Ngāti Porou Hauora
4 McKenzie Street
Te Puia Springs
New Zealand 4010
P (06) 864 6803
F (06) 864 1025
www.nph.org.nz

CENTRE FOR WOMEN'S HEALTH RESEARCH:
Te Tātai Hauora o Hine
VICTORIA UNIVERSITY OF WELLINGTON,
PO Box 600, Wellington 6140, New Zealand
Phone +64-4-463 5497
Email CWHR@vuw.ac.nz
Web www.victoria.ac.nz/health

He Tapu Te Whare Tangata:

a model for empowering rural solutions - a randomised controlled community trial

STUDY PROTOCOL draft – Ngati Porou Hauora Site

Feb 2022

Confidential

RESEARCH TEAM

Investigators	Role
Professor Bev Lawton	**Principal Investigator** – Director, Te Tātai Hauora O Hine, Centre for Women's Health Research, Faculty of Health, Victoria University of Wellington, PO Box 600, Kelburn, Wellington, 6012 bev.lawton@vuw.ac.nz
Charles Lambert	Co-investigator – research assistant and cultural advisor pahauwera.inc@gmail.com
Professor Stacie Geller	Co-investigator – G. William Arends Professor of Obstetrics and Gynaecology, Director, National Center of Excellence in Women's Health, University of Illinois, Chicago. sgeller@uic.edu
Anna Adcock	Co-investigator – Research Fellow, CWHR, Victoria University of Wellington anna.adcock@vuw.ac.nz
Francesca Storey	Co-investigator – Senior Research Fellow - Project manager Francesca.storey@vuw.ac.nz
Dr Leigh Duncan	Co-investigator – Obstetrician Leigh.Duncan@hbdhb.govt.nz
Ms Frances King	Co-investigator – Acting NPH Research Coordinator frances.king@nph.org.nz
Dr E Jane MacDonald	Co-investigator Senior Research Fellow – Project Manager CWHR, Victoria University of Wellington e.jane.macdonald@vuw.ac.nz
Dr Jo-Ann Stanton	Co-investigator - Senior Research Fellow University of Otago, Department of Anatomy. Jo.stanton@otago.ac.nz
Associate Professor Merilyn Hibma	Co-investigator – Pathology Department , University of Otago, Dunedin, merilyn.hibma@otago.ac.nz

Professor Peter Sykes	Co-investigator – Professor of Gynaecological Oncology, Christchurch Hospital and University of Otago, Canterbury peter.sykes@otago.ac.nz
Professor Marion Saville	Australian VCS Foundation – HPV testing and cervical screening expert- will contribute to advisory panel and the loan of two Cepheid machines and donation of swabs for the study.
Associate Professor David Hawkes	Australian VCS Foundation – HPV testing scientific expert- will contribute to advisory panel, the loan of two Cepheid machines and donation of swabs for the study.
Ngaire Sparkes	Research assistant - qualitative interviewer ngaire.sparkes@vuw.ac.nz
Varsha Parag	Statistical analysis for the study varsha.parag@auckland.ac.nz
Mel Gibson-Helm	Co-investigator, Senior Researcher and Data Manager, Te Tātai Hauora O Hine, Centre for Women's Health Research Melanie.gibsonhelm@vuw.ac.nz

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Overview

'He Tapu Te Whare Tangata- a model for empowering rural solutions', reflects the veneration of women within the Māori world as the sacred house of humanity, and the importance of our right to best health.

Whānau living in rural Aotearoa have barriers to appropriate and timely health care, resulting from distance, lack of community control and lack of prioritization of rural needs by District Health Boards (DHBs) and government. This iwi/community/researcher partnership, utilising the cervical cancer screening pathway as an example, will test an innovative model using new technology, to enable the community to control their health care delivery pathways.

Cervical cancer is PREVENTABLE. Māori women are twice as likely to have cervical cancer, and die from it, than non-Māori women. Screening can detect cervical pre-cancer that can be treated, preventing potentially fatal cancer. Currently delays and disparities occur at all stages of the clinical pathway for Māori, from screening to diagnosis and treatment. Human Papilloma virus (HPV) is the causative agent of cervical cancer with fourteen high risk types associated with 93% of cervical cancers. Testing for high risk HPV is a sensitive test better at detecting pre-cancer and preventing cervical cancer than cervical smears. HPV self-taken swabs (self-test) are as good as clinician taken swabs and are acceptable for Māori women. New technology enables processing a swab on site giving point of care results (POC results) in one hour. We hypothesise that HPV self-testing with onsite POC results, kanohi ki-te-kanohi (face-to-face) information, and immediate colposcopy appointments made for a secondary service for HPV positive results, will improve timely diagnosis and treatment for women, compared to HPV self-testing with usual result and referral pathways.

This Kaupapa Māori Research project builds on our long standing and productive partnership with Ngāti Pāhauwera and the Te Wairoa community, and the newly established relationship with Ngāti Porou Hauora (NPH). Governance of this project rests with Ngāti Pāhauwera, Tipu Whaipua and NPH. It addresses community control of this care pathway combined with innovative technology to enable timely access to diagnosis and treatment to prevent cervical cancer.

Background

The name of this project, He Tapu Te Whare Tangata, reflects the veneration of women within the Māori world as the house of humanity.

