Comparison of two invitation-based methods for Human Papillomavirus (HPV) self-sampling with standard recall for usual care among un- and under-screened Māori, Pacific and Asian women: a randomised controlled community trial to examine the effect of self-sampling on participation in cervical-cancer screening

Lay title:
Research into whether women prefer self-testing for HPV instead of going to the doctor/nurse for a smear test

Short title:
Cervical screening HPV self-test

Protocol for a three-arm community randomised controlled trial

Draft Version 2.1

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Protocol version 1.1	08/3/2017	Correct errors in original draft, add further details to draft
Protocol version 1.2	26/4/17	Amend text and add further details to draft
Protocol version 1.3	02/05/17	Further amend text, amend details of study process, and change type of usual care group
Protocol version 1.4	31/05/17	Change of randomisation procedure, minor amendments to text
Protocol version 1.5	14/06/17	Minor amendments to text
Protocol version 1.6	03/10/17	Addition of sub-study, study schematic and

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Protocol version 1.7	19/03/18	Amendments to sub-study & study schematic, further amendments to text, and removal of draft study materials for replacement with final versions
Protocol version 2.0	18/6/19	Updates to main study and sub-study, addition of standard operating procedures
Protocol version 2.1	29/3/21	Addition of co-investigator

Executive Summary

Although overall cervical cancer incidence rates have reduced, Māori women are still twice as likely to be diagnosed, and three times as likely to die from cervical cancer than European/Other women. Nationally, we have low Māori cervical screening coverage (66% for the three years ending 31 December 2016, against a target of 80%). This low coverage has persisted despite local and national initiatives to reduce barriers to screening for women. These longstanding ethnic inequalities in access to cervical screening also exist for Pacific and Asian women (77% and 64% coverage respectively). Auckland and Waitematā, and Hutt Valley and Capital & Coast District Health Boards (DHBs) have coverage rates that are below the 80% target for Māori, Pacific, and Asian women. Approximately 75% of cervical cancer cases among Pacific women in New Zealand have been shown to be in women who have not attended cervical screening. Similarly, 70% of Asian women, and 59% of Māori women diagnosed with cervical cancer were shown to have not been screened. Improving access to cervical screening for Māori women remains a priority for the Ministry of Health and in the Auckland and Waitematā, and Hutt Valley and Capital & Coast DHBs' Māori Health Plans (indicator 4). The National Cervical Screening Programme regional services undertake a coordination role for cervical screening, health promotion, some smear-taking and liaise with key Pacific health providers, in the same way that it does with Māori health providers and Primary Health Organisations. Innovative ways to address access barriers are required.

In the context of the announced change 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 whether the novel technology of self-sampling would improve screening coverage in 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 by a health professional. The sample can be taken at home or in a healthcare setting or even at another appropriate community setting. In a meta-analysis, HPV detection using vaginal self-sampling was found to be as accurate as clinician-sampling, provided that high performing assays were used to test the samples for the presence of HPV.

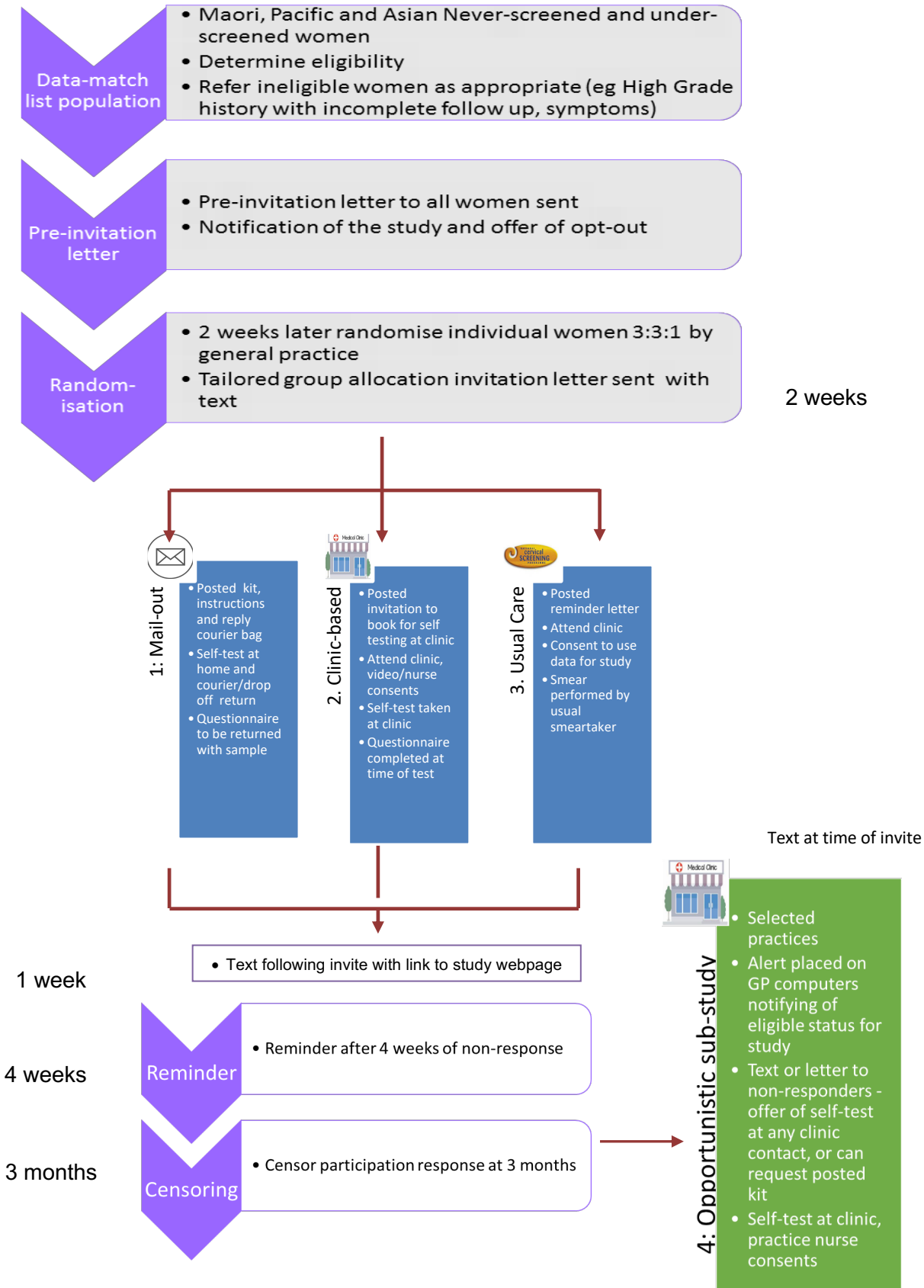
The aim of this Health Research Council-funded study is to examine the acceptability, as measured by screening uptake, of self-sampling in Māori, Pacific and Asian women as the key audience for this novel technology in NZ and to determine pathway requirements to follow-up HPV-positive women. The investigators are committed to health gain and working in partnership with Māori providers, primary care and hospital services. This work purposefully commences with Māori, Pacific and Asian women, to ensure that this novel technology is appropriate and optimised to address inequities before assessing the technology with other groups of women in our population.

Synopsis

Study design	Triple-arm community randomised controlled trial comparing the differences in uptake of cervical-cancer screening (acceptability) between two Human Papillomavirus (HPV) self-sampling invitation methods and usual care, followed by a sub-study of opportunistic offer of self-sampling for eligible women in all three arms (selected practices)
Timeframe	48 months; September 2016 to August 2020
Sample population	Māori, Pacific and Asian women in the Auckland and Wellington sites who have never been screened or who are overdue (≥5 years) for cervical screening
Inclusions	Age 30-69 years, Waitematā, Auckland, Hutt Valley or Capital & Coast District Health Board (DHB) residents
Exclusions	Exclusions as per National Cervical Screening Programme (NCSP) Guidelines, including women: who have had a benign total hysterectomy; who have previously had a high-grade lesion and have not attended for colposcopy in the last five years or have not completed test of cure; who are symptomatic; or who are currently pregnant. Women who are excluded because they are symptomatic or have a previous high-grade lesion without (complete) treatment or completing test of cure will have appropriate follow-up arranged.
Expected sample size	6,999 women invited
Recruitment	Primary Health Organisations' (PHOs) nominated Auckland site and Wellington site general practices
Objectives	**Primary objectives** 1. To determine the self-sampling participation rate in Māori, Pacific and Asian women. 2. To determine the follow-up proportion for oncogenic-HPV-positive women. 3. To determine the prevalence of oncogenic-HPV 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 oncogenic-HPV-positive women to attend a primary care smear taker or colposcopy. 2. To increase participating DHB ethnic-specific coverage for Māori, Pacific and Asian women by 1% within the study. 3. To provide policy relevant findings for the NCSP to facilitate policy development regarding national self-sampling within the next 5 years. 4. To determine some specific acceptability issues, including: • what preferences women have for invitation, sample return and follow-up methods. • whether the level of information in the printed material is appropriate and acceptable to Māori, Pacific and Asian women, and whether further localisation or refinement required. 5. To improve equitable health outcomes for Māori, Asian and Pacific women through the study aim and objectives.
Test device	Single sterile dry flocked swab. Sarstedt 12mL polypropylene dry tubes. Roche Cobas 4800 HPV molecular test.
Results management	HL7 message to NCSP-Register with research flag. • Positive and negative results provided to women • Cytology results provided in standard manner • As per the NCSP clinical guidelines, with a three year follow-up interval for women who test HPV negative • Aim to communicate positive results to women either by phone or face-to-face. • HPV 16/18 positive to colposcopy (note this will require a cytology

	test at the colposcopy visit, therefore 'blind' colposcopy), other oncogenic HPV cytology triage Tailored package of support to services provided.
Required permissions	Ethical approval. DHBs research office approval. National Screening Unit Research and Evaluation Committee, Māori Monitoring and Equity Group, National Kaitiaki Group. Primary Care Clinical Governance Forum (Auckland site), and the equivalent at the Wellington site. PHO Governance or Research approval process.

Study Schematic



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ASC-H	Atypical squamous cells – cannot exclude high-grade squamous intra-epithelial lesion (HSIL)
ASCUS	Atypical squamous cells of undetermined significance
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
HSIL	High-grade squamous intra-epithelial lesion (equivalent to cervical intraepithelial neoplasia 2/3)
LBC	Liquid-based cytology
LSIL	Low-grade squamous intra-epithelial lesion
NCSP	National Cervical Screening Programme
NCSP-R	National Cervical Screening Programme Register
NGO	Non-governmental organisation
NHI	National Health Index
PCR	Polymerase chain reaction
PHO	Primary Health Organisation
SAE	Serious adverse event
STI	Sexually transmitted infection

1. Introduction

1.1. 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 in women who are not screened or who are under-screened.[1] [2] In 2013, cervical cancer was the sixth most common cancer type in Māori women, and cervical cancer registration and mortality rates in Māori women were two-fold and three-fold, respectively, higher than those in non-Māori women.[3] The Pacific populations in New Zealand account for a disproportionately large share of the health burdens from certain disease conditions compared to most other New Zealand population groups.[4] The disease conditions include a number of health outcomes such as cancers that are highly amendable to early detection and prevention, such as cervical cancer.[4]

Approximately 75% of cervical cancer cases among Pacific women in New Zealand have been found to occur in women who have not attended cervical screening.[5] Similarly, around 70% of Asian women, and 59% of Māori women diagnosed with cervical cancer were shown to have not been screened.[5] Pacific women also have a lower uptake of cervical screening with just over half of eligible Pacific women having regular cervical screening compared to over 70% among the total population and over 80% among pakeha/palangi women.[6] [7] The NCSP is concerned about the low cervical screening coverage in Asian women, which was 64% in December 2016, and is working with providers to increase this coverage rate.[8]

In Aotearoa New Zealand there are 20 District Health Boards (DHBs) responsible for the health of their populations. Of these 20, four are part of the current study; Auckland, Waitematā, Capital and Coast, and Hutt Valley. The health target for cervical screening coverage for all DHBs is 80%.[9] Table 1 shows the coverage rates for each of the aforementioned DHBs, for the three years ending 31 December 2016 for Māori, Pacific and Asian women. Overall Māori coverage rates across the four DHBs is demonstrated to be lower than the other ethnicities. However, all the ethnicities are below the national target.

Table 1 – Cervical screening coverage rate in the three years ending 31 December 2016

Ethnicity	Coverage (%)[9]			
	Auckland DHB	Waitematā DHB	Hutt Valley DHB	Capital & Coast DHB
Māori	55.5	59.9	67.9	62.5
Pacific	72.7	74.7	73.1	67.9
Asian	59.2	68.0	74.9	63.8

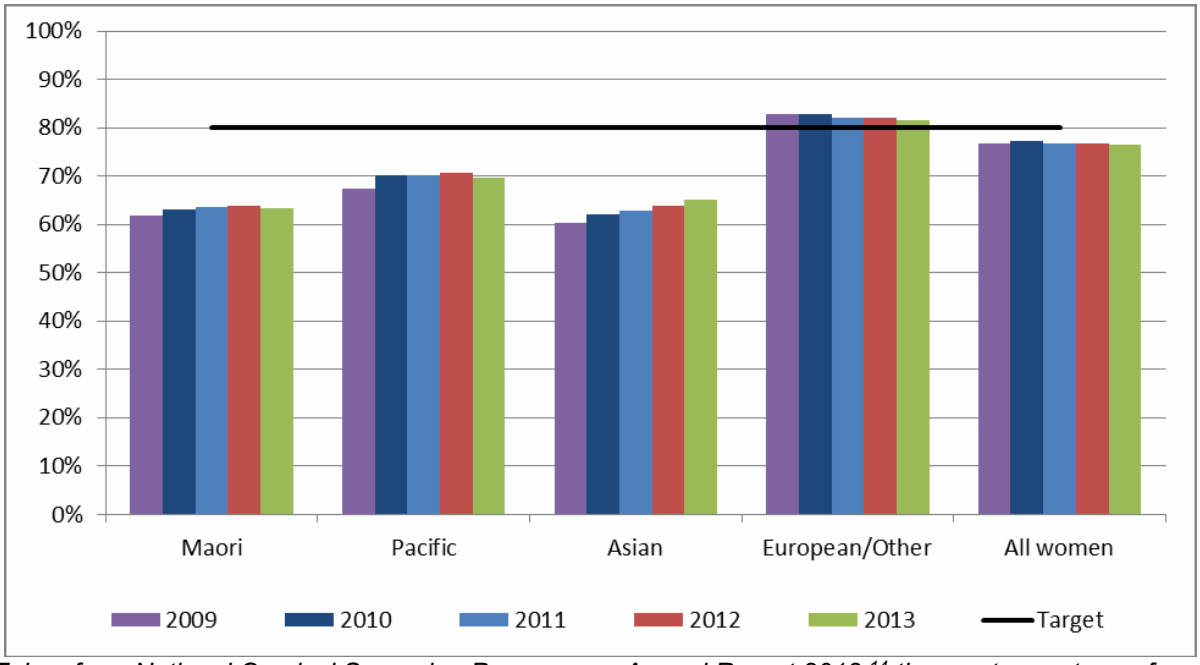
To improve the coverage rates in each DHB more women from each of the ethnic groups will need to be screened (see Table 2).

