A RANDOMIZED CONTROLLED TRIAL OF HUMAN PAPILLOMA VIRUS (HPV) TESTING FOR CERVICAL CANCER SCREENING

(HPV FOCAL Study)

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**HPV FOCAL Study**  
*Version 8.0*  
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## List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AIS</td>
<td>Adenocarcinoma in situ</td>
</tr>
<tr>
<td>ASC-H</td>
<td>Atypical Squamous Cells, cannot exclude high grade</td>
</tr>
<tr>
<td>AGUS</td>
<td>Atypical Glandular Cells of Undetermined Significance</td>
</tr>
<tr>
<td>ASC-US</td>
<td>Atypical Squamous Cells of Undetermined Significance</td>
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<tr>
<td>BCCA</td>
<td>BC Cancer Agency</td>
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<tr>
<td>BCCDC</td>
<td>BC Centre for Disease Control</td>
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<tr>
<td>BCCSP</td>
<td>BC Cervical Cancer Screening Program</td>
</tr>
<tr>
<td>CIN</td>
<td>Cervical Intraepithelial Neoplasia</td>
</tr>
<tr>
<td>CPRLL</td>
<td>Central Processing Receiving Lane Level</td>
</tr>
<tr>
<td>DSMC</td>
<td>Data Safety Monitoring Committee</td>
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<tr>
<td>ECC</td>
<td>Endocervical Curretage</td>
</tr>
<tr>
<td>FP</td>
<td>Family Practitioner/Physician</td>
</tr>
<tr>
<td>HPV</td>
<td>Human Papilloma Virus</td>
</tr>
<tr>
<td>HR-HPV</td>
<td>High Risk Human Papilloma Virus</td>
</tr>
<tr>
<td>HSIL</td>
<td>High Grade Squamous Intraepithelial Lesion</td>
</tr>
<tr>
<td>ICER</td>
<td>Incremental Cost-Effectiveness Ratio</td>
</tr>
<tr>
<td>LBC</td>
<td>Liquid Based Cytology</td>
</tr>
<tr>
<td>LSIL</td>
<td>Low Grade Squamous Intraepithelial Lesion</td>
</tr>
<tr>
<td>MOA</td>
<td>Medical Office Assistant</td>
</tr>
<tr>
<td>NPV</td>
<td>Negative Predictive Value</td>
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<tr>
<td>PCCCF</td>
<td>Pan Canadian Cervical Cancer Forum</td>
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<tr>
<td>PHSA</td>
<td>Provincial Health Services Authority</td>
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<tr>
<td>PPV</td>
<td>Positive Predictive Value</td>
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<tr>
<td>QALY</td>
<td>Quality Adjusted Life Year</td>
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<tr>
<td>RC</td>
<td>Recruitment Clerk</td>
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<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
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<tr>
<td>SIN</td>
<td>Study Identification Number</td>
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1 Summary

Cervical cancer screening based on cytology (the Pap smear) has been an extremely successful public health intervention, achieving reductions in cervical cancer incidence of up to 80% where practiced effectively(1). However, the Pap smear was introduced over 50 years ago and recent studies have shown it has significant limitations as a screening test. Data from organized screening programs indicate that initial declines in disease incidence have now levelled-off, and audits of organized programmes have shown that 40-50% of women who develop cervical cancer have been regularly screened(2, 3). Further, a recent meta-analysis indicated that the average sensitivity of a single Pap smear to detect cervical cancer precursors (cervical intraepithelial neoplasia/CIN) or invasive cervical cancer was only 51%(4). At present, 2 technologies are available that have the potential to improve Pap smear-based cervical cancer screening: liquid-based cytology (LBC) and HPV testing.

The Canadian Coordinating Office for Health Technology Assessment concluded that, compared to the Pap smear, LBC reduces the number of false negative results for ordinary populations of women but not for high-risk populations, and reduces the proportion of unsatisfactory specimens(5).