Cancer of the neck of the womb (cervical cancer) directly affects that sanctity and the ability to bear children. Māori women are more than twice as likely to be diagnosed with cervical cancer and almost three times more likely to die of cervical cancer than Pākehā women. [1] These cancers are preventable. It disproportionately affects young Māori women and is the 2nd leading cause of cancer death for Māori women aged 25-44.[2] [3] However, in Aotearoa New Zealand 32% of Māori women are unscreened or under-screened compared to 22% of NZ European women.[4]

Disparities in Screening, Colposcopy, Diagnosis and Treatment

The National Cervical Screening Programme (NCSP) is failing Māori with 32% of Māori unscreened (no smear) in the last 3 years compared to 22% of non-Maori. By DHB, three-yearly coverage for Māori women ranges from 53.6% to 73.3%. The target level of 80% of Māori women screened within the previous three years was not achieved in any DHB. Once screened there is a failure to achieve timely diagnosis and treatment of abnormalities for Māori. At 90 days, the proportion of women with histological follow-up after a high grade abnormal smear ranges from 74.3% of Māori women to 84.4% of European/Other woman (national target 90%). [5]

Fewer Māori women have a colposcopy in an appropriate time-frame following a high grade smear abnormality when compared to non-Māori women.[6] 74% and 92% of NZ European women had a colposcopy at 20 and 40 working days from referral following a high grade abnormal smear compared to 55% and 76% of Maori women. The proportion of women who had no record of any subsequent follow-up at 90 days is 4.4% for European but 8.6% for Māori women. The cervical cancer review found that of screened women, 44% of Māori women had a high grade abnormality in the 6-84 months prior to their diagnosis of cancer compared to 22% of NZ European women. [6]

This data reveals that Māori women experience specific barriers to access of diagnostic and treatment services following an abnormal screening test. These failures of the screening/diagnosis/treatment pathway lead directly to increased cervical cancer for Māori women.

This mixed methods Kaupapa Māori study combines a randomised controlled trial with qualitative work to address these inequities. It utilises a novel community controlled cervical cancer prevention care pathway paired with innovative 'Point of Care' technology providing timely results (see Fig 1). This mobile, automated, easy to use technology enables screening on site in one hour allowing for quick results for women kanohi-ki-te-kanohi (face-to-face) and the ability to provide immediate wrap around care including information, manaakitanga (support), whānau involvement, shared information and co-decision making with the community provider at the time of the test. This, in turn, allows for immediate referral to colposcopy appointments for follow up of positive tests. We hypothesise that this intervention will firstly lead to more timely colposcopy and treatment and secondly, by

reducing system barriers it will also reduce the number of Māori women who have a screen but are unable to access diagnosis and appropriate treatment due to these barriers.

Figure 1: POC: The Cepheid GeneXpert IV showing cartridge inserted into module 2 (left), and the GeneXpert HPV, fully contained reagent and sample processing cartridge (right).

Our ongoing He Tapu Te Whare Tangata work in Te Tai Tokerau (HRC 17-193) and work by others, have identified the need for improved pathways of cervical cancer prevention screening for rural Māori women.[6-8] For example, from our qualitative work we found that women require additional information and support when they have a positive HPV self-test beyond a letter or phone call (personal communication Kendall Stevenson).

Utilizing an innovative model for iwi/community involved partnerships can enable the community to control their health care delivery systems. Findings from this study will inform the new NCSP policy. If successful it will have significant implications for the broader delivery of other rural health care pathways such as POC and Rheumatic fever, Influenza, TB, measles and new technologies utilising AI (Artificial Intelligence).[9 10]

Human Papilloma Virus (HPV) and HPV testing

It is known that certain oncogenic types of the Human Papilloma Virus (HPV) are the causative agent of cervical cancer. Since 2011, international experts have been recommending HPV testing as first line cervical screening.[11-13] Self-collected specimens using a vaginal swab can be used for HPV screening, providing sensitivity and specificity comparable with clinician-collected specimens and this method detects cervical disease earlier than cytology. [14] Self-test swabs, especially home based, may overcome some barriers to cervical screening for Māori women.[7] Evidence now shows that HPV testing in primary screening is superior to cytology in reducing cervical cancer incidence and mortality. Australia has moved to HPV testing as the primary test using cervical/ speculum sample and this is projected to decrease cervical cancer incidence in Australia by 15–18% and cancer mortality by 16–18%, compared with current cervical smear practice.[15]

Point of Care Results (POC)

New technology enables on site POC results in one hour. Technology developed by Cepheid (CA, USA) allows the immediate, on-site testing of self-collected vaginal swabs in non-clinical settings, including limited access to trained personnel. The Cepheid Xpert-HPV test (see Fig 1) is fully validated for clinically significant HPV infections. That is, it tests for 14 high risk HPV (hrHPV) and differentiates genotypes HPV16 and HPV18/45. All these types are known to

cause more than 95% of cervical cancers. Its sensitivity and specificity is comparable to those of well-established HPV assays and it fulfils the criteria for use in primary cervical cancer screening. [16] The WHO has adopted the Cepheid Xpert HPV test as an accepted test, listing it in December 2017.[17] The test takes an hour from sample presentation to result, with a few minutes hands-on operator time. It has been shown to be as effective with self-taken vaginal samples as with clinician taken cervical samples.[18] [19] The technology is robust but user training and support will be vital. We will build user and instrument proficiency testing into our implementation processes that will conform to the New Zealand Best Practice Guidelines for Point-of-Care Testing.[20]

The aim of the study is to explore the acceptability and feasibility of community control of care pathways combined with innovative technology (POC results) to overcome the barriers existing for rural Māori communities using cervical screening as a model**.**

METHODOLOGY

Pathway 1 is HPV self-test with onsite POC results within one hour paired with kanohi ki te kanohi (face to face) information, support and immediate appointments for a secondary service for those who are HPV positive.
Pathway 2 is HPV self-test with swab sent to laboratory, and the usual result giving, information and support, and usual referral pathways for those who are HPV positive.