Table 2 – Additional number of women needed to be screened

Ethnicity	Additional number needed to be screened in order to reach target of 80% coverage			
	Auckland DHB[10]	Waitematā DHB[11]	Hutt Valley DHB[12]	Capital & Coast DHB[13]
Māori	2,496	2,618	679	1,425
Pacific	947	509	176	608
Asian	9,740	4,512	241	2,011

The reasons for low participation in the NCSP include cost, embarrassment, time, inconvenience, language barriers, tapu (for some women the area is considered to be sacred), attitudinal barriers, models of care, health literacy problems, misunderstanding of the appropriate screening age, and discomfort. Actions to reduce these barriers, including no-cost targeted testing ('free smears') and tailored practice-level data-matching with support, have been undertaken across the country; despite these measures there has been very little change in coverage for Māori, Pacific and Asian women 2009-2013 (see Figure 1). Novel strategies are required to change the landscape of cervical screening to ensure that all women benefit from cervical screening.

Figure 1 – Percentage* of women aged 25-69 years screened in the previous three years, 2009 to 2013, by ethnicity



*Taken from National Cervical Screening Programme: Annual Report 2013,[14] the most recent year for which annual data were available. *As a percentage of the hysterectomy-adjusted population in that age-group and year, based on projections from 2006 census population to the end of the relevant calendar year and hysterectomy prevalence estimates at the end of the relevant calendar year.*

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 oncogenic HPV causes virtually all cervical cancers,[15 16] the World Health Organization[17] 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.[16]

The recently published model developed for the NCSP change found that primary HPV screening – with partial genotyping and direct referral of HPV-16/18-positive women to colposcopy and cytology triage for women positive for other oncogenic HPV types; and with 12-month follow-up for cytology-negative and low-grade-cytology results – would be more effective in reducing cervical cancer incidence and mortality and less costly than the current cytology-based screening programme in New Zealand.[18] The strategy was predicted to give a 12-16% reduction in cervical cancer incidence and mortality and to save 4-12% of the total programme costs compared to current practice.[18]

New Zealand has an established HPV vaccination programme protecting young women against the two most important oncogenic HPV types, 16 and 18, which are estimated to cause 70% of cases.[19] From 1 January 2017, the HPV vaccination programme expanded to include all young women and young men, aged 9 to 26."[20] The vaccine that is now used is Gardasil® 9 which protects against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, which are "responsible for around 90 percent of cervical and other HPV-related cancers, and 90 percent [of] genital warts."[21] However, in 2014 (the most recent year for which data seem to be available) a large proportion (40–46%) of young women were not vaccinated[22] and the earlier vaccine, in particular, 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.[23] Therefore, screening remains important in preventing cervical cancer for the foreseeable future.

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 oncogenic HPV management, and acceptability to women.

The goal of this study is to evaluate the acceptability (assessed as the impact on uptake) of HPV self-sampling in the high-priority populations of Māori, Pacific and Asian women. Ultimately, this study 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 based on viral DNA 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.[24] Self-sampling for chlamydia is associated with high accuracy relative to clinician sampling,[25] and is preferred by Māori women.[26]

Vaginal HPV self-sampling is an intervention aimed to simplify the screening encounter and reduce barriers to programme participation.[27] The self-sampling approach has been used in international studies targeting underserved populations who bear a disproportionate burden of cervical cancer.[28-30] Self-sampling approaches are popular and research studies have consistently shown an improved participation rate in cervical screening, including among the least well-served women who have never been screened.[27 31-35] The iPAP trial in Australia, where HPV self-sampling kits were posted to under-screened women demonstrated 20.3% uptake compared with 6% for usual care.[33] Underserved women not only lack access to screening, they have a greater prevalence of oncogenic HPV infection and a higher risk of developing cervical cancer than the general population.[36 37] HPV self-sampling: has been included in in the Australian Renewal primary HPV screening programme to be rolled out in 2017;[38] has been incorporated into the cervical screening programme in the Netherlands for some time; and has recently been introduced in the Capital Region of Denmark.[39 40]

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 by sampling device, sample site (*e.g.* cervicovaginal *vs.* vaginal), and HPV-assay type.[32] 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.[41] A more recent study confirmed these findings (relative sensitivity 0.98 [95% CI 0.95–1.02], relative specificity 1.02 [95% CI 0.94–1.09]).[39] A subsequent study of >5,000 women in Scotland (not included in the meta-analysis) was conducted in the routine cervical screening setting rather than in under-screened populations.[42] In this study (called the PaVDaG study), the accuracy of vaginal self-sampling

was similar to cervical clinician-sampling as measured 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 oncogenic HPV 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]).[42]

Most studies did not compare different sampling devices; however, no statistically significant difference was reported between a brush-based and a lavage-based device for CIN2+ and CIN3+ detection rates (when using a high-performing PCR DNA assay) and user comfort.[43] An inexpensive and low-tech device, the dry flocked swab, had the same accuracy when used for wet or dry self-sampling in Australia.[44]

Internationally, HPV self-sampling has been used with a range of invitation approaches, including in general practice clinics,[30] community-health-worker delivery[31] and by mail.[44 45] A meta-analysis confirmed that a range of delivery approaches are acceptable to under-screened women, that there is improved participation among under-screened women, and that the approach should be tailored to local populations.[46]

There has been international discussion about whether self-sampling is a technology that should be offered to any woman who wishes to take it up or be limited to underserved 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[47] and Australian[48] models suggest that some of the benefits anticipated with offering HPV self-sampling, namely reducing cervical cancer diagnoses and mortality rates, would be lost if large numbers of women who are currently regularly screened (and would have a sample taken by a clinician for the newer HPV test rather than a cytology/Pap smear in the new NCSP) switch from cytology screening to self-sampling. The Dutch analysis, where self-sampling is already offered, reported that self-sampling will be cost-effective if the relative CIN2+ sensitivity and specificity is ≥0.95, unscreened attendees are recruited, and the total attendance increases by ≥6 percentage points, even if all regular attendees switch.[47]

The Australian modelling of 100,000 under-screened women aged 30-84 years found 908 cancer diagnoses and 364 cancer deaths would be averted with self-sampling but that potentially twice that many could have been prevented if the same women joined the mainstream primary HPV screening programme.[48] However, it is unknown what proportion of women might join the mainstream programme from this underserved population and, therefore, whether this comparison is valid (it may be self-sampling vs no participation for a large proportion of this group). Overall, self-sampling is considered to be most efficient and cost-effective if it is used to specifically target underserved women rather than the general population.[39]

In high-resource settings, such as New Zealand, self-sampling is a valid option to be considered, with particular focus on acceptability assessment, logistics, effectiveness in improving coverage (particularly for currently underserved populations such as Māori, Pacific and Asian women), and costs.[41] 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.[39] Although women in studies elsewhere prefer self-sampling over clinician-sampling, some women lack confidence that they can perform the procedure correctly; appropriate and adequate education and support will be needed to address this concern.[49 50]

1.2. Hypothesis

In addition to cost, there are many barriers to cervical screening for Māori, Pacific and Asian women. We hypothesise that access to self-sampling will reduce barriers to cervical

screening, such as cost, opportunity costs, primary care access, previous negative experiences, tapu, and embarrassment[2 51 52], thereby increasing NCSP participation in never- and under-screened Māori, Pacific and Asian women.

1.3. Aim

The aims of this project are: 1) to obtain valid information on the uptake of a new method for HPV screening involving two different self-sampling invitation approaches (mailed and clinic-based) in un- and under-screened Māori, Pacific and Asian women; 2) to estimate the prevalence of oncogenic HPV in these women; 3) to obtain robust information on the resource requirement to achieve 90% follow-up of oncogenic HPV-positive women; 4) to increase participating DHB ethnic-specific coverage for Māori, Pacific and Asian women by 1% within the study; 5) to provide direct policy relevant findings for the NCSP to facilitate national self-sampling policy development within the next 5 years; 6) to contribute to reducing the cervical cancer burden among NZ women through aims 1-5.

1.4. Justification for the study

Early detection, along with high HPV vaccination coverage, is a key intervention to reduce cervical cancer inequalities.[53 32 35] In our Feasibility Study, which is currently underway (co-investigators KB, CB, GMcP, HW), and a qualitative study,[51] Māori women have indicated a preference for self-sampling. In our Pilot study, which is also currently underway (co-investigators SF, NB, JP, JD, CB), Pacific women have also indicated that they would find self-sampling acceptable. The use of a novel HPV self-sampling technology in never- or under-screened Māori, Pacific and Asian women may improve participation (as observed in international studies discussed above) and thus address the burden of cervical cancer in these women.

2. Study objectives and purpose

Primary objectives

1. To determine the self-sampling participation proportion in Māori, Pacific and Asian women
2. To determine the follow-up proportion for oncogenic-HPV-positive women.
3. To determine the prevalence of oncogenic-HPV 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 oncogenic-HPV-positive women to attend a primary care smear taker or colposcopy.
2. To increase participating DHB ethnic-specific coverage for Māori, Pacific and Asian women by 1% within the study.
3. To provide policy relevant findings for the NCSP to facilitate policy development regarding national self-sampling within the next 5 years.
4. To determine some specific acceptability issues, including:
    - what preferences women have for invitation, sample return, and follow-up methods.
    - whether the level of information in the printed material is appropriate and acceptable to Māori, Pacific and Asian women, and whether further localisation or refinement is required.
5. To improve equitable health outcomes for Māori, Asian and Pacific women through the study aim and objectives.

3. Study design and procedures

This is an open-label, three-arm, community, randomised controlled trial, with a nested sub-study. A total of 6,999 un- or under-screened (≥5 years overdue) Māori, Pacific and Asian women (2,333 from each ethnic group) from the Auckland site (Waitematā DHB and Auckland DHB) and Wellington site (Hutt Valley DHB and Capital and Coast DHB) will be invited for screening. The study arms are: usual care in which women are invited to attend a clinic for a standard cytology sample (assessed through NCSP-Register and GP practice records); clinic-based self-sampling in which women are invited to take a self-sample at their usual general practice; and mail-out self-sampling in which women are posted a kit and invited to take a self-sample at home.

There will be a nested sub-study at selected clinics where women in all allocation groups are subsequently opportunistically offered self-testing through their clinic.

5.1. Participant selection and eligibility

1. Participants will be invited from general practice clinic populations in Auckland and Wellington.
2. Participants will be Māori, Pacific or Asian as identified by the PHO enrolment register which is used for the NCSP cervical screening data-match lists.
3. Participants will be under-screened (no screening recorded for the last five years, as per the NCSP guidelines) or never-screened, as determined by the NCSP-Register on the routine data-matched lists. Women who have previously had a low-grade lesion who are more than five years overdue will be eligible.
4. Participants will be Waitematā DHB, Auckland DHB (or Counties Manukau DHB, if necessary), Capital & Coast DHB or Hutt Valley DHB residents, based on their domicile code. Participant addresses (from GP Practice address records) will be geocoded to obtain a domicile code using ESAM and manually where necessary.
5. Participants will be aged 30-69 years.

3.2. Exclusions

Exclusions as per NCSP Guidelines, including women:

1. who have had a benign total hysterectomy
2. who have previously or currently have cervical cancer
3. who are symptomatic (abnormal bleeding, pelvic pain, or symptoms of a sexually transmitted infection).

In addition, women:

1. who have previously had a high-grade lesion and have not attended for colposcopy (remaining at high clinical risk)
2. who have previously had a high-grade lesion and have not completed test of cure according to NCSP guidelines
3. who are currently pregnant
4. not eligible for New Zealand health services
5. not active in clinic (includes women who have transferred to another DHB, a non-participating practice or overseas, and women who were last seen in clinic >3 years ago)
6. other clinical reason (*e.g.* terminal illness).

Women who are symptomatic or who have a history of an untreated/incompletely treated high-grade lesion will be appropriately followed up with primary care, support-to-services referral and the Women's Health colposcopy services to ensure clinical safety.

3.3. Withdrawal

Women will be able to withdraw from the study at any time for any reason without impacting on their medical care. If a woman tests positive for oncogenic HPV and then elects to withdraw, the potential risks involved will be discussed with her by the research nurse; she will be strongly encouraged to see a health professional and attend for follow-up outside of the study, and her primary care provider will be notified. 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.

3.4. Partnership

We will further develop existing relationships between study investigators, the relevant PHOs and general practices in the Auckland site and Wellington site, Independent Service Providers (ISPs), Māori, Pacific and Asian providers, and the DHB colposcopy service at the hospitals.

3.5. Provider education

We (KB, CB, HW and GMcP) have undertaken a self-sampling feasibility study in West Auckland, which was a single-arm study offering HPV self-testing to eligible Māori women. As part of that study, an education session model for participating general practices was developed in collaboration with Health Literacy NZ. 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 content is focused on knowledge about HPV, the study methods and processes, and specifically about general practice responsibilities for results management and the study safety-net. The feasibility study, including the education package, has been evaluated by WaiResearch.

We will use the education package from the feasibility study as the basis for the package in the randomised controlled trial. The education package will be delivered by the research nurse coordinators in negotiation with participating PHOs and general practices, probably at Continuing Medical Education/Continuing Nursing Education (CME/CNE) events, PHO education events or in clinic lunch breaks, as appropriate. Clinics or PHOs may wish to combine sessions. Additional education sessions for community groups, ISPs and others may also be provided, as appropriate. A clinic cannot begin recruiting until education and training of staff has been undertaken and recorded in the training log.

3.6. Materials development and focus group testing

With permission from the iPAP investigators, iPAP materials for women have been localised and redeveloped into a Participant Information Sheet (Brochure) as part of the feasibility study. Health Literacy NZ then conducted three focus groups with target audience Māori women for further specific localisation that includes review for health literacy and cultural appropriateness and inclusion of key messages identified in iPAP questionnaire responses 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 feasibility study, including the study materials, has been evaluated by WaiResearch with a focus on cultural competency. The materials from the feasibility study, which included tailored graphic and wording choices, have been modified for the current study (Appendix 1 – text for study participant information brochure). The consent form (Appendix 2 – laboratory request form and consent form) for the current study is also based on the one that was developed for the feasibility study. The test kit instructions, based on the iPAP instructions

and other self-test sexually transmitted infection instructions, have been developed by the feasibility study (Appendix 3 – test kit instructions) Error! Reference source not found.