Subsequently, the Pan-Canadian Cervical Cancer Forum (PCCCF) recommended the introduction of LBC within Canada(6). Other reviewers have been more equivocal in interpreting the impact of LBC on false negative rates, although most agree about the reduction of unsatisfactory specimens(7-11). This is in line with the results of a large-scale evaluation of LBC conducted in the United Kingdom (UK) which found that LBC did not provide an overall statistically significant increase in the detection of cytological abnormalities, although it did provide statistically significant reductions in the rates of inadequate Pap smears(12). Similar results were found in an evaluation undertaken by the BC Cancer Agency (BCCA)(13). A recent structured review concluded that, among high-quality studies, there was no evidence that LBC reduced the proportion of unsatisfactory slides or detected more high-grade lesions(14). Together, these data indicate that any reduction in cervical cancer rates achievable through the introduction of LBC will not be substantial, although LBC will contribute to the efficacy of cervical screening through reductions in unsatisfactory specimens. In the UK, the reduction of inadequate specimens was sufficient in itself to merit the introduction of LBC to their national screening program, but they are still evaluating other technologies (HPV testing) to see if these will achieve the desired reductions in cervical cancer rates. Therefore, while it is likely that we will see progressive implementation of LBC over the coming years in Canada, we must also evaluate other technologies to reduce cervical cancer rates, but these studies must account for the anticipated use of LBC.

Numerous studies have been undertaken which conclusively demonstrate that infection with high-risk types of the Human papillomavirus (HR-HPV) is the primary risk factor for the development cervical cancer and its precursors(15). The epidemiological data linking HR-HPV to the development of cervical cancer come from a wide variety of studies showing that:

● The prevalence of HR-HPV in women with cervical cancer is 80-95% compared to 5-20% in epidemiologically-matched controls, producing relative risks for the development of cervical cancer that range from 50-500 depending on the study(16)
● Persistent HR-HPV infection is necessary for development, maintenance and progression of CIN(17, 18).
● 15-30% of cytologically normal women who are HR-HPV positive will develop CIN2 or CIN3 within 4 years of detecting the HPV infection(19).
The incidence of CIN2 or worse is reduced in women who are vaccinated against HPV 16/18 (20-22).

On this basis, it has been proposed that testing for the presence of HR-HPV could improve cervical cancer screening and its use has been proposed for primary screening, for triage of equivocal Pap smears and for the follow-up of patients after treatment for CIN. For primary screening, it has been demonstrated that HPV testing has a higher sensitivity and negative predictive value (NPV) for the detection of prevalent CIN2 or worse than either the Pap smear or LBC, albeit with a lower specificity and positive predictive value (PPV) (23-28). Notwithstanding the methodological limitations of these studies (29), they have created worldwide interest in HPV testing and led to the approval of HPV testing in conjunction with cytology (combined testing) for primary screening by the US Food and Drug Administration (FDA) in 2003.

Although the US has chosen to implement combined testing, the literature shows that cytology adds little to the sensitivity and NPV of the combined test (0% - 5%), but does decrease the already low specificity and PPV (≤20%) of HPV testing. As a result, the benefits to be derived from combined testing in terms of safety are likely to be negligible while the drawbacks arising from the false-positive results (i.e. increased psychosocial stress and inconvenience for the women being screened, increased costs for unnecessary follow-up and monitoring, etc.) may be substantial.

In recognition of this, it has been proposed that a more efficient approach would be to use HPV testing as a single primary screening test with cytology reserved only for the triage of women having a positive test (30). This would offer several advantages over combined testing:

- Screening would be undertaken with the test having higher sensitivity and triage undertaken with the test having higher specificity, in compliance with accepted principles of screening and as is currently the case with syphilis and HIV screening.
- It would achieve 95-100% of the sensitivity and NPV of combined testing, while maximizing specificity and PPV. This would provide the same level of safety but with improved cost-effectiveness by minimizing the number of women with false positive results who need to be followed-up.
- 85-90% of women would be returned immediately to routine recall without incurring the cost of cytology, which would be reserved only for the triage of the remaining 10-15%.
- The high-volume testing of screening samples would be undertaken with a non-subjective test that can be automated, while the subjective, labour-intensive test would be restricted to high-risk samples that could be screened more intensively because of the reduced number that need to be processed. (Note: for the ongoing delivery of the service, this would also reduce labour demands to levels that are more compatible with the anticipated future availability of cytotechnologists).