Hypothesis
We hypothesise that **Pathway 1** will improve timely diagnosis and treatment access for women, compared to **Pathway 2**.

This is a cluster crossover intervention trial, with communities (study sites) as clusters. The two rural North Island communities (Te Wairoa, Ngāti Porou rohe of Tairāwhiti) will be randomised to either starting with Pathway 1 or Pathway 2 and then crossing to the other pathway after 15 months for the second period of the study. The trial governance will be led by Ngāti Pāhauwera with Tipu Whaipua (Te Wairoa steering committee) and Ngāti Porou Hauora.

Women in both pathways will be offered a HPV self-test as the HPV self-test is acceptable for Māori and is likely to be gold standard when the new HPV primary testing programme commences in NZ.

Study Objectives
1. To compare a community controlled innovative cervical cancer prevention care pathway with usual referral pathway to examine whether timely access to screening, diagnosis and treatment can be improved. (quantitative).
2. To assess acceptability and feasibility of community control of the care pathways (qualitative).

Ethics
Approval from the National Health and Disabilities Ethics Committee (HDEC) was given in Dec 2020 (20/NTB/311), the Hawkes Bay DHB and Tairāwhiti NPH locality were approved Feb 2021 which includes Māori directorates.

The Ngāti Porou Hauora Board also approved for the project to proceed with NPH primary care service and eligible patients.

The Wairoa directors and board have approved for the project to proceed in the Wairoa (Queens Street Practice) primary care service and eligible patients.

Kaupapa Māori Research Methodology
This mixed methods research will be implemented from a Kaupapa Māori Research (KMR) inquiry paradigm. This paradigm sees being Māori as normal and challenges how Māori have been, and continue to be, constructed within a colonized worldview. It promotes a structural analysis of inequities for Māori, seeking to more fully understand people's lives and the systemic determinants of their health and wellness.[21] [22] From this paradigm, Māori worldviews, ways of knowing and mātauranga Māori (Māori knowledge) are seen as valid and legitimate. With this KMR mixed methods approach, we seek to combine 'multiple ways of knowing and seeing the world'.

Our consultation plan is ongoing and is led by our Kaumātua. Māori are involved at all levels from protocol development, instigation and follow up, and trialling of this innovative clinical care pathway. Importantly the governance of this project rests with Ngāti Pāhauwera, Tipu Whaipua and NPH, giving community control of leading edge POC technology.

This protocol draws on the strengths of rural community practices who are successfully engaging Māori from a Whānau Ora approach through locally appropriate practices such as kanohi ki te kanohi, kaiawhina, and multiple venues for interventions. It will inform theory and practice about rural models of utilisation of innovative technology, addressing Māori cervical cancer inequities, facilitating Māori wellness, and the flexibility of methods to be implemented within KMR.

Study Population: Women aged 25-69 years in the Te Wairoa part of the Hawkes Bay DHB area, and those women who are Ngati Porou Hauora (NPH) registered patients in the Tairāwhiti DHB.

Inclusion and exclusion criteria: All women aged 25-69 years eligible for a cervical screen in these two rural areas who agree to an HPV test. This age group is in line with NCSP changing the national screening criteria to the 25-69 year age group in November 2019. In line with NCSP current protocol, women can present for first screen up to 6 months before their 25th birthday and be included. Women can present for their screen up to 6 months before their due date and be included.[23] Women who are due for a smear or who are under-screened (under-screened defined as never screened or 4 years or more since last screen) are invited to participate but in line with the iwi and community focus, priority will be under-screened or never-screened Māori women. Women with heavy bleeding at time or using a vaginal cream that might interfere with the test will be asked to return at a later date.
Women who opt for cervical cytology or whose GP advises a speculum examination/cervical cytology can also take part in the study by taking an HPV self-taken swab first. Women who

have symptoms such as abnormal bleeding can still be offered an HPV swab but as this is a screening test only, they should also be seen and assessed by a GP and may require assessment by secondary gynaecology services despite a negative HPV test.

Cohort lists

In discussion with the community and iwi and on advice from HRC biostatistician, the Wairoa Health and the NPH primary care service will identify the list of under-screened and never screened women through the patient management system before recruitment starts in February 2021. This list will not be altered during the study. To minimise bias, half the under-screened women will be offered the HPV test in year one and the remainder will be offered the HPV test in year two. All women due a cervical screen are eligible for study participation.

Objective 1 Quantitative

To compare a community controlled innovative cervical cancer prevention care pathway with usual referral pathway to examine whether timely access to screening, diagnosis and treatment can be improved (quantitative) (see Table 1). Recruitment of women to start by end of Feb/start of March 2021.