Testing and localisation of materials for Pacific and Asian women has also been conducted through Waitematā DHB in two Pacific groups and two Asian groups, which the Auckland site investigators organised with the assistance of Health Literacy NZ, our Pacific and Asian Advisors, and DHB, PHO and non-governmental organisation (NGO) staff. The women invited to participate in the focus groups were from participating clinics and met the study eligibility criteria so were representative of the study's target population. The materials have been revised and finalised based on the feedback from all of the focus groups. A series of video clips designed as an adjunct to the written participant materials have been developed and reviewed by Health Literacy NZ. These videos will be used to provide information to participants and have subtitled key-point translation (into Simplified Chinese, Korean, Samoan, Tongan and Māori). The videos will be used alongside the participant information brochure for consenting of women in all arms of the trial. The Participant Information Brochure (Appendix 1 – text for study participant information brochure), consent form (Appendix 2 – laboratory request form and consent form), and the test-kit instructions (Appendix 3 – test kit instructions) are included in the Appendices. The videos are available on the study webpage: www.waitematadhb.govt.nz/healthy-living/hpv-study/

3.7. Questionnaires

An acceptability questionnaire has been localised based on the Australian iPap study-responders post-test questionnaire[50] with permission from the iPAP investigators (Appendix 5). The questionnaire will be given to participating women in the clinic and mail-out groups.

A separate, short questionnaire will be developed and administered with verbal consent by telephone to a random sample of non-responding women to examine their reasons for non-participation. Approximately 30 women will be contacted, aiming for equal numbers of women of each ethnicity and study group. If further funding/resource (*e.g.* a Masters student) becomes available, further non-participating women may be contacted (*e.g.* up to 100 women).

3.8. Invitation

Once the necessary research, DHB, PHO, and ethical approvals have been obtained, a plan for gaining general practice agreement to participate will be determined with each PHO, prioritised by numbers and coverage for priority populations. Further collaborative work will be undertaken with the individual general practices involved.

In partnership with the nominated general practices, we will identify eligible Māori, Pacific and Asian women who have never been screened or who are overdue for a screen (according to NCSP guidelines[54]), see the draft CONSORT diagram (Appendix 5 – draft CONSORT diagram). Although cervical screening is recommended for all NZ women from age 20,[55] the prevalence of HPV infections in women <30 years is high and most infections clear without causing cervical abnormalities, which reduces the specificity of HPV testing.[55 56] The age range for our study is therefore 30–69 years, to minimise unnecessary colposcopy procedures in younger women, to avoid self-sampling being the first contact for cervical screening among women who might otherwise choose current routine procedures, and to maintain the specificity of the HPV testing. A considerable number of Māori, Pacific and Asian 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 the screening status of enrolled and eligible women is updated

monthly. All PHOs have access to these data, and some use it regularly. Those PHOs that do not currently use the lists will be supported to access them to have a standardised tool (based on the NCSP-Register as the 'source of truth') for identification of appropriate women. Invitations will be from the women's usual primary care provider in partnership with the research team. All of the women who meet the study inclusion criteria will be sent a tailored pre-invite letter briefly explaining the study and informing them that unless they request not to receive an invitation, they will soon be sent either: a) an invitation for cytology (usual care); b) a self-sampling kit (home-based); or c) an invitation to take a self-sample at their GP's clinic (clinic-based). Two weeks after the pre-invite letters have been sent women will be randomised (excluding any who have indicated that they do not wish to receive an invitation), using a computer-generated sequence, to one of the study arms and sent an invitation. At this point women will also be sent a text message from the study and their GP alerting them that an invitation has been sent, including study nurse contact details and a link to the study webpage.

Sending invitations to eligible women will be managed by the research team (research nurse and administration coordinator). In the feasibility study, general practices indicated that they would like the research nurses to contact women. This would allow a standardised approach to the invitation to participate in the study. The Health and Disability Ethics Committee (HDEC) has been asked to, and has approved, a protocol whereby the research nurses contact participants. Technically, this is 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 for the women to give permission for their contact details to be passed on to the researchers. This study is about an approach to reduce participation barriers for cervical screening; the investigators believe that these additional steps would create barriers, not reduce them, and are therefore seeking approval for the release of this information. In addition, with the general practice's permission, there is an exception under the Privacy Act and the Health Information Privacy Code (specifically rules one and 11, and the Health Act Section 22F) for release of information for the defined purpose of the offer of a service with a health benefit. Participating women will be receiving a cervical screen, the HPV test will be recorded on the NCSP-Register with a research flag.

3.9. Consent and sampling kit

Participating women in the usual-care arm of the study who attend will be consented by their usual smeartaker and a cytology sample taken.

Participating women in the self-sampling arms of the study will be asked to take a low-vaginal sample with a dry flocked swab (similar to those now widely used for self-sampling for other sexually transmitted infections) and to put the swab into a dry tube.

The clinic-based self-sampling group will receive an invitation letter and participant information brochure via their primary-care provider. The women will also be directed to a webpage with translated study documents. They will be invited to: a) attend the clinic, give informed consent, and perform the test (*e.g.* in the bathroom); b) return the kit to the practice nurse; and c) complete a questionnaire on: i) their experience; ii) the acceptability of the self-sampling process; and iii) their preferences. Practice staff will receive bookings from women invited to self-test at the clinic. When the woman attends, they will provide her with a quiet space and tablet on which she can watch the study video clips (with voice-overs in a range of languages). Practice staff will answer any questions, contacting the research nurse as necessary, and manage the consent forms. Clinic staff will be trained in order to be able to consent women to the study and to manage results. The resource and costs associated with the additional training will be measured.

If a woman is unable to take the sample when attending the clinic, she will be asked to return in a week's time to then take the sample. If the woman does not wish to take the sample at the clinic she will be able to take the kit home and return her sample to the clinic, but she will be counted as a refusal for study purposes. The woman will receive healthcare in the same way as a participating woman though.

The mail self-sampling group will receive an invitation letter and the self-sampling kit and information package in the mail. The self-sampling kit and information package will contain a) the Participant Information Brochure; b) an informed consent document; c) an acceptability questionnaire; d) a sterile flocked swab in a dry tube; e) instructions on how to take the sample; f) instructions to return the sample as soon as possible; and g) a return, free, pre-addressed courier bag. They will also be directed to a webpage with translated study documents and the study video clips.

Four weeks after the invitation letters have been sent, non-responding women will be sent a reminder text message. The reminder text message for the home-based self-sampling group will include a telephone number that the woman can use to request that a second sampling kit be sent.

The research nurses will answer any questions that the women have over the telephone.

It is estimated that participation will involve an approximately 30–45-minute time commitment (plus follow-up if required).

3.10. Opportunistic sub-study

The opportunistic sub-study aims to determine the marginal additional uptake through making HPV self-testing available opportunistically on any clinic visit or requesting a posted kit.

In selected practices, any woman who has not participated in the study three months after invitation will have an alert placed on the clinic practice management system (PMS) stating that she is eligible for opportunistic HPV self-testing. Women will be informed via letter and text that the self-test is now available at the clinic over the next six months, or they can request a home self-test kit to be posted to them. The PMS alert will notify the clinic staff to offer self-testing when the woman attends the clinic for any reason in this period. The woman will be able to do the test at the clinic, or she may take it home and return the sample by courier/lab collection centre/return to clinic. A post-test flyer for participating women will provide brief information about receiving results, follow-up, and a link to the study webpage (Appendix 9).

The HPV self-test will be available to women in the opportunistic sub-study for 6 months. Clinics may or may not send reminders to women during this time, as per their usual practice.

Clinic staff will be additionally trained in order to be able to consent women to the study and to manage results. The resource and costs associated with the additional training will be measured. The offer, acceptance or decline of an HPV self-test will be recorded by clinic staff on an advanced form in the PMS, linking to the study IT system.

The same outcomes will be measured for the sub-study as in the main study.

Independent service providers may be utilised to provide outreach support for women to attend screening (or colposcopy) in all study arms.

3.11. Test device

The study will use a single sterile copan cotton swab and a sarstedt 12mL polypropylene dry tube in each pack, along with test kit instructions and a specially designed form (coloured), clearly labelled as a research study. The copan flocked swab has been shown to increase both the pick-up and release of cellular material compared with non-flocked swabs. Special labels that will not smudge with exposure to liquid media will be used.

The 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.[42]

Figure 2 – A coban flocked swab and a sarstedt dry tube

3.12. Sample collection

Women will be told in the written materials to follow the instructions provided (written and video) in order to obtain a self-collected vaginal sample. The formal test-kit instructions, adapted from the feasibility study, are included as Appendix 3 – test kit instructions. The written materials have undergone focus-group testing with Māori, Pacific and Asian women.

Once samples are collected, the tubes will be placed in a biohazard bag together with the consent/laboratory test request form, and placed in the courier pick-up area for samples taken at a clinic, and into the courier bag for samples taken at home. Samples can be stored and transported at room temperature. The number of days between collection of the sample and receipt by the laboratory will be recorded, with the time interval measured as a study variable.

3.13. Laboratory testing

HPV test request forms

A specific laboratory test request form has been developed for the feasibility study, modified from the COMPASS study with the assistance of Anatomic Pathology Services. The current study will use a slightly modified version of the form (to reflect the different study name). The form is coloured and specially labelled, and clearly indicates that this is a research study.

The laboratory/consent test request form is given in Appendix 2 – laboratory request form and consent form.

On arrival in the laboratory, 4ml preservcyt media will immediately be added and the sample vortexed for 1 minute. The study samples will be entered in the laboratory management information system (LIMS) and go into the next available batch of HPV testing on the cobas 4800. Samples can be stored at room temperature up to 25°C for up to 6 months once the preservcyt media has been added.

Cytology test request forms and testing

The cytology test request forms will be the standard request forms used by participating clinics. Cytology testing will be carried out in the usual manner and in accordance with the NCSP OPQS. Results will be managed as per usual care by the primary care provider.

HPV testing

All samples will be tested for the presence of oncogenic HPV using the clinically validated cobas 4800 HPV assay[57] (Roche Molecular Systems, Pleasanton, CA, USA) at Anatomic Pathology Services. Anatomic Pathology Services performs cytological services within the current NCSP under the NCSP quality-assurance programme 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);[58] fulfils the NSCP criteria for HPV testing;[59] and has been selected by the Netherlands for primary HPV testing.[60] This assay specifically detects HPV types 16 and 18, as well as 12 other oncogenic HPV types as a group.[58] 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.[42] On receipt in the laboratory, samples will be vortexed for at least 30 seconds prior to decapping and loading in swab sample carriers on the cobas 4800. Samples will require batching because it is not possible to use both swab and liquid-based cytology vial carriers in the same run on the cobas 4800. 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 Operation and Quality Standards (OPQS). Results will be reported to both the research nurse coordinators and the nominated primary-care provider with a copy to the NCSP-Register. A frequent manual update process from the research nurse coordinators to the NCSP-Register via Secure File Transfer from a suitable location (*i.e.* a colposcopy unit) is required for a manual research flag to be applied at the NCSP-Register and for register settings to be adjusted. All failed and invalid samples will be recorded and a repeat sample requested (internationally, the proportion of invalid samples is very low at 0.6%[33]).

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.

Future laboratory analyses: We will freeze an aliquot of each self-test sample that had a positive test result for oncogenic-HPV and which came from a woman who gave permission for her sample to be stored. Permission will be sought from participating women so that any other HPV types present can be further differentiated (for example determining the specific oncogenic-HPV type in women who have a result of 'other' HPV). No analysis of human tissue or human genetic analysis will be performed, the only potential future analysis will be of specific viral DNA related to understanding the prevalence of HPV in these populations, which is a key aim of the study and is of policy relevance to the NCSP. Separate funding will be sought.

3.14. Results management

Non-participants: All women will be told (either verbally at the clinics or through explanatory letters) that declining to participate in the study will not affect their medical care in any way, and will be encouraged to attend for regular screening. They will be followed-up after the study by their usual primary-care provider for routine continuing NCSP recall.

Negative results management: Negative results will be provided to women by letter, text message or telephone call by the usual primary-care provider and the women will be advised to return for a routine cervical screen at the appropriate clinical interval as specified by the NCSP guidelines.

We have consulted with the National Screening Unit on the recall interval for women who test negative for oncogenic-HPV. As the proposed guidelines for primary HPV screening are not likely to become operational during our study recruitment period, a three year recall interval has been agreed.

Cytology results management: Women with abnormal or inadequate cytology will be followed-up according to standard NCSP procedures by the requesting smear-taker.

Oncogenic-HPV results management: Positive HPV results will be managed as per the current NCSP guidelines, with adjustments in accordance with NCSP clinical advice, as described below. We had aimed to provide positive results to women *kanohi ki te kanohi* (face-to-face) by their usual primary-care provider (or by one of the study research nurses if the time period of 10 working days has passed and the research nurse has contacted the clinic). However, in the feasibility study, more women indicated a preference for receiving positive results by phone than face-to-face, so the majority of women are likely to be informed of their test results over the phone.

Women who test HPV16/18 positive will be referred directly to colposcopy. In order to avoid these women having an additional cytology test, we have agreement from all participating colposcopy units to conduct 'blind' colposcopy (*i.e.* perform colposcopy before cytology, but not that no cytology result will be available to be considered alongside clinical findings because a cytology sample will be taken at colposcopy). We have agreement at Waitematā, Auckland, Hutt Valley and Capital & Coast DHB for blind colposcopy.

Women who test positive for the pool of 12 other oncogenic HPV types will be triaged (at no cost to the woman) with a health-professional-conducted cervical-cytology test (*i.e.* the current standard process). In accordance with NCSP clinical advice, a reflex HPV test on this follow-up smear is not required.

As per NCSP clinical guidelines [55]:

- Women whose cytology result shows any abnormalities will be referred to colposcopy.
- Women whose cytology is normal will be referred for management by their usual primary-care provider team for a repeat cytology test after one year.

Where a woman declines a follow-up smear despite offers of support to attend, on a case by case basis and after discussion with the lead colposcopist, she may be referred directly to colposcopy.

Refer to Appendix 7 for result management and study exit flow charts.

Clinical follow-up: As per the process used for the Bowel Screening Pilot recently concluded at Waitematā DHB, the return-of-results primary-care clinician will have 10 days

to bring women in for a consultation, at which time they will explain the results and, in the case of HPV 16/18-positive women, make a referral for colposcopy. In the case of women positive for other oncogenic HPV types, the return-of-results clinician will make an appointment to take a cytology sample. Our research nurses will monitor positive results and provide a failsafe follow-up process. If the 10-day timeframe is not achieved, the study research nurses will work with the general practice and the ISP to ensure that women are notified and offered support to attend appropriate follow-up or provide the follow-up themselves. Non-attenders for abnormal cytology results will be followed up by usual primary-care providers.