These observations are supported by the preliminary results from a large randomized controlled trial (RCT) conducted in the Netherlands to evaluate combined testing. These data show that cytology added nothing to the sensitivity of the combined test but decreased specificity by 4% (31). Indeed, concern about the poor specificity, PPV and cost-effectiveness of the combined test within the public health systems of Europe has led to the initiation of 2 large-scale RCTs (n=250,000) to evaluate HPV testing as a single primary screening test in Finland and Italy (32, 33).

In summary, evidence is steadily accumulating that new technologies have the potential to improve both the efficacy and efficiency of cervical cancer screening programs. As a result, the pressure to implement these technologies is steadily increasing in Canada and there is now an urgent need to establish the most effective means of using these technologies within our healthcare system. We
hypothesize, in agreement with rigorous interpretation of the available evidence, that the optimum balance between the benefits and drawbacks of HPV testing will be achieved by using it as a single primary screening test with cytology reserved for the triage of those testing positive. It is therefore essential to properly evaluate this approach within the context of an organized cervical cancer screening program which would serve as a model for cervical cancer screening in this country.

The results of this trial will demonstrate whether or not the use of HPV testing as a single primary screening test within an organized Canadian cervical cancer screening program will be able to provide further reductions in cervical cancer incidence, allow the screening interval to be extended, and improve the cost-effectiveness of cervical cancer screening.

If this trial demonstrates that HPV testing will provide these benefits, the BCCA will implement HPV testing as a single primary screening test within the provincial cervical cancer screening program and the trial will directly influence the provision of this service in BC. In addition, many other Canadian provinces and territories are either implementing or have plans to implement screening programs similar to the one in BC and by the time this trial is completed, many will have these programs operating. Therefore, the results of this trial will be directly applicable to these programs and constitute a demonstration project for the rest of Canada.

2 Background

There is now an overwhelming body of data to show that HPV testing has the potential to improve the effectiveness of cervical cancer screening programs and thereby reduce rates of cervical cancer. As a result, there is a growing ethical dilemma in that we potentially have the means to prevent disease and death among Canadian women, and yet the studies that have been undertaken do not offer the standard of evidence that is required to change large-scale public health programs such as cervical cancer screening. In recognition of this, PCCCF has called for the evaluation of HPV testing within the context of a Canadian organized cervical cancer screening program. Given the potential health benefits that could be achieved, and that a pan-Canadian expert group has issued a consensus statement calling for the evaluation of HPV testing for primary screening, it is now an imperative that a properly designed and powered study be conducted to definitively establish whether it will provide the hypothesised health benefits within Canada.

Subsequent to the US FDA approval of HPV testing with cytology for primary cervical cancer screening, combined testing has progressively become an accepted option for screening (see American Cancer Society, Guidelines on Screening) in that country, and this is increasing the pressure to follow this lead in other jurisdictions as well. It is likely that combined testing was selected in the US because the addition of cytology was perceived to provide an increase in sensitivity and this was deemed to be more important within the US medico-legal environment than the consequent decrease (≤20%) in specificity. However, the acceptable balance between sensitivity and specificity is likely to be different in Canada where the drawbacks in terms of increased inconvenience and psychological stress for the women receiving false-positive test results will have a higher priority, and where all the costs associated with of unnecessary follow-up and monitoring of these women have to be borne by provincial healthcare budgets. This is a very important consideration in Canada as the pressure to
implement HPV testing continues to build and in the absence of solid evidence to the contrary, it is inevitable that the US model of combined testing would be selected. Then, its implementation as an integral part of any provincial screening program would create a strong argument that it is the de facto standard of care for the entire country and lead to its implementation in the other provinces and territories, regardless of the longer-term repercussions for the provision of healthcare in this country. In order to avoid this, it is now essential to properly evaluate whether HPV testing as a single screening test with cytology triage of women testing positive would be more compatible with the provision of health services in Canada.