TABLE 1: Pathway 1 compared to Pathway 2

<table>
<tr><td colspan="2"><u>ALL WĀHINE HAVE HPV SELF-TEST</u>
  </td></tr>
<tr><td colspan="2">One site will start on Pathway 1 and the other site will start on Pathway 2. After 15 months the Pathways will then cross over for the second 15 month period recruitment so each site will experience each pathway over the 30 months of the study. NB this timeline has been extended see Page 19</td></tr>
<tr><th>Pathway 1</th><th>Pathway 2</th></tr>
<tr><td>POCResults in 1 hour
  </td><td>Test swab to off-site lab</td></tr>
<tr><td>Immediate on-site result to patient with information and support
HPV negative information given with follow up screening times</td><td>Results to GP/Nurse</td></tr>
<tr><td>Immediate referral date for colposcopy if HPV positive</td><td>Patient notified by text or phone
HPV negative information given with follow up screening times</td></tr>
<tr><td rowspan="2">Colposcopy</td><td>Letter/ phone/ text to patient if positive
Letter of referral to gynaecologist
Outpatient appointment generated & sent to patient</td></tr>
<tr><td>Colposcopy</td></tr>
</table>

Primary Outcome- Pathway 1 vs Pathway 2

Proportion of women with an HPV positive test having a colposcopy within 20 working days (MOH Indicator) of referral

Secondary Outcomes: Pathway 1 vs Pathway 2
Proportion of women with an HPV positive test having a colposcopy within 40 days of referral (MOH indicator)

1. Time from test to patient notification of results (positive or negative)
2. Time from test and time from receiving results to treatment for women with positive results/high grade histology

For both groups: (Intervention and Control)

3. Numbers of HPV positive, HPV negative results and invalid results
4. Numbers of high grade lesions (CIN2 CIN3, Carcinoma)
5. Proportion of under-screened / never screened women receiving test and follow up

Training
Both sites' doctors, nurses, kaiawhina and research assistant will receive an HPV update and information sharing session with experts in the research team before recruitment of women starts. These updates will include the role of HPV in cervical cancer, the HPV self–test, the potential role of POC testing, how to get informed consent, how to instruct women on taking a self-taken swab, following up results, the role of the research team and how the study will run.

The site randomised to Pathway 1 for the first year will nominate two or more primary care clinicians and/or two or more kaiāwhina to be trained by expert members of the research team in the operation and daily quality audit of the Cepheid GeneXpert IV machine. Four members of the research team have qualified training in the use and running of the Cepheid GeneXpert machine.The machines are being provided for this study from co-investigator David Hawkes' team in Australia. The POC machine training will be done in the 1-2 weeks prior to recruitment starting so that it is fresh in people's minds. We anticipate that the POC expert Assoc. Professor Jo-Ann Stanton will be able to stay for the first few days of recruitment to help the POC users with any issues and visit the site at regular intervals (e.g. 3 monthly). The technology is robust but user training and support will be vital. We will build user and instrument proficiency testing into our implementation processes that will conform to the New Zealand Best Practice Guidelines for Point-of-Care Testing for example this will included training to quality assure the machine every day before using on study samples.[20] In addition, the research team and site clinicians involved in Pathway 1 (POC testing) are participants in the Royal College of Pathologists of Australasia Quality Assurance Programme (RCPA QAP).

One to two weeks before the Pathways cross over at the end of year one, the second site will receive the same additional training as described above on how to use the Cepheid GeneXpert IV machine.

Process of study for women- both arms
All women in the both pathways will be offered an HPV self-test. This test can be offered in the clinic, off- site in the home, marae and/or at other events. The women will be given participant information and sign a consent form for taking an HPV self-test if they wish to take part. If they are in **Pathway 1** they will also be given information about the POC, results, support and follow up referral if required. Consent for both pathways will include:

- Consent for copy of HPV results, (and if colposcopy is required, copies of histology results) to be sent to the ordering health practitioner and the senior researcher.

- Consent and contact details (mobile phone, email address) if the woman is happy to be contacted at a later date by the qualitative research team for interview or hui about the HPV self-sample and process.

Consented women will receive verbal, written and /or pictorial instructions from a doctor, nurse or kaiāwhina (community health worker) about how to perform the HPV self-sample, a self-collected vaginal sample. Women will self-collect a vaginal sample using a nylon-flocked swab (COPAN FLOQSwabs, ITALY). The instructions will detail how to insert the swab into the vagina and place it into a collection container.

Women in both arms who have positive HPV results will be offered usual support to attend colposcopy. This will include petrol vouchers, transport and/or a support person to accompany them.

Pathway 1

- Woman identified as fulfilling inclusion criteria
- Given and discussed participant information about HPV self-test and POC results
- Patient consent signed
- Self –test taken
- Test run through the Cepheid GeneXpert IV machine and result automatically downloaded into patients Medtech file
- POC results given face-to-face (kanohi-te-kanohi)
- HPV negative result - woman informed of the result and its significance and advised that she will not need a smear test (or HPV test if the NSU policy has changed) for 3 years
- Women with hrHPV positive results will receive immediate on-site information about result, its significance, colposcopy explained, support and a date for colposcopy (the follow up diagnostic test).
- If a woman is unable to stay for an hour to receive her test results this will be documented, her contact details will be taken and she will be contacted as soon as the result is available and information and appointment for colposcopy made at the time when the health worker is able to contact her with the result.