All screening elements for the self-sampling groups will be free to women (primary care practices that have free smear contracts are able to claim on these) and we aim to achieve the goal of having at least 90% of women who test positive for oncogenic HPV being seen in clinic. We will partner with local primary care, ISPs, Māori/Pacific/Asian Providers, and DHB colposcopy services to design and test appropriate support-to-service strategies to fulfil this aim; specifically contracting with the local ISP to resource this more intensive support package appropriately. These processes, including new referral forms, are being tested in the feasibility study. This support will be tailored to meet women's needs and may include transport, childcare, and visit-attendance support. We will determine what effort is needed to achieve the 90% follow-up.

Collection of clinical results: We will obtain the results of any subsequent cervical cytology, colposcopy, and histology from the NCSP-Register or GPs, ISPs, Māori/Pacific/Asian Providers, and DHB colposcopy services in order to determine prevalence of cervical abnormalities.

Women's participation in this study will be recorded on the NCSP-Register (with a research flag) for additional safety and follow-up, as per the COMPASS study protocol.[62] Women will be advised of this in the Participant Information Brochure.

3.15. Follow-up commitment

Our study aims to follow-up ≥90% of women who test positive for oncogenic HPV. Our study cohort comprises hard-to-reach women, who are known to be at greater risk of developing cervical cancer. In partnership with colposcopy services, ISPs, and community health workers, we will design/develop appropriate support (*e.g.* assistance with transport, child care, visit-attendance support) to assist women with a positive oncogenic HPV result to be followed-up.

Having received information that oncogenic HPV increases the risk of cervical cancer as part of the informed recruitment process, women with a positive oncogenic-HPV result have been demonstrated to have high rates of follow-up (as observed in the Australian iPap study).[64] A 100% follow-up may not be achievable as we respect a woman's right to make an informed choice to refuse a follow-up speculum examination. Even 90% follow-up may be aspirational but remains our goal.

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 national screening programme. There will be no charge to women for support-to-services.

3.16. Colposcopy management

Reimbursement: The study will fund the relevant DHB the current national price for a colposcopy visit for any colposcopy attendances. Usually, any work within the NCSP that

aims to increase cervical-cancer screening coverage, particularly for NCSP priority women, will be likely to increase colposcopies and the healthcare provider initiating the new work would not be expected to pay for those colposcopies. However, the co-investigators recognise that this research is outside of the current NCSP and that there will be additional paperwork required (Case Report Form (CRF)) by colposcopists for the small number of women expected (positivity was 6-8%, with 2% 16/18 positivity, in the iPAP study; we therefore estimate 33 women being referred directly to colposcopy (after a positive 16/18 HPV test), and 66-99 women having a reflex cytology test after a positive test for other oncogenic HPV).

Referral Process: Referral to the colposcopy clinic will occur through the usual 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 are electronically messaged to the NCSP-Register as per the current process.

Timeliness of Assessment: Our aim is that women referred to the colposcopy clinic who are positive for HPV 16 or 18 will be seen within 20 working days. We aim that women with a positive other oncogenic HPV test and a reflex cytology result >ASC-H/HSIL will be seen within 20 days of receipt of referral as per the current NCSP guidelines. We also aim that women who have a positive oncogenic HPV test after follow-up of a positive oncogenic HPV other test and an ASCUS/LSIL cytology result will be seen within 20 working days.

Colposcopy Management: Women referred with a 16/18 positive HPV test will have a cervical smear taken at the time of their colposcopy visit to avoid the requirement of a cervical smear in primary care prior to referral. As part of the feasibility study, CRFs have been developed (and are being trialled) 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 will receive HL7 messages relating to the woman's care and can ensure appropriate follow-up mechanisms. Dependent upon the results, women will be managed as per the new draft NCSP guidelines. In any instances where there is a discrepancy between results, the case will be reviewed at the colposcopy multidisciplinary meeting.

Management of Non-Attendance: Non-attendance at colposcopy is to be managed in accordance with the study colposcopy DNA protocol, which has been agreed with DHB lead colposcopists (see Appendix 8). If women do not attend their colposcopy appointment, the research nurses will be notified of the non-attendance and will arrange follow-up with the project support-to-service providers or the DHB support-to-service providers, as appropriate. As per current colposcopy clinic practice, women will be sent a text reminder and a letter explaining the importance of attendance. If the woman does not attend her second appointment, as per current clinic process, the colposcopist will write to the woman (with a copy to the referring practitioner) advising of the importance of attendance and the recommendation of being re-referred to the service for assessment. Non-attendance will be documented in the colposcopy databases so that the NCSP-Register will receive HL7 messages. A study completion form will be developed to capture women who do not attend and are therefore discharged back to their primary-care provider, and the form will also be provided to the research nurse.

3.17. Data analyses

The main analyses will focus on the primary outcome of the study: participation, *i.e.* the proportion of women who provide a self-sample compared with the proportion who attend for cytology, by ethnicity. These will initially be assessed simply by comparing the proportions who 'participated' in each group; this will be followed by a multiple logistic regression

analysis to adjust for potential confounders (*e.g.* age, ethnicity, screening history, socio-economic position, study site) and to assess which factors (in addition to the intervention) affect participation. The source of the ethnicity data will be the PHO data-matched lists, although we recognise that the ethnicity recorded on these lists may not be the same as that recorded on the NCSP-Register. The same analyses will be repeated for un- and under-screened women separately, providing important information on whether screening history affects participation.

We will also analyse the prevalence of oncogenic HPV in the self-sampling groups, and the prevalence of cervical abnormalities in the cytology group. Prevalence odds ratios[65] will be calculated using logistic regression and compared across ethnicities, adjusting for age. Secondary analyses will assess the association between acceptance of self-sampling and demographic and other factors. For comparisons across ethnicity and screening-history (un- and under-screened) groups, multiple linear or logistic regression (as appropriate) will be used, adjusting for age and other potential confounding variables. Time for return of sample will be calculated for self-sampling groups as a policy-relevant indicator of sample integrity;[66] laboratory turnaround time and proportion of unsatisfactory samples will be monitored.

Experience of the test, knowledge of HPV, enablers/barriers of screening (including preference, measured through uptake, for returning samples by courier or through clinics/laboratories), and factors associated with screening preferences will be described for each group (self-sampling or cytology), by ethnicity and demographic factors. Standard descriptive statistical methods will be used. t-tests and Chi-square tests will be used to assess statistical significance. Multiple linear or logistic regression (as appropriate) will be used to compare these responses between the two groups (self-sampling or cytology), adjusting for potential confounders.

We will document whether we achieve our aim of following-up 90% of oncogenic HPV positive women and what is required to follow-up these women. In addition, the data will deliver information on: 1) the level of comprehension of instructions for self-sampling to ensure future clarity and acceptability; and 2) a cost-benefit analysis.

As this is a controlled trial in a public-health setting, it utilises public-health methods to assess acceptability, feasibility, and uptake/participation rather than the safety and efficacy of the self-sampling itself (which have already been established). As such, the interim analyses that would be necessary in a *clinical* trial are not necessary in this public-health trial.

All women will be given a study ID number and data will be de-identified for analysis; however, as noted in the Participant Information Brochure (see Appendix 1 – text for study participant information brochure) and laboratory/consent form (Appendix 2 – laboratory request form and consent form), data will be held in an identifiable format indefinitely on the NCSP-Register in order to inform clinicians/NCSP-Register staff about the next appropriate screening interval and to form part of the screening history of each woman. Participating women will be able to withdraw their information from the NCSP-Register in the usual way.

3.18. Sample size

The sample size (2,333 Māori, 2,333 Pacific, and 2,333 Asian women) gives 99.99% power to detect a 15% difference between the usual care and the self-sampling mail group within each ethnic group, assuming a 25%[67] response proportion in the self-sampling mail group and a 10% response proportion in the usual care (cytology) group,[67] with an α of 0.05. We have 100% power to detect a difference of 20% between usual care (10%) and self-sampling clinic (30%). We have 70% power to detect a difference of 5% between self-sampling clinic

(30%) and self-sampling mail (25%); we have 86% power to detect a difference of 6%, and 94% power for a difference of 7%. We have greater power for all ethnic groups combined.

The sample size was selected in order to achieve both statistical power and an approximately 1% ethnic-specific coverage improvement at a DHB level. Table 3 shows the estimated response based on international literature (approximately 30% participation in self-sampling), including the number of self-sampling kits required.

Table 3 – Sample size

Ethnic Group	Number of women invited*				No of women who are expected to respond to invitation and be screened**			
Arms	**Usual care**	**SS Clinic**	**SS Mail**	**Total**	**Usual care**	**SS Clinic**	**SS Mail**	**Total**
Māori	333	1000	1000	2333	33	300	250	583
Pacific	333	1000	1000	2333	33	300	250	583
Asian	333	1000	1000	2333	33	300	250	583
Total	1000	3000	3000	6999	100	900	750	1750

Usual care: Pap smear and liquid-based cytology test as per current NCSP guidelines
SS: Self-sampling in either a clinic setting or at home following receipt of a mailed-out kit
**Number of women to invite to show a 5% difference in self-sampling delivery arms*
***Assume a response proportion of 10% for usual care, 30% for self-sampling in the clinic group and 25% for self-sampling in the mail group*

If participation in either or both of the self-sampling arms is higher than expected, we will have to reconsider how many women we invite to participate in the study because the budget is not sufficient for more than the anticipated 1650 HPV tests.

3.19. Endpoint measures for data analysis tools and timeframes

Table 4 – Endpoint measures

Measure	Tool / measurement	Timeframe / censoring	Comment
Primary endpoints			
Self-sampling participation, by ethnicity, sampling group, and screening history The marginal additional uptake in opportunistic group	Proportion of eligible population able to be contacted (eligible women identified from primary care data-matched lists, who do not opt-out) who take a self-sample and for whom a laboratory result is received	3 months after invitation for Groups 1-2 6 months after allocation to opportunistic Group 4	Confirm results from NCSP-Register at 18 months
Prevalence of oncogenic HPV positivity and the prevalence of cervical abnormalities in the cytology group	Proportion of self-sampled low vaginal swab HPV laboratory results received that are positive for oncogenic HPV (any oncogenic type, and specifically genotypes HPV 16 and HPV 18), and proportion of cytology results received that are not 'normal'	12 months post invitation for self-sample kit or cytology test	Confirm results from NCSP-Register at 18 months
Secondary endpoints			
Follow-up proportion among oncogenic-HPV-positive women	Proportion of women who self-sample and receive a positive oncogenic-HPV result who attend for cytology and/or colposcopy (as indicated in the NCSP guidelines algorithm**Error! Reference source not found.**)	Censored at 6 months post oncogenic-HPV-positive test recorded in the NCSP-Register	Confirm cytology and histology results from NCSP-Register at 18 months
To determine the level of support needed to achieve the aim of at least 90% follow-up of oncogenic-HPV-positive women to attend for cytology or colposcopy	Resource requirements for follow-up. Number of women who are referred to support-to-service provider. Uptake and recording of support-to-service activities (recorded as none, phone contact (number), childcare, transport, financial, visit attendance support, further information/education, rescheduling support, other)	6 months post oncogenic-HPV-positive test recorded on the NCSP-Register	Referral recorded by research nurse. Support-to-service provider to record activities (including multiple activities)
Association between acceptance of self-sampling and demographic and other factors	Logistic regression analysis. Acceptability questionnaire	End of study	
Time for return of sample	Number of days from when sample taken to when sample received by laboratory	End of study	
Percentage of unsatisfactory cytology tests, HPV tests and colposcopy examinations	Proportion of cytology tests, HPV tests and colposcopy examinations that are recorded as unsatisfactory	End of study	
Experience of the test, enablers/barriers of screening, and factors associated with	Acceptability questionnaire	End of study	Questionnaire completed on the day of sampling

Measure	Tool / measurement	Timeframe / censoring	Comment
screening preferences			

3.20. Procedures table for women

Table 5 – Procedures for women

	Pre-visit	Initial visit	After visit	Follow-up of positive results
Usual care group				
Pre-invite letter	**X**			
Standardised invitation letter	**X**			
Cytology sample taken		**X**		
Return of results			**X**	
Cytology (primary care) or colposcopy (hospital clinic)				**X**
Support to service				**Optional**
Clinic-based self-sampling group				
Pre-invite letter	**X**			
Standardised invitation letter	**X**			
Take self-sample		**X**		
Questionnaire		**X**		
Return of results			**X**	
Cytology (primary care) or colposcopy (hospital clinic)				**X**
Support to service				**Optional**
Mail-out self-sampling group (no visits)				
Pre-invite letter	**X**			
Standardised invitation letter	**X**			
Questionnaire		**X**		
Take self-sample		**X**		
Return of results			**X**	
Cytology (primary care) or colposcopy (hospital clinic)				**X**
Support to service				**Optional**

3.21. Criteria for discontinuation of the study

This is a low-risk intervention; therefore, a need for discontinuation is not anticipated. We have confirmed with the HRC Data Monitoring Core Committee (DMCC) that no external Trial-Specific Data Monitoring Committee (DMC) is needed and we will therefore use an internal DMC, following international best practice. The DMC will be established to: 1) periodically review and evaluate the accumulated data for participant safety, study conduct, and progress; and 2) make recommendations concerning continuation, modification, or termination of the trial. If a serious adverse event does occur, it will immediately be investigated and a decision about termination will be taken by the internal DMC and the other investigators. The study may be ended early in the case of uptake being higher than expected (due to budget limitations), or substantially lower than expected, impacting on the study's ability to determine statistically significant differences between study groups.

3.22. Definition of End of Project

6,999 women have been invited to participate. If substantially more or substantially fewer women than expected accept the invitation to be screened, the total number of women to be

invited to participate in the study may be reduced (in such cases approval from the HRC will be sought by Massey). Therefore, the definition of the end of the project may need to be changed to reflect the lower number of women to be invited.

4. Ethical and cultural considerations

There are a range of ethical and 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 substantial research expertise with Māori health, kaupapa Māori methodology, research with women, screening, 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. Pacific peoples' attitudes in general towards cervical screening is a combination of cultural, family, social and economic factors. Confidentiality can also be a concern because of being part of health service in a close community because emphasis is often given to Pacific peoples' role and social standing. Our Pacific researchers and advisors will liaise closely with collaborating providers and utilise community fonos to address and inform the research teams on appropriate Pacific cultural approaches and considerations.

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 discussions 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 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 to access a novel technology to enhance their wellbeing.

The HDEC has approved the disclosure of non-consented contact details for invitation by the research nurse for the feasibility study, and this has been requested for this study, as noted above. This was discussed specifically in the HDEC application form and cover letter.

5. Confidentiality

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

The study data will be kept in an electronic database on the Waitematā DHB and Massey University servers protected by DHB and University firewalls and password protected. Only the study researchers (nurses, co-investigators, biostatistician) 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, cytology, 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.