2.1 Literature Review and Rationale for Trial:
The only systematic review of the literature pertaining to the use of HPV testing for primary cervical cancer screening was published in 1999 by the Health Technology Assessment Office of the Department of Health in the United Kingdom(34). This report concluded that the high sensitivity of HPV testing offered the potential for it to replace cytology as a single primary screening test and recommended that research be conducted to further evaluate this use. The authors also recommended that any such studies should:
- Follow women for a period of at least 5 years.
- Evaluate the appropriate screening interval for women testing HPV-negative.
- Use end-points and be of sufficient size to make estimates of the impact on cervical cancer incidence.
- Be coordinated with other studies internationally in order to maximize the accuracy with which any potential reductions in the incidence of cervical cancer can be estimated.

A more recent review of the literature (not systematic) was published in 2003 by an investigator on the study(29). This review of 13 different studies evaluating the use of HPV testing for primary cervical cancer screening noted that the average (unweighted by study size) sensitivity of HPV testing in combination with cytology was 27% higher than that of cytology alone with the HPV test being the primary contributor to the observed difference, a conclusion that supports the use of HPV testing as a single test for primary screening. The author also noted that most or all of the studies reviewed were compromised by:
- The use of simple cross-sectional designs rather than a randomized controlled trial designs
- The assessment screening performance based on the detection of either prevalent lesions or prevalent and short-term incident ≥CIN2 lesions rather than more relevant end points such as the incidence of CIN2, CIN3 or cervical cancer at subsequent screening rounds
- The concomitant testing for HPV and cytology using a split-sample procedure which provided a sub-optimal sample for one test or the other or both, and does not represent real screening conditions
- Verification bias which prevented the unbiased estimation of absolute sensitivity and specificity and therefore produced data that cannot be generalized for cost-benefit comparisons or public health uses

This review then concluded that the published literature does constitute proof of principle that HPV testing has the potential to improve cervical cancer screening programs and to increase the screening interval. However, additional trials are required to provide the standard of evidence required to change public health programs and these should: 1) use RCT designs; 2) use more relevant outcomes such as reductions in histologically confirmed incident CIN3 lesions at subsequent screening rounds and 3) include cost-effectiveness analyses.
A recent review of North American and European studies using HPV testing in primary cervical cancer screening\(^{(35)}\) reconfirmed the higher sensitivity and lower specificity of HPV testing versus cytology. The authors concluded that their findings supported “the use of HPV as the sole primary screening test, with cytology reserved for women who test HPV-positive. Large demonstration projects are needed to fully evaluate this strategy.” Included in this review were the early results from a randomized trial (CCCasT) conducted in Montreal by one of the investigators which provided consistent results\(^{(36)}\).

In addition to these reviews, the PCCCF has published consensus recommendations based on an extensive review of the literature. They state: “It is recommended that evaluation of HPV testing in primary screening be conducted within a Canadian organized program to optimize screening intervals, screening modalities (including cytologic method, and primary screening tool(s)), and target age ranges. These evaluations should establish appropriate assessment and management strategies to triage positive women, cost-effectiveness, and the acceptance of screening policies by health service providers and women and permit the assessment of emerging technologies that are indicated by strong evidence\(^{(6)}\).”

In all the cases noted above, after careful evaluation of the literature, the reviewers have concluded that the available evidence clearly indicates that HPV testing has the potential to improve cervical cancer screening but there is still a need for properly designed RCTs to provide the level of evidence required to change public health policy and this study has been designed to address all of these issues by:

- Using a randomized controlled design
- Assessing comparative reductions in histologically confirmed incident CIN3 at subsequent screening rounds as a primary trial outcome
- Using a single primary sample for each screening test
- Avoiding verification bias by having two arms screened with an identical test at the exit screening round (verification bias is not relevant at the recruitment screening round because the trial is not evaluating the screening tests for the detection of prevalent lesions)
- Setting within the context of an organized Canadian cervical cancer screening program that is similar in structure to those existing or being implemented elsewhere in Canada
- Directly evaluating the appropriate screening interval without using interim interventions in the 4-year HPV-negative cohort which could alter the course of disease and confound the results
- Assessing the appropriate age range to be screened with HPV testing
- Including a cost-effectiveness evaluation of HPV testing within the context of a Canadian organized screening program
- Including a number of adjunct studies that will assess the acceptability of HPV testing as a screening test, the potential psychological impact of HPV testing, etc.