Pathway 2

- Woman identified as fulfilling inclusion criteria
- Given and discussed participant information about HPV self-test
- Patient consent signed
- Patient asked how she would prefer to obtain the results – documented in clinical notes as per usual care with cervical screening (text, phone, kanohi ki te kanohi)
- Self -test taken
- Labelled as per usual - name, date of birth and NHI
- HPV self-test sent to the laboratory for analysis
- Results will be reported to the GP or nurse though Medtech
- Clinician notifies patient
- HPV negative result - woman informed of the result and its significance. Advised she will not need a smear test (or HPV test if the National Screening Unit (NSU) policy as changed) for 3 years.

- For women with hr HPV positive results - woman informed of the result and its significance usually by phone or in person, and about the follow up referral process & support to attend this appointment
    - Colposcopy explained
    - GP refers to gynaecology outpatients
    - Patient triaged for colposcopy
    - Appointment time sent to patient by mail with or without phone follow-up
    - NPH kaiawhina organises petrol voucher/transport support

Note for all women with hrHPV positive results
Women may have results that are positive for HPV 16, 18, 18/45 or 'other' high-risk HPV types. Results will be given in person, face-to-face (kanohi-ki-kanohi) or by telephone (depending on participants chosen method and pathway of study) in a sensitive and appropriate way. Women may choose to have whānau or friends to support them when receiving the results. It will be emphasised by the clinician that having a high risk HPV positive results DOES NOT mean that the woman has cancer – this is very unlikely - but it may indicate that there are pre-cancer changes on the cervix. These changes can be identified and treated BEFORE they develop into cancer. Women will receive as much information as they need about the referral process to colposcopy and the colposcopy process itself using National Screening Unit (NSU) information already available as well as verbal information from the primary care clinician.

For Pathway 2
Transport to lab
Specimens will be transported at room temperature to the laboratory who have the contract with the Research Trust Victoria University (TBC) for this study.

Laboratory Test and Process
HPV genotyping will be carried out using a PCR platform assay which will be validated for cervical swabs not dry vaginal swabs. However, the use for this study has been validated in international published studies and the laboratory will agree to do this 'off instructions use (IFU) license' testing as part of this study and this is included in the consent form. This project has contracted laboratory services from Medlab Central Palmerston North (Head Molecular Scientist Dr Rebecca Lucas-Roxburgh). The PCR platform used is Roche cobas® 4800 system for HrHPV testing. This system detects 14 high risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) and provides a result which distinguishes types 16 and 18 from "other" high risk types and distinguishes from negative samples.

Results
Results of the HPV test from the Pathway 2 will be sent electronically encrypted (as other routine results) to the ordering primary care clinician at the primary care health clinic with a copy sent to the co-ordinating researcher at the Centre for Women's Health Research. All results from both arms will be entered into a secure password protected database. Once linked to a study number the identifying details will be removed before the research team analyse this data.

Colposcopy

Based on our preliminary qualitative research under-screened women requested that if they had a HPV high-risk result of any type other than 16, 18 that they be referred for colposcopy for definitive diagnosis rather than referred for a cervical smear. Based on overseas figures and our recent research 10-12% of women will have a positive high risk HPV test result. For 1200 screenings we would expect 120-144 women to need colposcopy over 2 years. That is an estimate of 30 per year for each site with approximately 3-4 of these women with CIN 2+ disease requiring treatment. Colposcopies will be done at each DHB gynaecology service as arranged with lead colposcopists, Dr Bill Weiderman (Tairāwhiti DHB) and Dr Lynda Croft (Hawkes Bay DHB).

The woman will be registered on the NSU database when they attend colposcopy. A cytological sample will be taken. Colposcopy will be performed in the routine fashion and documentation of colposcopy will be recorded on the Gynae - plus database. In view of the fact that cytology will not be available at the time of colposcopy further reducing the sensitivity of colposcopy the threshold for biopsy should be low. In the case of an abnormal transformation zone (TZ) of cervix, it is recommended that more than 1 biopsy is taken and if the TZ is normal, a random biopsy should be taken to confirm normal histology. If the TZ is not visible, the patient will be reviewed in the light of the cytology result, HPV type and other clinical details.

Funding for HPV tests and colposcopies

The study will fund all the HPV tests and there will be no cost to the woman. The NSU have been approached to fund those colposcopies where the hrHPV results shows either 16 or 18 and the study will fund those hrHPV result for other oncogenic types. We have consulted with the heads of the respective DHB's gynaecology departments about the increase in colposcopies expected for the duration of the study and they have agreed to this potential increase in colposcopies as part of their desire to provide best evidenced based care to women in their community and are supportive of the study.

Special circumstances

- COVID-19 - In view of the changing global pandemic we will incorporate MOH, and each participating health providers' infection prevention and control procedures around the wearing of PPE if the country or region is at Alert Levels 3 or 4; and/or postponement of kanohi ki te kanohi (face to face) interactions. We anticipate that the HPV self-test will be able to be done despite most alert levels as close clinician – patient contact (compared to the taking of a cervical smear) is not necessary. However, those decisions for each Alert Level will be made by the participating healthcare providers' management.
- If the test is 'unsatisfactory' for testing the lab will request another sample from the woman taken ideally after 6-12 weeks.
- The woman in either arm may opt for the clinician to take the 'HPV swab'. This should be noted on request form.
- If the woman in either arm opts for cervical cytology or the GP advises a cervical cytology she can still take part in the study by taking a self-test swab before she has her speculum examination.
- Women who have had a hysterectomy but who are still being screened because of previous cervical abnormalities can be offered the HPV test.