6. Clinical safety

All adverse events will be assessed for seriousness by the research nurses, study clinicians or GP immediately.

A serious adverse event (SAE) is any adverse event that occurs, having received the study intervention 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 SAEs directly attributable to the HPV self-sampling are anticipated; however, the adverse events management process will be followed at each site for any reports received.

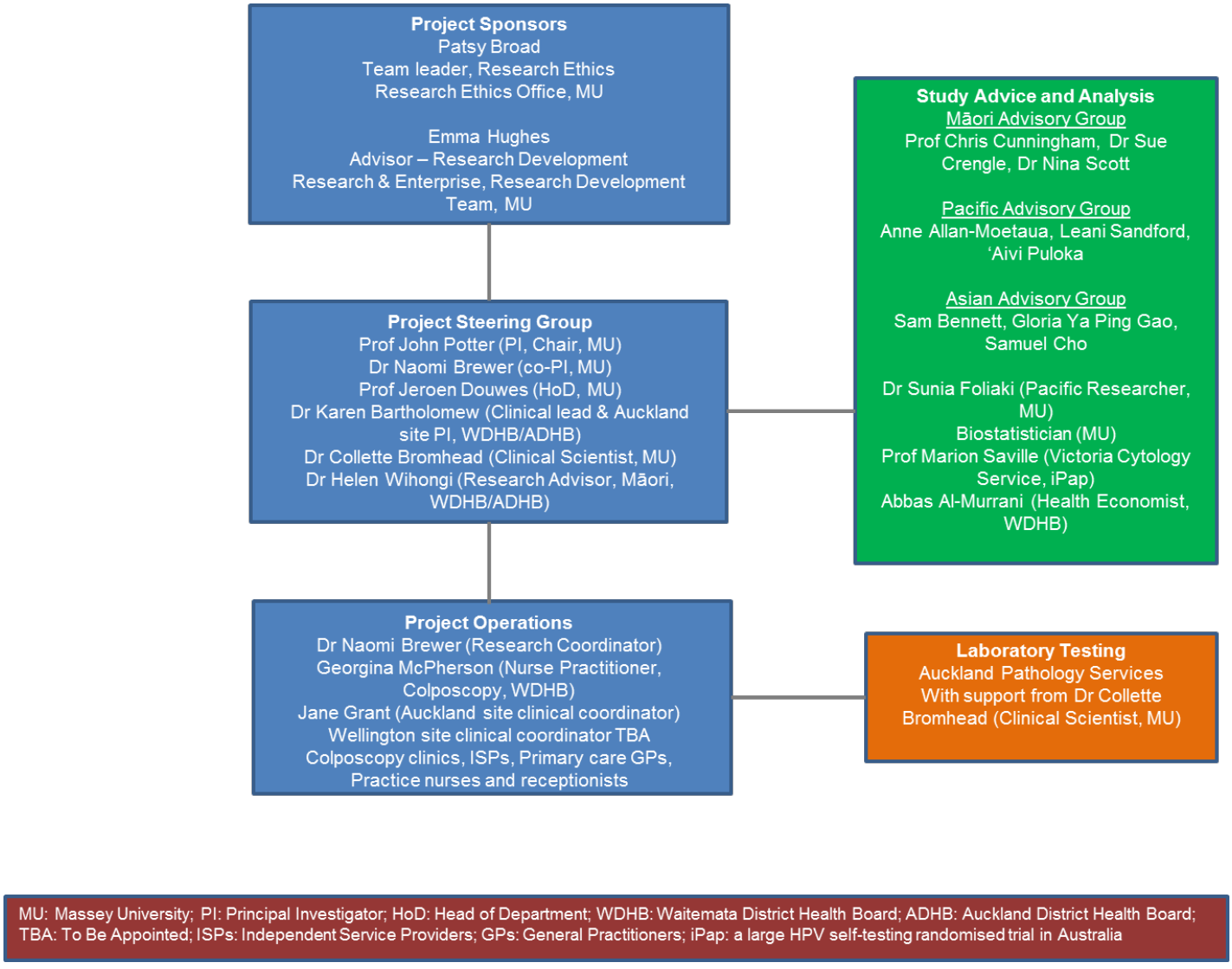
Taking the HPV self-sample does not cause any physical harm, although some women may experience mild discomfort. If a woman is pregnant, we will advise her not to perform a self-sample, although pregnant women who have used the self-sample overseas have not reported any problems.

7. Study governance, roles and responsibilities

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 HDEC approvals and requirements. The Auckland site clinical lead and research coordinator are GCP trained.

The project and the activity of the operations group is governed by a project Steering Group (see Figure 3).

Figure 3 – Project governance schematic



MU: Massey University; PI: Principal Investigator; HoD: Head of Department; WDHB: Waitemata District Health Board; ADHB: Auckland District Health Board; TBA: To Be Appointed; ISPs: Independent Service Providers; GPs: General Practitioners; iPap: a large HPV self-testing randomised trial in Australia

Table 6 – Research team roles and responsibilities

Team member	Organisation	Role in project	Functions and time commitment	Qualitative or quantitative expertise	Clinical	Māori/Pacific/Asian health expertise
Governance						
Prof John Potter	Professorial Fellow Centre for Public Health Research, Massey University	Principal Investigator Chair Steering Group	0.1FTE Oversee implementation and analysis of project	Quantitative		
Dr Naomi Brewer	Research Fellow Centre for Public Health Research, Massey University	Co-Principal Investigator Steering Group Member Research coordinator (project manager)	Average 0.57FTE Lead protocol development, implementation and analysis of project. Document preparation, project management, results oversight and maintenance, reporting	Quantitative		
Prof Jeroen Douwes	Director Centre for Public Health Research, Massey University	Co-chair Steering Group	0.5FTE contributed in kind Overall implementation and management of project	Quantitative		
Dr Karen Bartholomew	Public Health Physician Waitematā and Auckland DHB Māori Health Gain Team/Child, Women and Youth Team, Chair Metro-Auckland Cervical Screening Advisory Group	Clinical Lead & Auckland site Principal Investigator Steering Group Member	Average 0.17FTE Oversee implementation of the study in Auckland and contribute to analysis of project	Qualitative and Quantitative	✓	
Dr Collette Bromhead	Senior Lecturer Molecular Microbiology, Clinical Scientist Massey University	Steering Group Member Oversee sample testing with APS	0.1FTE Protocol development, implementation, study analysis and sample testing	Qualitative and Quantitative	✓	
Dr Helen Wihongi	Research Advisor – Māori Waitematā and Auckland	Steering Group Member	0.05FTE Involvement in	Qualitative and	✓	✓

Team member	Organisation	Role in project	Functions and time commitment	Qualitative or quantitative expertise	Clinical	Māori/Pacific/Asian health expertise
	DHB		development and delivery of project, ensuring the project is culturally appropriate, relevant and has benefit for Māori	Quantitative		
Operations						
Georgina McPherson	Women's Health Nurse Practitioner Waitematā DHB Colposcopy Clinic	Oversight clinical management of HPV results	0.05FTE Auckland clinic attendance of study participants and meeting attendance	Qualitative and Quantitative	✓	
Jane Grant	Auckland site research nurse, employed by Waitematā DHB	Auckland site clinical coordinator Smear-taker nurse	0.8FTE Liaison between PHO/general practices and collaborating partner organisations, research co-ordination, invitation and consent of women, results follow-up and support-to-service/colposcopy clinic liaison as required		✓	
Anna Maxwell	Waitematā DHB	Auckland site study coordinator	0.5 FTE	Qualitative		
Mellissa Murray	Waitematā DHB	Auckland site administration coordinator	1.0 FTE			
TBA		Wellington site clinical coordinator/Research smear-taker nurse	0.2FTE Liaison between PHO/general practices and collaborating partner organisations, research co-ordination, invitation and consent of		✓	

Team member	Organisation	Role in project	Functions and time commitment	Qualitative or quantitative expertise	Clinical	Māori/Pacific/Asian health expertise
			women, results follow-up and support-to-service/colposcopy clinic liaison as required			
Laboratory staff	Anatomic Pathology Services, ADHB	Laboratory Testing	Processing and reporting HPV samples for the study		✓	
Primary care staff TBA	TBA		Direct interaction with women as per protocol		✓	✓
Study Advice and Analysis						
Dr Sue Crengle	Primary Care Invercargill	Māori Health and screening expert advisor	Māori Advisory Group		✓	✓
Dr Nina Scott	Waikato DHB	Māori Health and screening expert advisor	Māori Advisory Group		✓	✓
Prof Chris Cunningham	Massey University	Māori Health expert advisor	0.05FTE contributed in kind Māori Advisory Group, advice on study design, peer review of findings and report writing	Quantitative and qualitative		✓
Anne Allan-Moetaua	Health Development Manager Central Pacific Collective, Wellington	Pacific Health and screening expert advisor	Pacific Advisory Group			✓
Leani Sandford	Portfolio Manager Pacific Health Team, Auckland and Waitematā DHBs	Pacific Health expert advisor	Pacific Advisory Group			✓
Dr ‘Aivi Puloka	Manager – Practices The Fono Health & Social Services	Pacific Health expert advisor	Pacific Advisory Group		✓	✓
Sam Bennett	Funding Manager, Asian,	Asian Health expert	Asian Advisory Group			✓

Team member	Organisation	Role in project	Functions and time commitment	Qualitative or quantitative expertise	Clinical	Māori/Pacific/Asian health expertise
	Migrant and Refugee Health Planning, Funding and Outcomes, Auckland and Waitematā DHBs	advisor				
Gloria Ya Ping Gao	Social Services Manager, Chinese New Settlers Services Trust	Asian Health expert advisor	Asian Advisory Group			✓
Samuel Cho	Asian Public Health Coordinator, The Asian Network Inc. (TANI)	Asian Health expert advisor	Asian Advisory Group			✓
Dr Sunia Foliaki	Pacific Research Fellow, Centre for Public Health Research, Massey University	Advisor and analysis	0.05FTE contributed in kind Involvement in development and delivery of project, ensuring the project is culturally appropriate, relevant and has benefit for Pasifika	Quantitative and qualitative	✓	✓
Biostatistician	Centre for Public Health Research, Massey University	Analysis	Average 0.07FTE Develop project database, assist with data management and analysis	Quantitative and qualitative		
Prof Marion Saville	Executive Director Victoria Cytology Service, Melbourne, Australia; co-principal investigator of the iPAP study	Advisor	Advice on study design and research protocol, peer review of findings and report writing	Quantitative and qualitative	✓	
Abbas Al-Murrani	ADHB/WDHB Health Gain Team, Health Economist	Economic Analysis	Advice on collection of cost data and assistance with analysis	Quantitative		

7.1. Sponsor/Funding

The study is funded by the Health Research Council of New Zealand.

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7.2. Conflict of interest

Investigator	Conflict of interest	
	None to declare, or	Details

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9. Appendices

1.1 Appendix 1 – text for study participant information brochure

[This is the text only, not the final formatting.]

Information for women

Research into whether women prefer a new self-test for HPV instead of going to the doctor/nurse for a smear test

What is this study about?

This study is to find out if women like using a new test for cervical screening. In the new test women use a swab in their vagina to find out if they have the human papillomavirus (HPV). HPV is a virus spread by skin-to-skin contact and is linked to cervical cancer. The new self-test is different from, but as good as, the usual smear test which a nurse or doctor does.

This study will help the Ministry of Health decide how women will be tested in the future. The goal of the study is to find out if using the self-test means that more women get checked to prevent cervical cancer. We would like to invite Māori, Pacific and Asian women in Auckland and Wellington to take part in this study. Later this self-test may be offered to other groups of women in New Zealand.

To compare this new self-test with the usual screening test, some women in the study are being offered the usual smear test done by your doctor or nurse, and some women are being offered the new self-test.

What am I being asked to do?

You have been put into one of three groups. A computer program has decided which group you are in. Two of the groups are being offered the new self-test and one group is being reminded to come in for the usual smear test. Women offered the self-test are either being posted a self-test kit or asked to come into the clinic.

All of the self-tests, usual smear tests, and any follow-up tests that you might need are being provided free during this study.

If you decide to take part in the study you will need to sign a consent form.

- If you have been asked to come into the clinic the nurse will show you a video explaining what the study is about and answer your questions. You will then use the kit and instruction sheet to do the self-test in the bathroom at the clinic. You will give your test back to the clinic who will send your test to a laboratory for testing for HPV.

- If you have been reminded to come in for a usual smear, your doctor or nurse will do the smear.

- If you are posted the test kit at home, you will do the test at home using the kit and written instructions, and return your test following the instructions. You will be given a telephone number to use if you have any questions.

If you are in one of the HPV self-test groups

How will I find out the results of my self-test?

The study nurse or your nurse or doctor will contact you with your results within 10 days after your test. If your test results show you do not have HPV, you don't have to do anything else. Your nurse or doctor will let you know when you are due for your next smear test.

What if my test results show I have HPV?

A test that shows you have HPV does NOT mean you have cervical cancer. We will ask you to come into the clinic to talk about what the results mean.

It is your decision whether you have follow-up tests or not. We strongly recommend that you do have a follow-up test to look for any cell changes that might need treatment. In this follow-up test a nurse or doctor at a GP or hospital clinic looks at your cervix, either to take a smear or do a colposcopy or both. A colposcopy is a simple procedure by a specialist to look at the cervix. There will be no charge for any follow-up tests.

The study nurse can arrange help so you can get to the clinic, or talk more about what the test results mean. We will talk to you about the follow-up tests and answer all your questions. We can also talk to your family/whānau if you want us to.

How did you find doing the self-test?

We may ask you to answer some questions about any smear tests you have had and how you found the self-test. You do not have to answer any of the questions if you do not want to.

More information

On this page there is more information about HPV, cervical cancer, reducing your risk of cervical cancer and the HPV test.

More about HPV

Being infected with HPV is very common. Four out of five men and women will have HPV at some time in their lives.

Some types of HPV stay in the body for a long time. For most women, having HPV does not cause any problems. Your body gets rid of the virus by itself.

Having HPV doesn't mean that your partner is being unfaithful to you. You could still have HPV even if you are in a long-term relationship with one person, are not currently having sex, or have not had sex in a long time.

More about how HPV is linked to cervical cancer

Certain types of HPV stay in the body for a very long time and can cause cell changes in the cervix that can lead to cervical cancer.

The most common types of HPV that cause cell changes that lead to cervical cancer are called HPV 16 and HPV 18. There are another 12 types of HPV that can cause cell changes that can lead to cervical cancer. There are also other types of HPV that can cause minor changes to the cells of the cervix, or sometimes genital warts. These types are usually cleared by your body within one to two years and do not cause cervical cancer.

How can I reduce my risk of cervical cancer?

The best way to reduce your risk of cervical cancer is to have regular cervical screening with your nurse or doctor.

How is HPV treated?