The single recommendation that is not being addressed by this study is the evaluation of the combined HPV/cytology test. It must be recognized that circumstances have changed since the publication of the reviews noted above with data accumulating to indicate that the combined test offers little or nothing in terms of sensitivity and NPV, while decreasing the specificity, PPV and cost-effectiveness when compared to HPV testing as a single screening test. Given these more recent data and the fact that the results of this trial will not be available for 7-8 years, we have anticipated the future direction of the field and designed this trial to accommodate those needs.
3 Trial Objectives

3.1 Primary Objective:
- To establish the efficacy of HPV testing as a stand-alone screening test followed by cytology (LBC) triage of HPV-positive women through a comparison of the estimated decreases in cervical intraepithelial neoplasia (CIN) 3 or greater that can be achieved by each screening test.

3.2 Secondary Objectives:
- To establish the appropriate screening interval for HPV-negative women, using the current standard of a 2-year recall interval for cytology negative women as the benchmark of acceptable risk.
- To establish the appropriate clinical follow-up for women who are HPV-positive.
- To establish the cost-effectiveness of HPV testing for primary screening, all within the context of an organized Canadian cervical cancer screening program.

4 Study Design

4.1 Overall Trial Design
This is a randomized, controlled, three-armed evaluation of Pap cytology (LBC) screening (control arm) compared to HPV testing with LBC triage of HPV-positive women over 2 years (2-year safety check arm) and over 4 years (4-year intervention arm). Accrual prior to 1st January 2011 randomized women equally to the three arms but after this date women randomized (equally) to the control and intervention arms. Although LBC is not universally used in Canada at present, the Pan Canadian Cervical Cancer Forum has recommended its use. Further, LBC will improve the cost-effectiveness of HPV testing because the LBC medium is suitable for both HPV testing as well as cytology and thereby allows the triage testing to be undertaken from the same sample without having to recall the women.

4.2 Study Population
The study population is comprised of approximately 24,500 women recruited from participating Family Practice clinics, who meet all inclusion criteria and exhibit none of the exclusion criteria below.

4.3 Inclusion Criteria:
Women aged 25 to 65 registered with Medical Services Plan in BC who see a study collaborating healthcare provider for routine cervical screening.

4.4 Exclusion Criteria:
1. Women who have a history of histologically proven ≥CIN2 requiring treatment in the last 5 years
2. Women who have ever had a history of histologically proven invasive cervical cancer
3. Women who have had a Pap test less than one year ago
4. Women with no cervix
5. Women who are pregnant at the time of first sample collection
6. Women who are HIV positive or on immunosuppressive treatments (note: If a participant is on immunosuppressive treatments and the Family Practitioner (FP) confirms the participant would not require enhanced cervical screening, she may participate in the trial)
7. Women who are unwilling or unable to provide informed consent

5 Trial Interventions

Women will be recruited through collaborating Family Practice clinics. Within the BC Cervical Cancer Screening Program (BCCSP), the BCCA currently identifies all women who are due for screening based on their screening history and then conveys this information to the FP. The FP is subsequently responsible for contacting the women and ensuring they are screened. For the trial, the study staff (who will be hired directly by the BCCA and legally able to access the required databases) will identify women registered with a participating FP who are due for screening. On a monthly basis, the study staff will send this list of women to the Medical Office Assistants (MOAs). A pre-assembled invite package will also be provided for each woman on the list. The “invite package” will include an invitational letter, a study informational pamphlet and the Information and Consent form. The MOA will address and send a pre-assembled package to each woman on the list. The invitational letter will inform the woman to phone her FP to make an appointment for her cervical cancer screening exam and also provide her with the opportunity to contact, or be contacted by study staff to learn more about the trial and potentially participate if interested and eligible. The Study Centre will not receive contact information of any potential participants, unless the woman has provided her permission to be contacted.