National Screening Unit (NSU) register –National Cervical screening Programme (NCSP)

The NSU system will not allow for the woman to be automatically registered on the NCSP database, as there will be no accompanying cytology. If a woman does also have a cervical smear this will be processed and registered as usual. The NSU have decided that for this study laboratory HPV results should not be sent to the register. However, at the request of the NCSP, it has been agreed that an updated list of women having the HPV tests in both pathways will be sent by the research team securely to Sue Wilson (Data Manager at NSCP) so that these women will be flagged as 'research participants' in the NCSP data base.

The ordering health practitioner is responsible for follow up on the HPV results. The research team will assist as needed and be the back for follow up. If a woman has a positive hrHPV result then it is the responsibility of the ordering health practitioner to organise the referral for colposcopy and the senior co-ordinating researchers Prof Bev Lawton, Dr EJ MacDonald or project manager Ms Fran Storey will also liaise with the health practitioner to ensure clinical safety. The referral letter sent to the colposcopy clinic will state that the woman is part of this study and why cytology is not available nor NSU registration. As stated above the woman will be registered on the NSU database when they attend colposcopy.

Because of the inability of the NSU to record the HPV tests as a screen the women will not be reminded by the NSU register when their next smear will be due (or HPV test if programme has changed). This will be the responsibility of the primary care practice with back up from the senior research team.

Data Collection by the CWHR Research Team

Women who meet the inclusion criteria will be identified in primary care. Socio-demographic information: ethnicity, deprivation index (socioeconomic status) and age will be obtained from primary care and validated against nationally held data from the Ministry of Health (MOH) National Health Index (NHI) dataset. Clinical information and screening data from local practices will be used to obtain information on clinical and screening history and this will be validated against nationally held screening data. Using women's NHI number, a unique patient identifier used in all MOH data collections, we will link to the National Screening Unit database to confirm screening history as some women may have had a screen in another DHB area.

Randomisation

The order of treatment for each practice will be randomly allocated by the study statistician using computer generated random numbers.

Sample size

The primary outcome is the proportion of women having a colposcopy within 20 working days from referral, for those women with a positive HPV test result. The target communities are predominantly Māori women in a rural setting. Based on the latest percentage reported for Māori women throughout New Zealand, we assume that 56.4% of women in the control arm will have a colposcopy within 20 working days following referral for a positive HPV test (ref). We aim to detect a 50% increase (RR=1.5) from 56.4% to 84% in the primary outcome for the intervention arm. A sample size of 80 women (40 in each arm) in a two-period, two-cluster randomised crossover trial will give 80% power at 2-sided alpha of 0.05 to detect a 50% increase in the intervention arm. With only 2 practices serving as the clusters, the sample size does not

account for the cluster effect which was considered as a fixed effect in the final analysis.

Analysis

All statistical analyses will be performed using SAS version 9.4 and R version 3.4.2 Analyses will be Intention to treat and conducted at the individual participant level. All tests of significance were two-tailed and a 5% significance level throughout the analyses. Continuous variables were compared with t-tests or Mann-Whitney tests and categorical data with chi-squared tests as appropriate.

A generalised linear regression model with a binomial distribution and logit link will be used to analyse binary outcomes, and a linear regression model will be used to analyse continuous outcomes, with treatment and period fitted as fixed effects. For the primary outcome both unadjusted and adjusted analyses for potential covariates measured at baseline will be conducted. Time to notification and time to colposcopy will be analysed using Kaplan-Meier curves, log rank test and Cox proportional hazard models.

Data safety and monitoring

We will have an internal data and clinical safety monitoring committee. Members of an internal committee will include Professor Bev Lawton, Professor Peter Sykes, Associate Professor David Hawkes (molecular virologist), Assoc. Prof Merilyn Hibma, Biostatistician (data) and Dr E J MacDonald. The group will meet monthly by teleconference during the course of the study to review any issues. The research team based in the community and primary care will have immediate access by phone to one of the group members to discuss any issues as they arise. The monitoring committee will report to the wider research team. An external data safety monitoring committee has been formed by HRC and the research group report regularly to this committee. A second external statistician will audit the data before we analyse and write up the results.

Qualitative Arm of the Study

Objective 2
To assess the acceptability and feasibility of community control of the care pathways (qualitative)

Hypothesis:
Community/iwi control of the care pathways is acceptable and feasible for rural Māori communities.

Primary outcome:
To explore and understand the successes and challenges of both pathways from the perspectives of the governance groups, clinical staff (nurses, doctors, kaiāwhina, specialists), and women participants (and whānau supporters) at both sites.

Secondary outcome:
To understand this new screening pathway to advise and inform a more culturally responsive NCSP.

Recruitment
Key informants at both sites will be invited to take part in hui (either interview or focus group). The governance groups (<4 focus groups) and clinical staff (<10 focus groups) in both regions will be identified and recruited through their involvement in the project.
Women (and any supporting whānau if desired) who participate in each pathway will be asked to indicate on the original consent form if they are happy to be contacted by a researcher about the qualitative research, and if they are, they will be invited to participate (and consented again). Up to 20 women (RCT participants) from each site (both pathways) will be interviewed (total N<40 women plus any whānau).