There are treatments for cell changes to your cervix caused by HPV. This is why it is important for you to have follow-up tests if your test results show you have one of the types of HPV that can cause cervical cancer. Treatment

happens at a hospital clinic and is very successful at stopping serious cell changes from becoming cervical cancer.

More about the HPV self-test

The new self-test is a very accurate test to check for HPV. You don't need to know where your cervix is to do this test. The new self-test does **not** check for other sexually transmitted infections (STIs), such as chlamydia or HIV.

Some HPV tests are currently available with a cervical smear taken by a doctor or nurse.
The self-test is currently not offered to all women. The self-test is only being offered to women as part of this study. If, at any time, you wish to opt-out of self-testing and have a smear test, talk to the study nurse or your own doctor or nurse.

Is doing the HPV test myself right for me?

Some women find doing the self-test is easier than getting a smear with their nurse or doctor.

If you have had a hysterectomy, ask the study nurse whether the self-test is right for you.

If you have had the HPV vaccine, you can still take part in this study.

Are there any possible risks with the self-test?

In New Zealand we advise you not to do this self-test if you are pregnant. However, overseas, pregnant women have done this self-test and have not reported any problems.

Who is doing this study?

Massey University, Waitematā District Health Board, Auckland District Health Board, Hutt Valley District Health Board and Capital & Coast District Health Board are working with local clinics to do this study.

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 the information we have collected to the date you withdraw. We will not collect any new information after that.

Consent for further testing and contact (optional)

We will also ask for your agreement that if you do have one of the types of HPV that can cause cancer, we can keep part of your sample for possible further testing of the HPV virus types present. This will help us understand more about the HPV virus in New Zealand. Only testing for types of HPV will be done on your sample. The samples will remain in New Zealand, and will be stored at the Massey University Centre for Public Health Research laboratory in Wellington for up to 10 years. If you withdraw from the study you can ask for your sample to be destroyed.

We would also like to contact some women after doing the self-test to ask some more questions about their experience. You can choose whether you talk to us again or not. Your care will not be affected if you do not wish to talk to us again.

Privacy and confidentiality

All information collected from you as part of this study will be confidential. You will be given a study number so that your name will not be used on the study documents. The study team will see the information and your test results. Your test results will be shared with your usual nurse or doctor, to make sure you get the correct follow-up. In the same way as with a smear, your name and test results will also be held on the National Cervical Screening Programme Register and one of the laboratory registers (TestSafe/Éclair). The information from this study will be marked as research on the registers. The information will also be available to health professionals involved in your care. Only approved National Cervical Screening Programme staff and health professionals will be able to get access to the research information.

Your self-test or smear will be stored by the laboratory for the usual amount of time (for quality checking).

National Cervical Screening Programme (NCSP)

You can find out more about cervical screening and follow up tests at www.timetoscreen.nz

All women who participate in this study will be invited back for another smear test when next due. The NCSP advises all women who have unusual bleeding, pelvic pain or discharge to see their doctor and not wait for their next smear test.

ACC statement

It is not likely that you will get injured in this study. If you do, you will be able to get compensation from ACC just the same as if you were injured in an accident at work or at home. You will have to put in a claim to ACC, which may take some time to be assessed. If your claim is accepted, you will receive funding to help you recover.

Further information

Thank you for thinking about being part of this study. If you have any further questions, or complaints about the study, you can contact the clinical lead of this study: Dr Karen Bartholomew, Public Health Physician, Waitematā DHB and Auckland DHB, Phone: 09 486 8920 ext 5434, Mobile: 021 211 5629, Email: Karen.Bartholomew@waitematadhb.govt.nz
or
Dr Helen Wihongi, Director – Maori Health Research, Waitemata DHB and Auckland DHB
PH: 09 486 8920 ext 43204, Mobile 021 020 31167
Helen.Wihongi@waitematadhb.govt.nz

For cultural support please contact:
He Kamaka Waiora Ph **09 486 8324 ext 42324**
Grace Ryu (Asian) **Ph: 09 442 3232**
Sulu Samu (Pacific) **Ph: 021 914 790**

This study has received ethics approval (number: 17/NTB/120).

9.2. Appendix 2 – laboratory request form and consent form

FOR YOU TO COMPLETE

Please write the date and time you did this test:

Date: __/__/____

Time you did the test: _____

Which ethnic group do you belong to?

☐ New Zealand European ☐ Tongan
☐ Māori ☐ Niuean
☐ Samoan ☐ Chinese
☐ Cook Island Maori ☐ Indian
☐ Other e.g. Dutch, Japanese, Tokelauan; please state_____

Do we have the right details about you? If not, please write them here:

Address

Phone number

Please turn over and complete the consent form

IMPORTANT THINGS TO CHECK

- Have you written the date you took the sample on the label?
- Have you stuck the label on the tube?
- Is the consent signed?

~~FOR LAB AND CLINICIAN USE ONLY~~

RESEARCH

Study Title: Cervical Screening HPV Self-test

cphr CENTRE FOR PUBLIC HEALTH RESEARCH

Waitemata District Health Board Best Care for Everyone

AUCKLAND DISTRICT HEALTH BOARD Te Toka Tumai

Family name*			**Order Code** **D14326** **HPV-SS RCT STUDY**
First name*			
Date of birth*		**NHI**	Smeartaker: **Research Nurse Specialist** **Ph. 0211953439** Registration number: **164681/N164681** Facility Code **A1090**
Patient address*			
Patient phone*			**Copy to** (initial, surname, clinic)
Participant ID:			

Test details	***For APS office use only***	
PRIMARY **HPV PCR** TEST FOR CERVICAL SCREENING RESEARCH **ONLY** **NO** CYTOLOGY TO BE PERFORMED NOT SUITABLE FOR OTHER INFECTIOUS TESTING Send to **Anatomic Pathology Services** for processing immediately. ***Required fields**	APS Specimen Reception Test code **9674** (RCTS)	☐ Received via External Courier Delivery Service Date: .....
	Practitioner/smeartaker to complete and sign	
	☐ Written patient consent obtained Signature..... Date.....	

CONSENT FORM

Please read each statement and tick each box if you agree.

I have read and understood the information about this research project. ☐

I have been given enough time to consider, review and discuss this study with my whānau/family and decide whether or not to participate in this study. ☐

My questions about the research project have been answered. ☐

I understand that my participation in this research project is voluntary (my choice). ☐

I understand that information collected from me will be confidential and that no material, which could identify me personally, will be used in any reports on this study. ☐

I understand that the information will be seen by the research team, by my nurse or GP, and will also be held on the National Cervical Screening Programme Register and Éclair/TestSafe. ☐

I agree to take part in this research project. ☐

I understand that my sample will be tested for some types of human papillomavirus (HPV). ☐

Further testing: I give my permission for my sample to be tested for other types of HPV, to help us understand their role in causing cancer or for clinical management. I understand that this is the only testing that my sample will receive.

Yes ☐ No ☐

I give my permission to be re-contacted by the research team if they want me to answer other questions or give more information.

Yes ☐ No ☐

I want to receive a copy of the summary of the results of the research project.

Yes ☐ No ☐

Name of participant _____ **Signature**_____

Email (if you want a summary of the results emailed)_____

Family/whānau member:

_____

Name Address or email/phone

9.3 Appendix 3 – test kit instructions

How to take your HPV test

cphr CENTRE FOR PUBLIC HEALTH RESEARCH

AUCKLAND DISTRICT HEALTH BOARD Te Toka Tumai

Waitemata District Health Board Best Care for Everyone

1. What is in the kit?

- an information brochure – please read this first
- this instruction sheet
- a swab in a sealed pack
- a plastic tube with cap
- a plastic zip lock bag
- a sticky label for the tube with your details
- a consent form for you to fill in
- a pre-addressed courier bag
- may include a questionnaire.

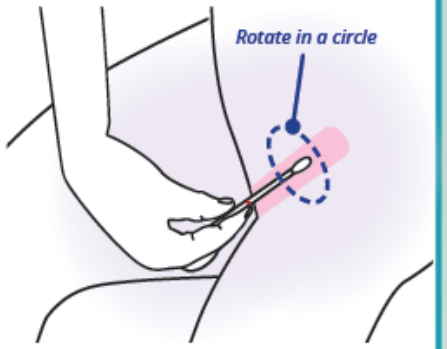
Important

- *Don't use this kit if you are pregnant.*
- *If you are having your period, take the test once your period has finished.*
- *Return the test as soon as possible.*
- *It is best to take your test on a weekday so the test can get back to the lab quickly.*

2. Complete the consent

Make sure you have read about the study and filled in the consent form

3. Take the test

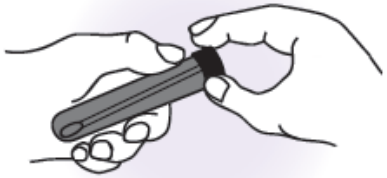


- Wash your hands
- Take the lid off the empty tube.
- Open the sealed pack and take out the swab, holding it close to the red mark on the stick. This helps to guide you about how far to insert the swab.
- Insert the swab into your vagina.
- Turn the swab gently for about 20 seconds. This shouldn't be painful or uncomfortable.

4. Put the swab in the tube

- Try not to let the swab touch anything or it could get contaminated

- Break the stick off at the red mark by bending the stick against the rim of the tube



- Tightly screw the cap onto the tube
- Wash your hands

What if I make a mistake?

It is okay to continue with the test if you

- *have touched the swab with your fingers*
- *have dropped it onto a dry surface*
- *have inserted the swab into your vagina but are unsure if the distance is correct.*

If you are still worried you have made a mistake, phone the study nurse.

5. Label the test

- IMPORTANT: write the date that you took your test on the label and stick it on the tube
- Place the labelled tube into the ziplock bag.

We will send another kit if we cannot get a result from your swab for any reason

If you have any questions about doing the test, please contact our study nurse:
Jane Grant:
hpvstudy@waitematadhb.govt.nz
021 195 3439

Remember you can watch videos about the test. See more information in your invitation letter.

6. Returning the test

1. Make sure you write the date and time you took the test, and your ethnicity on the consent form.

2. Put the consent form and any completed questionnaire into the side pocket of the ziplock bag.
3. Put the ziplock bag into the pre-addressed courier bag.
4. Return the test pack in the courier bag to the lab as soon as possible.

Keep the test at room temperature until you send it.

To send your test pack in the courier bag, you can choose to either...

- *Drop it at a LabTests collection centre near you www.labtests.co.nz/collectioncentres*
- OR *Take it to your GP clinic*
- OR *Phone a free courier to pick it up PH 0800 268 743*
- OR *Book a free courier online at http://courierpickup.courierpost.co.nz/*
- OR *Hand it in at a NZ PostShop (free) – do not put in the post boxes as the test may take too long to get back to the lab*

9.4 Appendix 4 – questionnaire for self-test responders

Questionnaire

Study ID Number

XX				

Research into whether women prefer self-testing for HPV instead of going to the doctor/nurse for a smear test

1. Thinking about your experience today of using the '<u>self-test kit</u>', please rate how the following statements apply to you:

	Not at all	A little	Very much	Unsure/don't know
1. It was easy to use the swab	☐	☐	☐	☐
2. Taking the test using the swab was painful	☐	☐	☐	☐
3. Taking the test using the swab was uncomfortable	☐	☐	☐	☐
4. I felt embarrassed	☐	☐	☐	☐
5. It was convenient	☐	☐	☐	☐
6. I am confident I did it correctly	☐	☐	☐	☐

2. Were the instructions for using the "<u>self-test kit</u>" clear and easy to understand?

☐ Yes, go to question 4

☐ No

3. If not, please tell us why:

_____

_____

4. Did you watch the study video-clips?

☐ Yes

☐ No, go to question 7

5. If yes, which ones?

☐ **About the HPV self-test study**

☐ **How to take part in the study**

☐ **Getting your test results**

☐ **How to do the test**

☐ **About cervical screening, and your rights**

6. Was it/were they helpful?

☐ Yes

☐ No

7. Please write down any comments about the video-clips

_____

_____

<u>Only answer this question if you have had a smear test before:</u>

8. Think about your last smear test performed by a nurse or doctor and the self-test you took, which of the two tests was:

	Self-test	Smear test	No difference between the 2	Unsure/don't know
1. Easier	☐	☐	☐	☐
2. More convenient	☐	☐	☐	☐
3. Less embarrassing	☐	☐	☐	☐
4. Less uncomfortable	☐	☐	☐	☐
5. More accurate	☐	☐	☐	☐

9. What are your main reasons for not having a smear test recently (or ever)? *Please tick all that apply to you, **and then** circle the main reason*

1. I don't think I need a test	☐
2. I don't know if or when I should have a test	☐
3. I am not having sex	☐
4. I have never had sex	☐
5. I have had a hysterectomy	☐
6. A test from a nurse or doctor is embarrassing	☐
7. A smear test from a nurse or doctor is too painful or uncomfortable	☐
8. I have had a bad experience in the past having a test	☐
9. I don't feel comfortable asking for a test from my nurse or doctor	☐
10. My nurse or doctor has not suggested a test	☐
11. It is hard to find the time to have a test	☐
12. It is hard to find or get an appointment with the right nurse or doctor	☐
13. It is hard to find a nurse or doctor of the right sex	☐
14. It is hard to find a nurse or doctor of the right ethnicity	☐
15. It is hard to find a nurse or doctor who speaks my language	☐
16. It is hard to travel to an appointment	☐
17. It is too expensive to have a test	☐
18. I have not received a reminder letter to have a test	☐
19. I don't think test results are accurate enough	☐
20. Other (please write down):	☐
21. Rather not say	☐

Of the reasons you have ticked above, please circle the main reason.