When women speak with study staff, they will be provided with more information about the study, have any questions answered, and be administered the “Eligibility Form” (Appendix 1) to determine eligibility. If the woman is eligible, and if she wishes to proceed, the Information and Consent form will be discussed with her. When a woman agrees verbally to participate in the study, she will then be administered the “Epidemiological Questionnaire” (Appendix 2). She has the option not to answer any or all of the questions on the questionnaire if she chooses. Prior to the conclusion of the phone call, the woman will be instructed to take the unsigned Information and Consent form to her FP when she has her screening appointment, at which time, the appropriate signatures will be obtained prior to sample collection.

FP collaborators are encouraged to discuss the study, and obtain consent on any eligible women in their practices who have appointments for cervical cancer screening, who weren’t previously identified as above. These women are identified for study purposes as “FP identified” participants. The FP must ensure the “FP identified” participant meets all inclusion and exhibits no exclusion criteria, and appropriate signatures on the information and consent form are obtained prior to sample collection. When the FP appropriately identifies and obtains consent on these participants, the same procedures below will occur.

Women will have two LBC samples taken (a primary and secondary sample). LBC samples can be used for both HPV testing and cytology and both samples will be sent to the Provincial Health
Services Authority (PHSA), Central Processing and Receiving Lane Level Laboratory (CPRLL) (Located at the BC Centre for Disease Control (BCCDC)) for processing. The primary samples that were taken from women at the screening visit will be “batched” when received at the lab. Once per day, the samples received at CPRLL will be randomized to one of the three following arms:

1. **Control arm:** The initial sample collected will undergo cytology testing (LBC).
   On the basis of this result women will be managed as follows:
   - Within normal limits (negative results): Recalled for their next routine screen at 2 years, where the sample will undergo cytology testing. If negative again at the 2 year screen, recalled, for the exit screen at 4 years. At the 4 year exit screen, the sample obtained will undergo both HPV and cytology testing with those positive on either test being referred for colposcopy and then treated based on the colposcopy results.
   - ASC-H or ≥LSIL: (at recruitment visit or at the 2 year screen) will receive immediate colposcopy and treated based on the colposcopy results.
   - ASC-US: (at recruitment visit or at the 2 year screen) the residual of the specimen collected will undergo HPV testing. Follow-up based on the result of the HPV test:
     a) HPV-positive: referred for immediate colposcopy and treated based on the colposcopy results.
     b) HPV-negative: recalled for repeat cytology testing in 12 months. If ≥ASC-US, referred for colposcopy and treated based on the colposcopy results. If cytology negative they will be returned to the routine screening pool for this arm.

Note: ASC-H (atypical squamous cells, cannot exclude high grade); HSIL (high grade squamous intraepithelial lesion); ASC-US (atypical squamous cells of undetermined significance); LSIL (low grade squamous intraepithelial lesion)

2. **Two Year Safety Check Arm (subjects accrued prior to January 1, 2011):** The initial sample collected will undergo HPV testing.
   On the basis of this result women will be managed as follows:
   - HPV-negative: recalled at 2 years for their exit screen where the sample collected will undergo cytology testing. Those who are cytology negative will be returned to the care of their family physician and followed in the BC Cervical Cancer Screening Program according to the standard of care in the province. Those who are cytology positive to any degree at the two year recall, will be managed the same as cytology positive women in the control arm at the two year mark.
   - HPV-positive: the residual LBC specimen will be processed for cytology and the women will be managed with the same protocol as HPV-positive women in the 4-year intervention arm.
   - Women no longer accrued to this arm after January 1st 2011.

3. **Four Year Intervention Arm:** The initial sample collected will undergo HPV testing.
   On the basis of this result women will be managed as follows:
- HPV-negative: recalled at 4 years for their exit screen, where the sample obtained will undergo both HPV and cytology testing and those positive on either test referred for colposcopy and treated based on the colposcopy results.
- HPV-positive: the residual LBC specimen will be processed for cytology:
  a) If cytology negative, recalled at 12 months for HPV and cytology testing. At 12 months, referred to colposcopy if $\geq$ASC-US OR HPV positive and subsequently treated based on colposcopy results. If HPV AND cytology negative at 12 months returned to the routine screening pool for this arm.
  b) If cytology is $\geq$ASC-US immediately referred to colposcopy and managed according to the colposcopy results.

