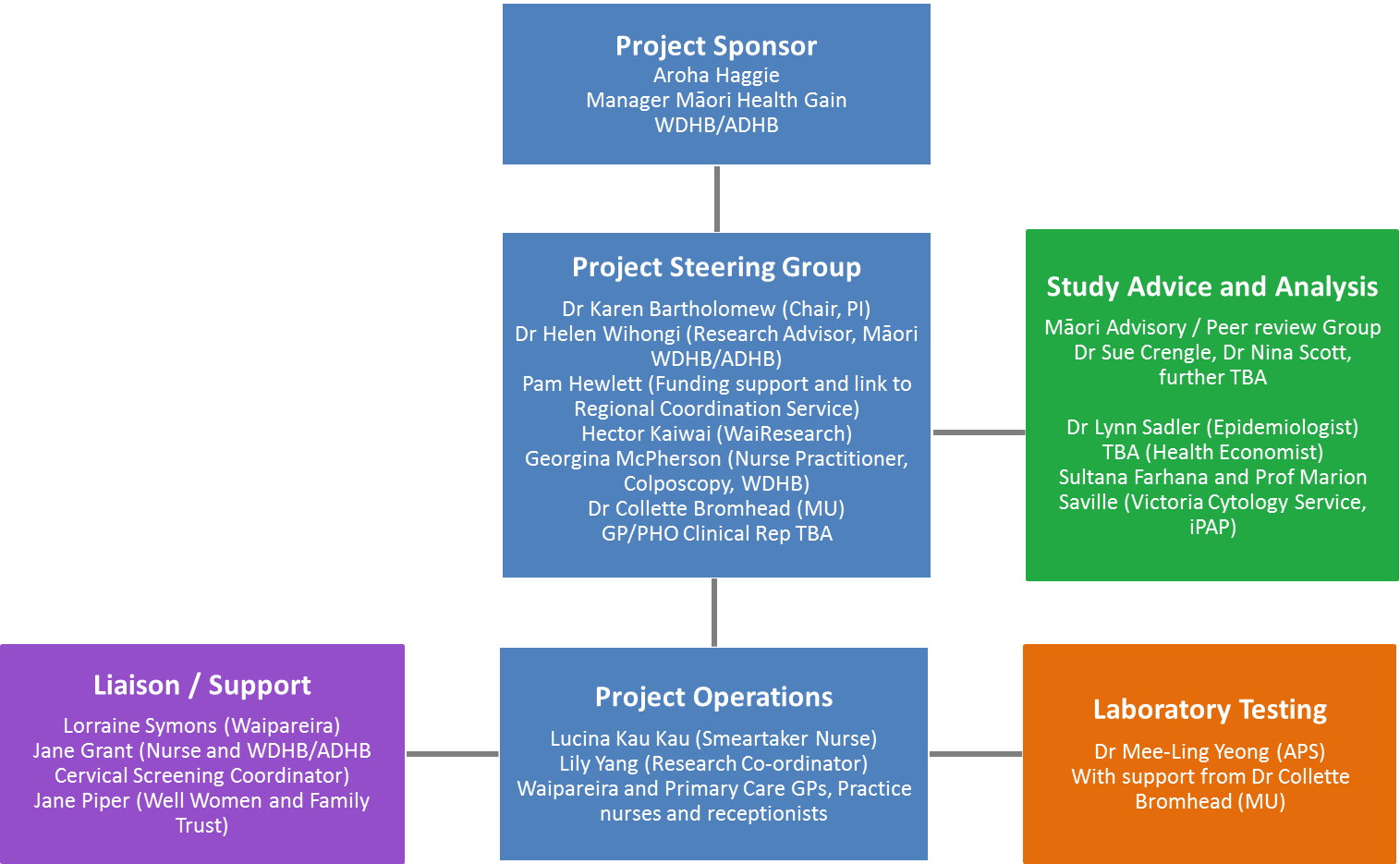
## 7. study Governance

The trial will be conducted in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH-GCP) and the applicable regulatory requirements including Health and Disability Ethics Committee approvals and requirements. The principal investigator and research coordinator are GCP trained.

The project and the activity of the operations group is governed by a project Steering Group (see the schematic below).