The following questions are about how you would like to have a cervical screening test in the future

10. Would you prefer to do your own test or have a nurse or doctor do the test?

	Select only 1
1. I would prefer a nurse or doctor, *go to question 11*	☐
2. I would prefer to take my own test at home, *go to question 12*	☐
3. I would prefer to take my own test at a medical clinic, *go to question 12*	☐
4. I don't intend to do a test again	☐
5. Don't know/can't say	☐

11. If you would <u>prefer to have a test taken by a nurse or doctor</u>, please tick your main 2 reasons for this:

	Tick 2 main reasons
1. The test is accurate	☐
2. The test is less embarrassing	☐
3. The test is simple to do	☐
4. The test is convenient	☐
5. The test may find other problems	☐
6. I can ask the nurse or doctor about something else	☐

12. If you would <u>prefer to take your own test</u>, please tick your main 2 reasons for this:

	Tick your 2 main reasons
1. The test is free	☐
2. I do not need an appointment with a nurse or doctor to do the test	☐
3. The test is accurate	☐
4. The test is less embarrassing	☐
5. The test is simple to do	☐
6. The test does not require the use of instruments (eg. speculum)	☐

13. If you were going to use this self-test kit again would you prefer to receive the kit:

☐ in the mail, to do at home

☐ collect it from a clinic (such as your family doctor), to do at home

☐ collect it from a clinic (such as your family doctor), to do at the clinic

☐ collect it from a pharmacy, to do at home

☐ collect it from a community laboratory, to do at home

☐ other – please write down

_____

☐ would not use the self-test kit again, *go to question 19*

14. Why would you prefer to receive the kit this way?

_____

15. If you were going to be mailed a self-test kit would you prefer to be:

- ☐ 'automatically' sent the kit when you were due for your next smear
- ☐ get a letter or call first
- ☐ order the kit online from a health professional
- ☐ other – please write down

_____

16. Why would you prefer this?

_____

17. If you were going to use this self-test kit, would you prefer to return your test:

- ☐ by courier
- ☐ return it to a clinic (such as your family doctor)
- ☐ return it to a pharmacy
- ☐ return it to a community laboratory
- ☐ other – please write down

_____

18. Why would you prefer to return your test this way?

_____

19. Would you recommend using the self-test to a friend or whānau?

	Choose 1 option
1. Yes	☐
2. No	☐
3. Unsure/Don't know	☐

20. If you were able to do the test yourself, is it more likely that you would regularly take part in cervical screening in the future?

	Choose 1 option
1. Yes	☐
2. No	☐
3. Unsure/Don't know	☐

The following questions are to help us to look at any differences in women's views about self-tests and smear tests. We want to ask you some questions about your personal circumstances.

21. What is your highest level of schooling?

1. Primary school ☐
2. Secondary school (college) ☐
3. Technical or trade school diploma ☐
4. Undergraduate university degree ☐
5. Postgraduate university degree ☐
6. None ☐

22. What is your household's approximate gross (before tax, levies, etc) annual income?

☐ $1 - $20,000

☐ $20,001 - $50,000

☐ $50,001 - $70,000

☐ $70,001 - $100,000

☐ $100,001 - $150,000

☐ $150,001 or more

☐ Prefer not to say

23. Which generation of your family came to New Zealand?

☐ I was born in New Zealand

☐ I moved to New Zealand from another country

☐ My parents moved to New Zealand

☐ My grandparents moved to New Zealand

☐ My family moved to New Zealand before my grandparents were born

☐ Prefer not to say

24. Is English your first language?

☐ Yes

☐ No

25. If you identify as Māori, do you know the name(s) of your iwi (tribe or tribes)?
A list of iwi can be found at the end of this questionnaire.

☐ Yes Mark your answer and print the name and home area, rohe or region of your iwi below:

☐ No, *go to question 26*

☐ I'm not Māori, *go to question 26*

Iwi _____

Rohe
(iwi area) _____

Iwi _____

Rohe
(iwi area) _____

Iwi _____

Rohe
(iwi area) _____

Iwi _____
Rohe
(iwi area) _____

Iwi _____
Rohe
(iwi area) _____

26. Are there any other comments about the self-test that you would like to make, including any comments about what you think of the kit or the instructions?

_____

_____

_____

Thank you for your time!

Please return this questionnaire to the laboratory with your sample or hand to the clinic nurse

List of iwi to help answer question 25. This list is a guide only. All iwi names are counted even if they are not listed below.

Te Tai Tokerau / Tämaki-makaurau (Northland / Auckland) Region
Te Aupöuri
Ngäti Kahu
Te Kawerau
Ngäti Kurï
Ngäpuhi
Ngäpuhi ki Whaingaroa-Ngäti Kahu ki Whaingaroa
Te Rarawa
Te Roroa
Ngäi Takoto
Te Uri-o-Hau
Ngäti Wai
Ngäti Whätua

Hauraki (Coromandel) Region
Ngäti Hako
Ngäti Hei
Ngäti Maru (Hauraki)
Ngäti Paoa
Patukirikiri
Ngäti Porou ki Harataunga ki Mataora
Ngäti Pükenga ki Waiau
Ngäti Rähiri Tumutumu
Ngäi Tai (Hauraki)
Ngäti Tamaterä
Ngäti Tara Tokanui
Ngäti Whanaunga

Waikato / Te Rohe Pōtae (Waikato / King Country) Region
Ngäti Haua (Waikato)
Ngäti Maniapoto
Ngäti Raukawa (Waikato)
Waikato

Te Arawa / Taupō (Rotorua / Taupō) Region
Ngäti Pikiao (Te Arawa)
Ngäti Rangiteaorere (Te Arawa)
Ngäti Rangitihi (Te Arawa)
Ngäti Rangiwewehi (Te Arawa)
Ngäti Tahu-Ngäti Whaoa (Te Arawa)
Tapuika (Te Arawa)
Taräwhai (Te Arawa)
Tūhourangi (Te Arawa)
Ngäti Tüwharetoa (Te Arawa)
Uenuku-Köpako (Te Arawa)
Waitaha (Te Arawa)
Ngäti Whakaue (Te Arawa)

Tauranga Moana / Mätaatua (Bay of Plenty) Region
Ngäti Awa
Ngäti Manawa
Ngäti Pükenga
Ngaiterangi
Ngäti Ranginui
Ngäi Tai (Tauranga Moana / Mätaatua)
Tühoe
Whakatöhea
Te Whänau-a-Apanui
Ngäti Whare

Taranaki Region
Te Atiawa (Taranaki)
Ngäti Maru (Taranaki)
Ngäti Mutunga (Taranaki)

Ngä Rauru
Ngä Ruahine
Pakakohi
Ngäti Ruanui
Ngäti Tama (Taranaki)
Tangähoe
Taranaki

Te Tai Räwhiti (East Coast) Region
Te Aitanga-a-Mähaki
Ngäti Porou
Rongowhakaata
Ngäi Tämanuhiri

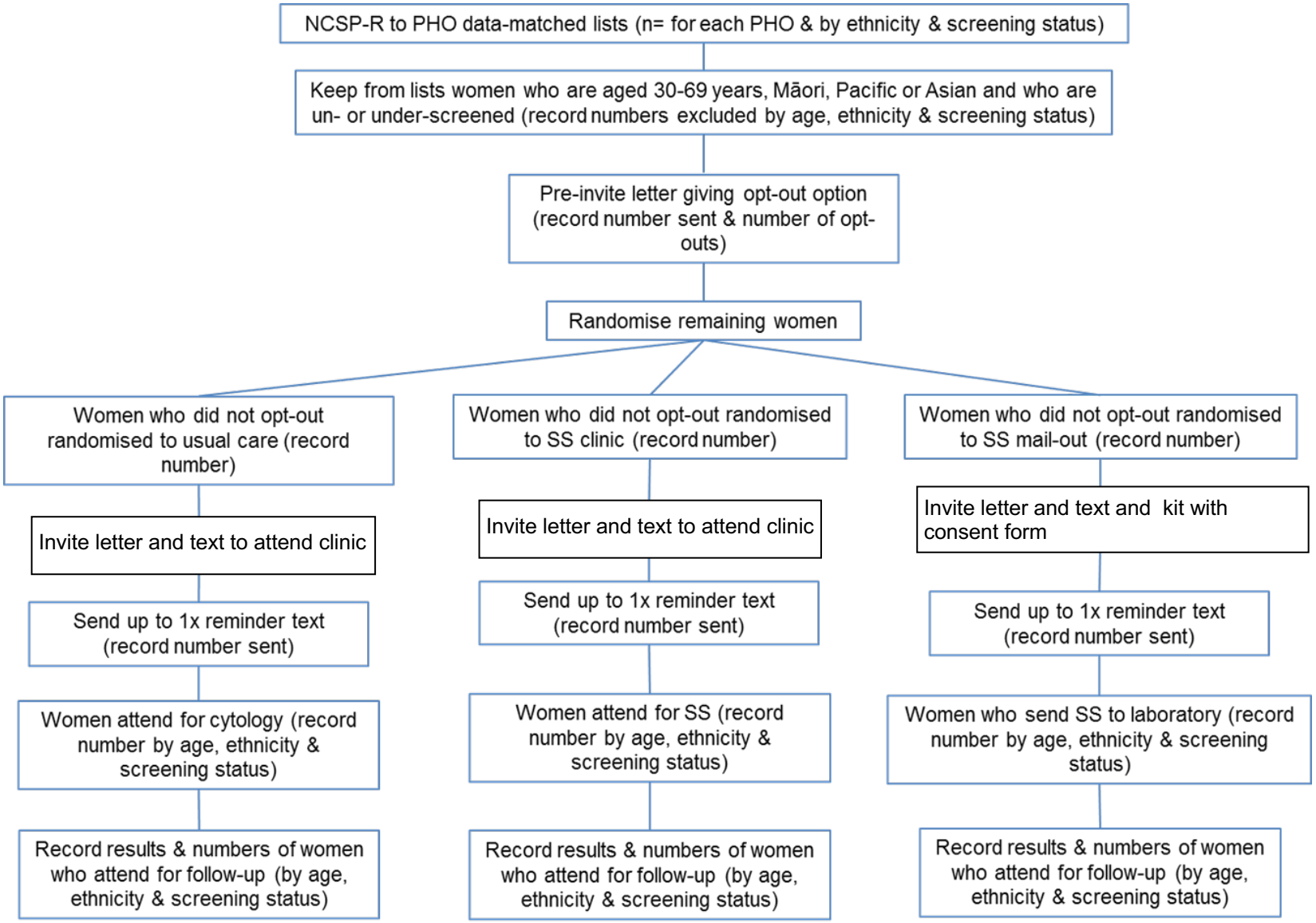
Te Matau-a-Mäui / Wairarapa (Hawke's Bay / Wairarapa) Region
Ngäti Kahungunu ki Heretaunga
Ngäti Kahungunu ki Tämakinui-a-Rua
Ngäti Kahungunu ki Tamatea
Ngäti Kahungunu ki Te Wairoa
Ngäti Kahungunu ki Wairarapa
Ngäti Kahungunu ki Te Whanganui-a-Orotu
Rangitäne (Te Matau-a-Mäui / Hawke's Bay / Wairarapa)
Rongomaiwahine (Te Mähia)
Ngäti Pähauwera
Ngäti Räkaipaaka

Whanganui / Rangitïkei Region
Ngäti Apa (Rangitīkei)
Te Ati Haunui-a-Päpärangi
Ngäti Haua (Taumarunui)
Ngäti Hauiti

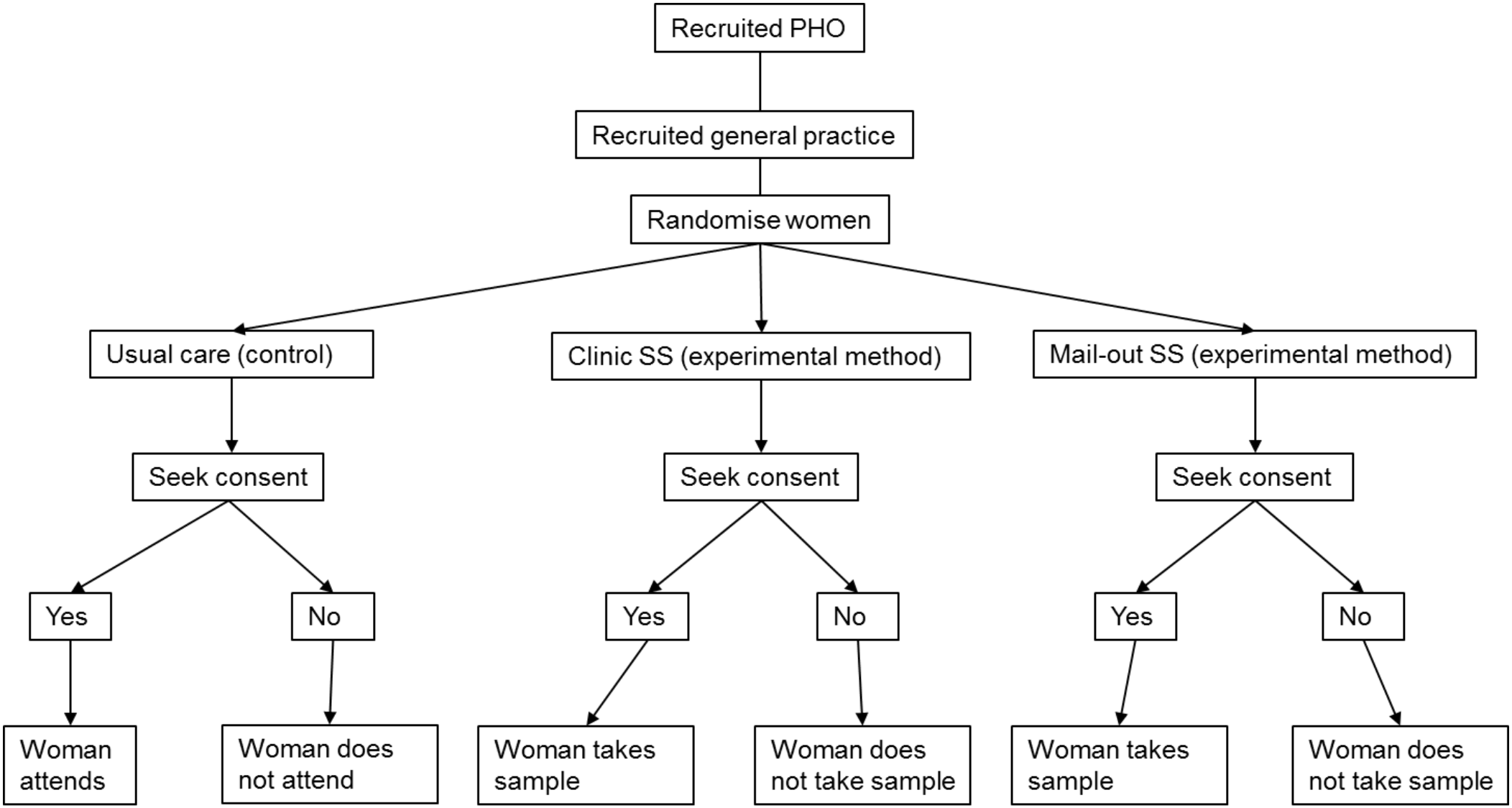
Manawatü / Horowhenua / Te Whanganui-a-Tara (Manawatü / Horowhenua / Wellington) Region
Te Atiawa (Te Whanganui-a-Tara / Wellington)
Te Atiawa ki Whakarongotai
Muaüpoko
Rangitäne (Manawatü)
Ngāti Kauwhata
Ngäti Raukawa (Horowhenua / Manawatü)
Ngäti Toarangatira (Te Whanganui-a-Tara / Wellington)
Ngäti Tama ki Te Upoko o Te Ika (Te Whanganui-a-Tara / Wellington)

Te Waipounamu / Wharekauri(South Island / Chatham Islands) Region
Ngäti Apa ki Te Rä Tö
Te Atiawa (Te Waipounamu / South Island)
Ngäti Koata
Ngäti Kuia
Käti Mämoe
Moriori
Ngäti Mutunga (Wharekauri / Chatham Islands)
Rangitäne (Te Waipounamu / South Island)
Ngäti Rärua
Ngäi Tahu / Käi Tahu
Ngäti Tama (Te Waipounamu / South Island)
Ngäti Toarangatira (Te Waipounamu / South Island)
Waitaha (Te Waipounamu / South Island)

9.5 Appendix 5 – draft CONSORT diagram



9.6 Appendix 6 – randomisation process



9.7 Appendix 7 – HPV test result management and study exit points

Follow-up of women with HPV positive 'other' results

The HPV Self-test Study procedure where women have a test result of HPV positive 'other' follows advice from NCSP clinical advisors that:

i. there is no need for a reflex HPV test on the follow-up smear – the woman is already known to be HPV positive

ii. where the follow-up smear indicates ≥ ASC-US cytology, the woman is referred to colposcopy (without another HPV test), as per current NCSP guidelines.