5.1 Liquid Based Cytology (LBC):
LBC has been chosen for this trial because the PCCCF has recommended that cervical cancer screening in Canada be undertaken with LBC and the trial therefore must account for its progressive implementation over the next 6 to 7 year period that the trial will be conducted. FPs will be trained on how to obtain samples using LBC according to manufacturer’s instructions. In addition, information regarding sample collection using LBC will be available in written material provided to FPs and also available on the study specific website.

5.2 HPV Testing:
HPV testing will be conducted with the Qiagen Hybrid Capture-II test. This test has been evaluated for use in clinical trials and there is a wealth of data characterizing the clinical performance of the Hybrid Capture II product and it is Health Canada approved. The CPRLL at the BCCDC will be conducting the HPV testing, and has the capacity and technical ability to provide HPV testing using the Hybrid Capture-II test. All tests will be conducted exactly according to the manufacturer’s recommendations and the results entered into existing provincial and the study databases.

All specimens will be collected and stored in accordance with manufacturer’s specifications.

5.3 Colposcopy:
Women whose samples show $>\text{LSIL}$, persistent ASC-US, HPV-positive with any degree of dyskaryosis and those who are persistently HPV-positive will be referred to colposcopy for further investigation. The study coordination center database will receive the results of subject LBC and or HPV testing. Based on the results, the study coordination center will inform the FP if the woman is to be referred for colposcopy. Colposcopy will take place at study identified provincial colposcopy clinics by one of the study colposcopists at the clinic.

Women referred for colposcopy will fall in the following major hierarchical groups (for rounds other than the final round):
  a) Cytology – AG-US (atypical glandular cells of undetermined significance) (HPV positive or not done)
  b) Cytology: ASC-H or $>\text{LSIL}$ (HPV positive or not done)
  c) HPV – persistently positive
Women in group “a” will undergo standard colposcopy with endocervical curettage (ECC) and endometrial sampling. Identified lesions will be managed according to existing guidelines according to level of neoplasia. Women <40 years of age with no lesion identified and <HSIL on ECC will be recalled at 4-6 months for repeat colposcopy. Women ≥40 years of age will have excisional treatment.

Women in group “b” and “c” will undergo standard colposcopy with management of identified lesions in accordance with existing guidelines. All colposcopic examinations done as part of this trial require histology (biopsy for complete assessment and evaluation). Women with no lesion identified will undergo ECC. Women with no lesion identified and <HSIL on ECC will be recalled at 4-6 months for repeat colposcopy and managed according to standard protocol. Women with ≥HSIL on ECC will have excisional treatment. Pregnant women (those who have become pregnant after enrolment into the trial) will be managed according to standard protocol.

Trial participants who require colposcopy during participation may be re-entered into the trial screening schedule for the appropriate study arm. Women who do not require any treatment post-colposcopy (no LEEP, lazer, cone biopsy etc) and are discharged back to the care of their FP in the screening program, will be routed back into the screening schedule for their appropriate study arm. Women who do require treatment post colposcopy (LEEP, lazer, cone biopsy etc) are considered “higher risk” and are not appropriate to return to regular screening in the FOCAL Study. See Colposcopy algorithm.

Exit screens from the control and 4-year intervention arms will be conducted using the same combined HPV/cytology test with all women positive on either or both tests being referred to colposcopy to eliminate intervention asymmetry.

5.4 Histology:
Pathologists will be blinded to cytology and or HPV results. Histology results are captured in the same Laboratory Information System (LIS) as the cytology results. Therefore, the pathologist will not access the LIS when reading histology slides. The histology laboratory will present the pathologist with the histology slides together with a printed copy of the gross description with the tissue on the slide as an essential part of the histologic evaluation.