Semi-structured hui (interviews and focus groups)
All hui will take place at a time/place appropriate for the participants. For example, bi-monthly governance group meetings (for the governance groups), weekly/monthly clinic meetings (for clinical staff), at home or a public place (for women and whānau), or via zoom/telephone (if face-to-face is not convenient or possible due to COVID-19 requirements).

Interviewers will obtain written informed consent (by email or paper consent form) and will follow appropriate rituals of encounter, e.g. mihimihi (greetings), karakia (prayer/incantations) if desired by participants, sharing of kai (food), koha (supermarket voucher) for RCT participants, and acknowledgements.

All hui will be recorded and later transcribed verbatim. They will be semi-structured around 5 questions/talking points, with emphasis relevant to the participants. 1) Acceptability of the screening pathway/s for the community; 2) Level of community empowerment/co-decision making in the pathway/s; 3) Preferred screening pathway or processes; 4) Recommendations for future screening policy/practice and other future pathways; 5) Anything else to add or ask.

Qualitative Analysis

Qualitative data will be analysed thematically. This entails reading and rereading the transcripts for an emergent conceptual framework, themes and subthemes. The transcripts will be coded using NVivo qualitative data analysis software. Each sub-theme will be organised so that the feedback from participants can be written in a way that groups the participants talk about common issues, and how these issues are inter-related. In interpreting the findings, objectives 1 and 2 will be addressed. This Kaupapa Māori Research prioritises the needs and aspirations of the community, and as such, the governance groups will guide the mobilization of knowledge from this research and identified preferences for translation into policy, practice, and future pathways.

Project Timeline Amended

The first seven months of the project will include obtaining ethics approval, co-designing materials and protocols with the iwi, community and practices. The first phase was to be **Pathway 1** in one arm (ie, study site) and **Pathway 2** in the other arm running from Feb 2021 to Jan 2022 with the arms crossing over for a further 12 months, Feb 2022 until Jan 2023. As a recommendation from the HRC Data Monitoring Committee, the first year of recruitment has been extended by 3 months and will run in both pathways till end of April 2022. The crossover will occur in May 2022 and will run for up to 15 months in each pathway.The remaining project time will be spent analysing, writing up and disseminating results, with particular emphasis on reporting back with iwi and community and to consider further pathway models with the iwi/community. The qualitative phase will run in parallel to the intervention/control trial once recruitment has started.

Task	Jul 2020-Feb 2021	Feb/March 2021 – April 2022	May 2022-July 2023	August Sept 2023
• Ethics • Iwi/Community/Practices consultation • Recruitment and training primary care practices				
• Randomisation of areas to **Pathway 1 or 2** • Intervention commenced • Data collection • Qualitative interviews • Regular progress meetings				
• Crossover of **Pathways** • Qualitative interviews continued				
• Analysis • Write up • Dissemination of Results				

Write up of results

All co-investigators will contribute to the write up of the results under the lead authorship of the principal investigator.

Dissemination of Results

We have a dissemination plan specific to our project "He Tapu Te Whare Tangata". Our goal is to improve outcomes and this requires our partnership (researchers, community and primary care) having ongoing consultation with multiple groups. Our priority for the dissemination of results will be firstly the community and Māori health organisations and strategic organisations that have been part of the research process. Maintaining the link between academia and Māori communities is part of our commitment to ongoing consultation and dissemination. Dissemination and consultation with the clinical workforce, health services (DHBs) and policy makers is a priority to inform about results and to bring about change. Importantly we will have ongoing consultation with the National Screening Unit with the goal that this community intervention if successful will directly inform the future changes to the National Cervical Screening Program to prioritise Māori and lead to a program

that meets the needs of Māori. Dr Lawton (PI) is on the Technical Advisory Group for the introduction of the NZ primary HPV testing program. She is a previous member of the National

Kaitiaki Group and the Māori Equity Advisory Group for the introduction of the HPV vaccine into NZ.

We have established multidisciplinary clinical networks in all 20 DHBs that are keen to be involved in receiving this knowledge and in change management activities. Multiple opportunities will be taken to disseminate results at a range of Māori health and other hui such as: Māori health provider Board and staff hui, and Marae committees. At a regional and central level, our focus is to achieve change and influence policy and practice hui may include: Māori Women's Welfare League, National Kaitiaki group, workshops, educational courses, policy groups, advisory committees, Te Ora, Ngā Neehi Māori, He Hono Wahine etc. In addition, we plan to publish our findings in high ranked peer review publications and presentations at indigenous forums to share and learn.

Conflict of interest statement

Co-investigators include primary care clinicians with clinical responsibility for participants. This is acknowledged by the research team as potential for conflict of interest. However, the dual role of clinician being also researcher in this study would appear to be appropriate as the participant will have her usual clinician providing care, advice and follow up. This will be fully disclosed and discussed with the participants. Co-investigators are not remunerated on the basis of recruiting participants to the study.

Any community researcher employed will be on a term contract for the duration of the recruitment period and the employment or remuneration will not be dependent on recruiting participants into studies.