### 

### 7.1 PROJECT STRUCTURE SCHEMATIC



### Research team roles and responsibilities

| **Team member** | **Organisation** | **Role in Feasibility project** | **Functions and time commitment** | **Qualitative or quantitative expertise** | **Clinical** | **Māori health/ kaupapa Māori expertise** |
| --- | --- | --- | --- | --- | --- | --- |
| **Governance** | | | | | | |
| Karen Bartholomew | ADHB/WDHB  Public Health Physician  Māori Health Gain Team/Child, Women and Youth Team, Chair Metro-Auckland Cervical Screening Advisory Group | Principal Investigator  Chair Steering Group | Estimated 0.2FTE contributed in kind  Lead protocol development, oversee implementation and analysis of the study | Qualitative  and  Quantitative |  |  |
| Helen Wihongi | ADHB/WDHB Research Advisor – Māori | Steering group member  Chair Māori Advisory / Peer Review Group | Involvement in development and delivery of project, ensuring the project is culturally appropriate, relevant and has benefit for Māori | Qualitative  and  Quantitative |  |  |
| Tanya Allport | Te Whānau O Waipareira Trust, Director of Research and Evaluation;  Collaborating organisation | Steering Group Member | Involvement in development and delivery of project, ensuring the project is culturally appropriate, relevant and has benefit for Māori women in West Auckland | Qualitative |  |  |
| Georgina McPherson | Waitemata DHB Women’s Health Nurse Practitioner, Colposcopy Clinic | Steering Group Member and oversight clinical management of HPV results. Management of discordant results via MDT | Clinic attendance of study participants and meeting attendance | Qualitative  and  Quantitative |  |  |
| Dr Collette Bromhead | Massey University,  Senior Lecturer Molecular Microbiology, HPV expert | Steering Group Member and involved in sample testing with Dr Yeong | Contribution FTE in kind for protocol development, study analysis and sample testing assistance as required | Qualitative  and  Quantitative |  |  |
| GP Rep TBA | PHO/General Practice Rep | Steering Group member | Provide general practice advice to assist in protocol development and study implementation |  |  |  |
| Aroha Haggie | ADHB/WDHB  Māori Health Gain Team Manager | DHB Project Sponsor  Funder | Meeting attendance and document review  Project sign-off  Budget approval |  |  |  |
| Pam Hewlett | ADHB/WDHB Women’s Health Funding Manager, Chair Metro-Auckland Cervical Screening Operations Group | Steering Group Member  Funder | Estimated 0.1FTE contribution in kind  Relationship management with collaborating organisations and other relevant groups (e.g. PHOs, primary care governance groups, NSU etc.) |  |  |  |
| **Operations** | | | | | | |
| Lily Yang | Waitemata DHB | Research coordinator  (project manager) | 0.4FTE  Document preparation, project management, results oversight and maintenance, reporting |  |  |  |
| Lucina Kaukau | Waitemata DHB | Research smear-taker nurse | 0.4FTE  Invitation and consent of women  Results follow up and support-to-service/ colposcopy clinic liaison as required |  |  |  |
| Jane Grant | Waitemata DHB and Auckland DHB cervical screening coordinator | Liaison  Smear-taker nurse | Liaison between PHO/general practices and collaborating partner organisations, research co-ordination where required |  |  |  |
| Ngaire Harris and/or  Lorraine Symons | Te Whānau O Waipareira Trust, DHB Relationship Manager | Liaison  ISP | Liaison between Waipareira and collaborating partner organisations  Support-to-service if required |  |  |  |
| Jane Piper | Well Women and Families Trust (WWFT) | Liaison  ISP | Host Research coordinator role  Support-to-service (screen or colposcopy)  Project support |  |  |  |
| Mee-Ling Yeong | Auckland Pathology Service, ADHB | Laboratory Testing | Processing and reporting HPV samples for the study | Quantitative and qualitative |  |  |
| Primary care staff TBA | East Tamaki Healthcare  National Hauora Coalition  ProCare |  | Direct interaction with women as per the study protocol |  |  |  |
| **Study Advice and Analysis** | | | | | | |
| Dr Sue Crengle | Primary Care  Invercargill | Māori Health and screening expert advisor | Māori Advisory / Peer Review Group |  |  |  |
| Dr Nina Scott | Waikato DHB | Māori Health and screening expert advisor | Māori Advisory / Peer Review Group |  |  |  |
| TBA |  | Advisory | Māori Advisory / Peer Review Group |  |  |  |
| Prof Marion Saville | Executive Director Victoria Cytology Service, Melbourne, Australia; co-principal investigator of the iPAP | Advisor | Advice on study design and research protocol, peer review of findings and report writing | Quantitative and qualitative |  |  |
| Lynn Sadler | ADHB, Women’s Health Intelligence | Advisor and analysis | Advice on study design and research protocol, oversight of analysis and report writing | Quantitative |  |  |
| TBA | ADHB/WDHB Health Gain Team, Health Economist | Economic Analysis | Advice on collection of cost data and assistance with analysis | Quantitative |  |  |

### 7.3 Sponsor/Funding

The study is funded by an Awhina Charitable Trust grant, Waitemata DHB and Auckland DHB. The named sponsor is:

Dr Debbie Holdsworth

Director Funding

Planning, Funding and Outcomes

Waitemata DHB and Auckland DHB

### 7.4 Conflict of Interest

|  |  |  |
| --- | --- | --- |
| Investigator | Conflict of interest | |
| None to declare, or | Details |
| Dr Karen Bartholomew |  | Employee Waitemata DHB and Auckland DHB  Current Chair, Metro Auckland Cervical Screening Governance Group (MACSGG) |
| Dr Helen Wihongi |  | Employee Waitemata DHB and Auckland DHB |
| Ms Georgina McPherson |  | Employee Waitemata DHB |
| Dr Mee Ling Yeong |  | Employee Auckland DHB |
| Dr Collette Bromhead |  | Employee of Massey University |
| Ms Ngaire Harris |  | Employee of Waipareira |
| Dr Tanya Allport |  | Employee of Waipareira |

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