Where a woman declines a follow-up smear despite offers of support to attend, on a case by case basis and in discussion with the lead colposcopist, she may be referred directly to colposcopy.

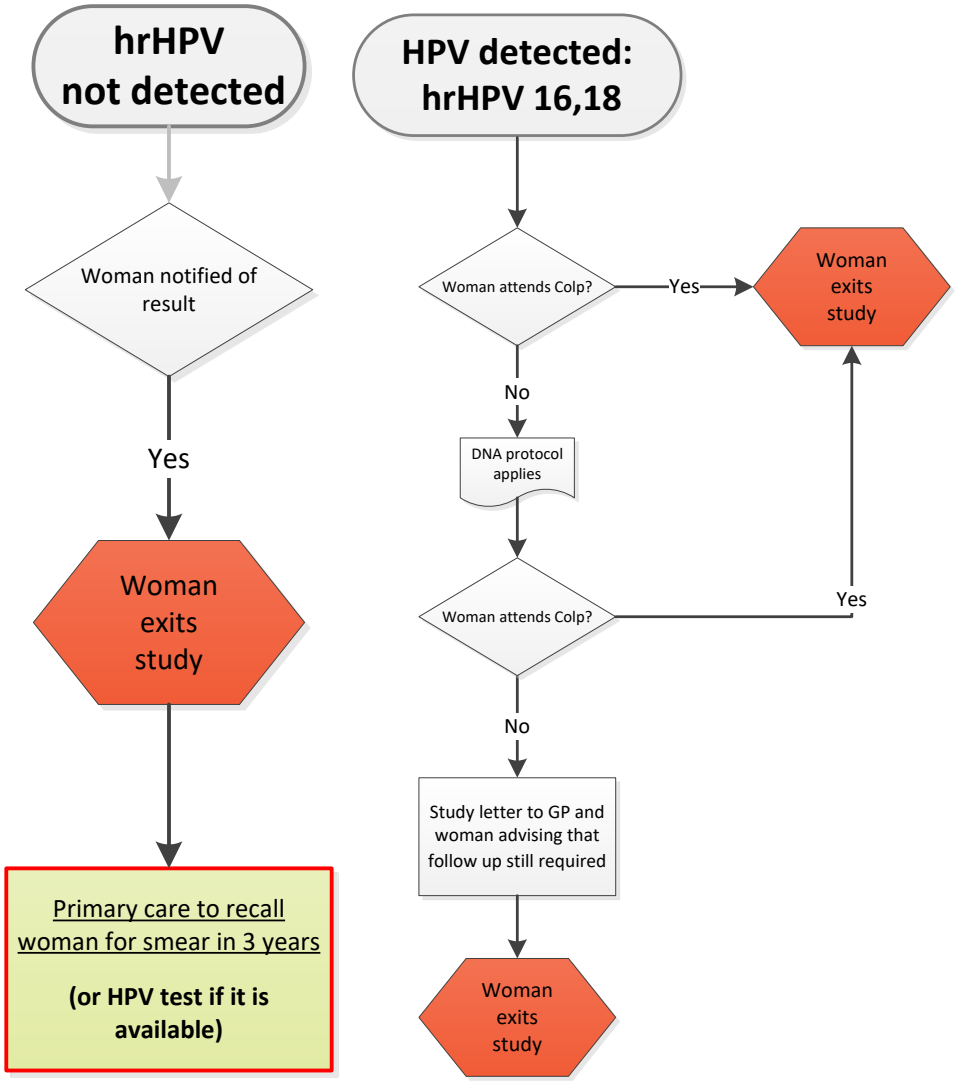
Study parameters

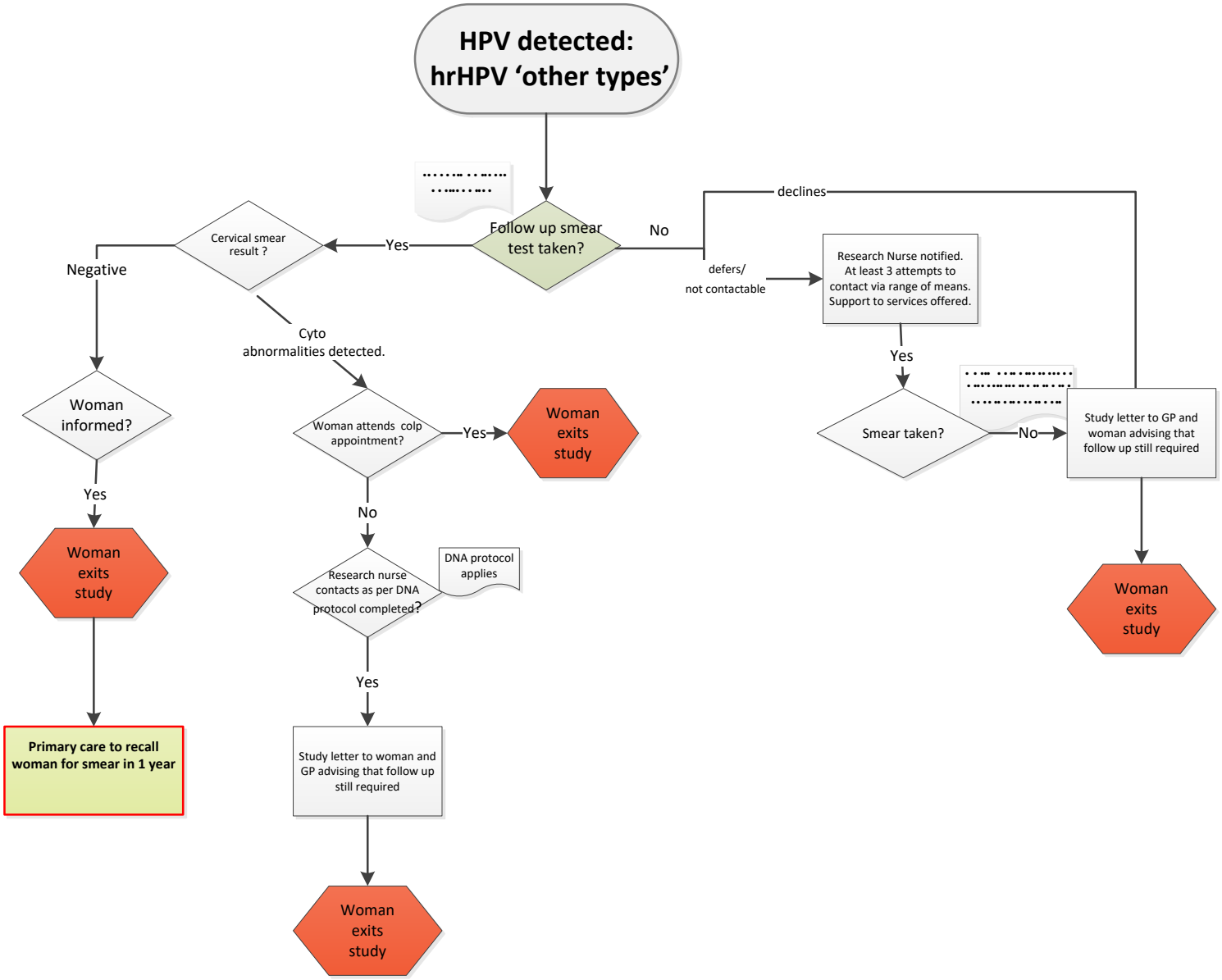
The following flow charts indicate where HPV Self-test Study responsibilities end in relation to follow-up of women in the study:

i. hrHPV not detected

ii. hrHPV type 16, 18 detected

iii. hrHPV positive 'other' detected

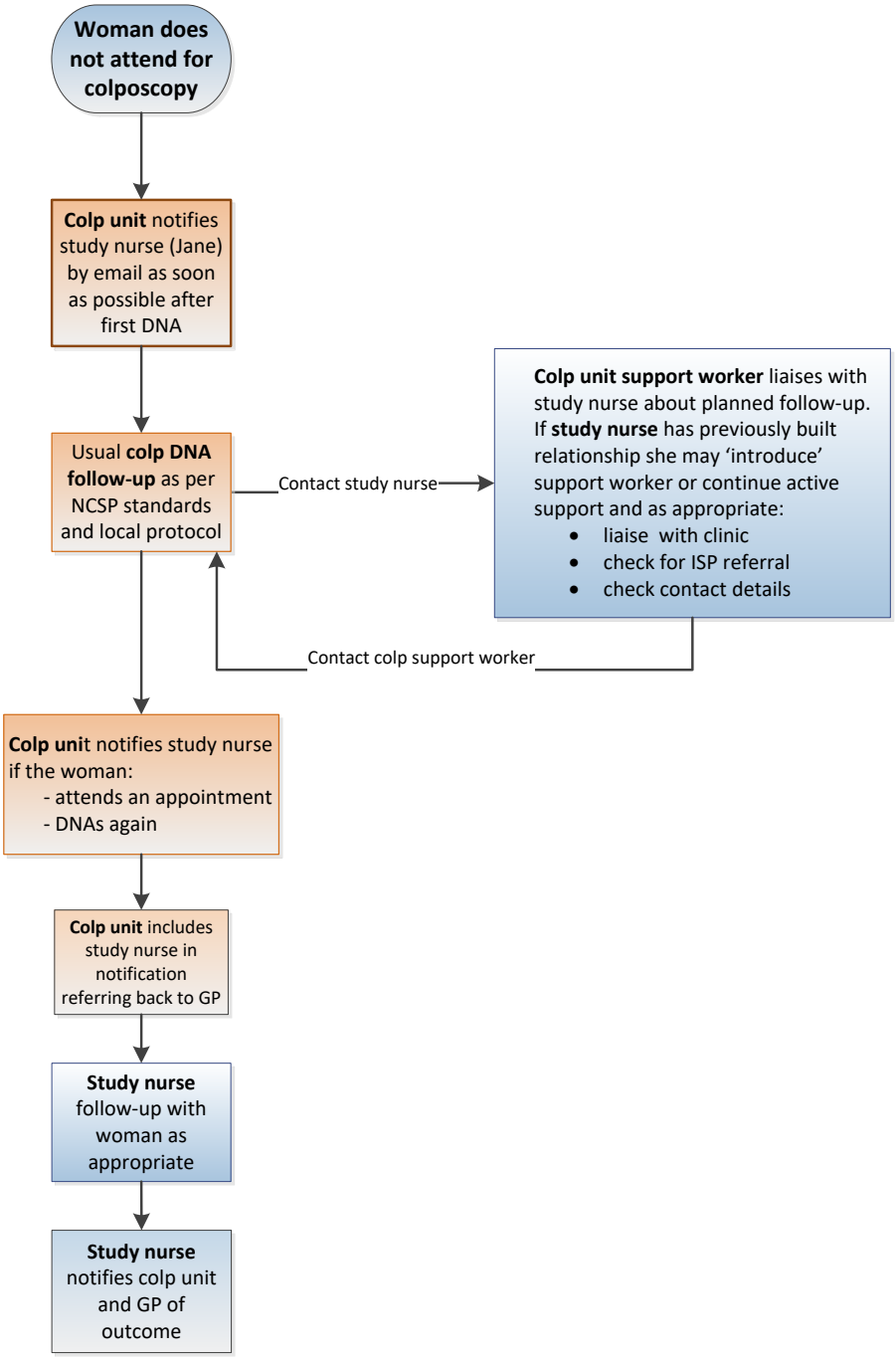

hrHPV not detected
Woman notified of result
Yes
Woman exits study
Primary care to recall woman for smear in 3 years
(or HPV test if it is available)
HPV detected: hrHPV 16,18
Woman attends Colp?
Yes
Woman exits study
No
DNA protocol applies
Woman attends Colp?
Yes
No
Study letter to GP and woman advising that follow up still required
Woman exits study


HPV detected: hrHPV 'other types'
Follow up smear test taken?
Yes
No
declines
defers/ not contactable
Research Nurse notified. At least 3 attempts to contact via range of means. Support to services offered.
Yes
Smear taken?
No
Study letter to GP and woman advising that follow up still required
Woman exits study
Cervical smear result ?
Negative
Cyto abnormalities detected.
Woman informed?
Yes
Woman exits study
Primary care to recall woman for smear in 1 year
Woman attends colp appointment?
Yes
Woman exits study
No
Research nurse contacts as per DNA protocol completed?
DNA protocol applies
Yes
Study letter to woman and GP advising that follow up still required
Woman exits study

9.8 Appendix 8 – HPV Self-test Study: Protocol for colposcopy DNA management

The following process applies for women who are referred from the HPV Self-test Study who do not attend a scheduled colposcopy appointment at ADHB or WDHB colposcopy clinics.

The study aims to achieve 90% follow-up of women with HPV detected. Women in the study with positive HPV results will have had contact and support from the study team to attend the first colposcopy appointment.



9.9 Appendix 9 – Post-test information for participants

After your cervical screening test

important information about your results

Thanks for being a part of the Women's Health HPV Self-test Study.

It's really important that we have your correct contact details so you can get your result and any follow-up that you might need.

Please let your nurse know if your contact details need to updated before you go today.

What happens next?

1. Your nurse will contact you with your result within 10 days.
2. There are three types of results:

HPV not found – you don't need to do anything. Your next test will be due in three years.
HPV other type found – you will need to have a follow up smear test to check if there are any cervical changes. Your nurse can arrange this, or you can choose to be referred to see a nurse specialist to do the follow-up smear test.
HPV 16/18 found – you will need to see a specialist to check for cervical changes. Your family doctor will contact you and arrange this.

All follow up tests are completely free. We can arrange for extra support for follow-up – if you would like this please contact the Study Nurse, Jane Grant.

Questions?
Please contact the study nurse…

Jane Grant
Ph. 021 195 3439
Email: hpvstudy@waitematadhb.govt.nz