REFERENCES

1. 1. Robson B, Purdie G, Cormack D. Unequal Impact; Māori and Non-Māori Cancer Statistics 1996-2001. Wellington Ministry of Health, 2006.
2. 2. Robson B, Cormack D, Purdie G. Unequal Impact II: Māori and Non-Māori Cancer Statistics by Deprivation and Rural-Urban Status 2002-2006: Ministry of Health Wellington 2010.
3. 3. Ministry of Health. Cancer statistics [updated 2nd August 2018. Available from: https://www.health.govt.nz/our-work/populations/maori-health/tatau-kahukura-maori-health-statistics/nga-mana-hauora-tutohu-health-status-indicators/cancer accessed July 10 2019.
4. 4. Ministry of Health. NCSP New Zealand Total District Health Board Coverage Report: period ending 31 March 2019. Wellington Ministry of Health, 2019.
5. 5. Smith M RL, Canfell K. National Cervical Screening Programme Monitoring Report Number 47 (1 January – 30 June 2017). In: Unit: NS, ed., 2018.
6. 6. Hider P, Dempster-Rivett K, Williman J, et al. A review of cervical cancer occurrences in New Zealand 2008–2012. *NZ Med J* 2018;131:53-63.
7. 7. Adcock A, Cram F, Lawton B, et al. Acceptability of self-taken vaginal HPV sample for cervical screening among an under-screened Indigenous population. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 2019;59(2):301-07. doi: 10.1111/ajo.12933
8. 8. McLeod M, Harris R, Purdie G, et al. Improving survival disparities in cervical cancer between Māori and non‐Māori women in New Zealand: a national retrospective cohort study. *Australian and New Zealand journal of public health* 2010;34(2):193-99.
9. 9. Tabrizi SN, Unemo M, Golparian D, et al. Analytical evaluation of GeneXpert CT/NG, the first genetic point-of-care assay for simultaneous detection of Neisseria gonorrhoeae and Chlamydia trachomatis. *Journal of clinical microbiology* 2013;51(6):1945-47.
10. 10. Fogel AL, Kvedar JC. Artificial intelligence powers digital medicine. *NPJ digital medicine* 2018;1(1):1-4.
11. 11. Ronco G, Dillner J, Elfstrom KM, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. *Lancet* 2014;383(9916):524-32. doi: 10.1016/s0140-6736(13)62218-7 [published Online First: 2013/11/07]
12. 12. Ronco G, Giorgi-Rossi P, Carozzi F, et al. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. *Lancet Oncol* 2010;11(3):249-57. doi: 10.1016/s1470-2045(09)70360-2 [published Online First: 2010/01/22]
13. 13. Sankaranarayanan R, Nene BM, Shastri SS, et al. HPV screening for cervical cancer in rural India. *N Engl J Med* 2009;360(14):1385-94. doi: 10.1056/NEJMoa0808516 [published Online First: 2009/04/03]
14. 14. Arbyn M, Verdoodt F, Snijders PJ, et al. Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: a meta-analysis. *Lancet Oncol* 2014;15(2):172-83. doi: 10.1016/s1470-2045(13)70570-9 [published Online First: 2014/01/18]

15. 15. Medical Service Advisory Committee. National Cervical Screening Program Renewal: Executive Summary Commonwealth of Australia. Canberra: Medical Service Advisory Committee, 2013.
16. 16. Cuschieri KG, D.; Cuzick, J.; Cadman, L.; Moore, C.; Vanden Broeck, D.; Padalko, E.; Quint, W.; and Arbuyn, M. Performance of a Cartridge-Based Assay for Detection of Clinically Significant Human Papillomavirus (HPV) Infection: Lessons from VALGENT (Validation of HPV Genotyping Tests). *Journal of Clinical Microbiology* 2016;54(9):2337-42. doi: 10.1128/JCM.00897-16. [published Online First: 6 July 2016]
17. 17. WHO. WHO Prequalification of In Vitro Diagnostics PUBLIC REPORT, WHO reference number: PQDx 0268-070-00 (2018) 171221_final_pq_report_pqdx_0268_070_00, 2017.
18. 18. Toliman P, Badman S, Gabuzzi J, et al. Field evaluation of Xpert HPV point-of-care test for detection of human papillomavirus infection by use of self-collected vaginal and clinician-collected cervical specimens. *Journal of clinical microbiology* 2016;54(7):1734-37.
19. 19. Catarino R, Vassilakos P, Bilancioni A, et al. Accuracy of self-collected vaginal dry swabs using the Xpert human papillomavirus assay. *PloS one* 2017;12(7):e0181905.
20. 20. New Zealand Point-of-Care Testing Advisory Group. New Zealand Best Practice Guidelines For Point-of-Care Testing. Christchurch: THE NEW ZEALAND INSTITUTE OF MEDICAL LABORATORY SCIENCE (INC), 2018.
21. 21. Smith L. Decolonising methodologies: Research and indigenous peoples. New York & Dunedin: Zed Books & Otago University Press 1999.
22. 22. Cram F, Mertens DM. Transformative and Indigenous frameworks for mixed and multi method research. New York: Oxford University press 2015.
23. 23. National Cervical Screening Programme. Age range change for cervical screening Wellington: Ministry of Health,; 2018 [Available from: https://www.nsu.govt.nz/health-professionals/national-cervical-screening-programme/age-range-change-cervical-screening accessed 24th Oct 2019.