In cases of significant discordance between the cytologic and histologic evaluation and where this will affect patient management, the managing colposcopist will contact the laboratory to request review of the histology and cytology in order to resolve the discrepancy (for ex: a case where HSIL cytology is noted, but negative histology, full review is needed to decide whether the patient can be safely followed in cytology, or needs a LEEP).

A review of exit screen histology is an essential component of the design of the trial. Approximately 50% of exit screen histology results will require second review by a senior study pathologist. If the primary and review histology results agree, this will be the final study diagnosis, but in the case of disagreement between primary and review histology, the final study diagnosis will be established by multihead discussion and consensus review.
Additional Sampling:
The second sample obtained from study subjects and residuals of the primary sample will be used for further analysis. When the second sample is received at CPRLL it will be prepared for freezing. The sample will be labelled with a unique study identifier that is linked to the original data set. Prior to processing of the samples for analysis, they will be “de-identified” such that personal identifiers (ie., name, date of birth, or personal health number) are not assigned to the specimen, but relevant clinical data remains linked to the specimen. All additional test results will not be revealed to the subjects, or their FPs. Some of the analyses proposed for these samples are: comparing different HPV testing technologies available for screening; establishing which HPV type(s) are present; whether certain HPV genes are active or not; detection of certain immune characteristics (such as HLA types); and establishing prevalence of genital coinfections, such as *C. trachomatis*, *N. gonorrhoea*, *M. genitalum*, *H. simplex I* and *II*. These samples may also be used to develop new tests to identify biomarkers that could determine cervical cancer risk. Once these tests have been completed, the remainder of the sample will be stored for future testing, at the BCCDC, if new scientific discoveries indicate this would be useful.

Randomization and Blinding:
Randomization will occur when samples are received at the laboratory. An HPV FOCAL study employee will separate the specimens from the study requisitions and signed consents and enter the information into the study database. Upon entry of the requisition information into the study database the individual will be randomized to one of the three arms (control, safety or intervention prior to January 1st 2011) or one of two arms (control or intervention after January 1st 2011) using a random number generator contained in the database software. At this point, a Study Identification Number (SIN) will be allocated to the participant. Simple equal 1/3 probability (prior to January 1st 2011) or 1/2 probability (after January 1st 2011) random allocation will be used and a computer file will be kept.
of sequence of entry and group allocation to permit monitoring of conformity to anticipated randomness. After sample randomization has occurred, samples will be directed for appropriate processing (cytology or HPV testing).

All samples will be collected in the same way. FPs and women participants will be blinded to allocation at the time the sample is collected. Participant results will be communicated from the BCCA to the FP office as soon as they are known. If the participant’s initial screening visit results are HPV or cytology “negative” the report will state “no abnormality detected”, and the recommended follow-up for that particular participant will be communicated to the FP in two years. This will ensure blinding is maintained for as long as possible and prevent any bias that may potentially occur from knowledge of negative results. If the screening results are HPV and or cytology positive, the results will be communicated from the BCCA to the FP along with the recommended follow-up. Recommended follow-up for HPV and or cytology positive results will depend on the result obtained and the arm in which the participant is randomized.

Cytologic interpretation required for samples in the HPV arms will be performed with knowledge of HPV results.. Pathologists will be blinded to cytology and or HPV results when performing histology interpretation of diagnostic procedures.. Colposcopists will not be blinded to initial cytology and or HPV results if colposcopy referral is required, as all participants will receive a biopsy regardless of the results. However, colposcopists will be blinded to study arm allocation.

6 Data Collection and Management

There will be a single study database which will contain a series of linked files on specific study components. The study trial master will consist of records on all women approached to participate in the study. Study databases will be maintained on the PHSA data network which is a secure firewall protected network used for the management of patient data within the BCCA and BCCDC. For women declining to participate in the trial no further information will be added but this record will be retained to prevent the same woman being re-approached to participate. For women consenting to participate, information collected will include demographic data, questionnaire responses and lab results. Data from individuals attending colposcopy will be obtained using a computer scanable report which will be directly obtained and transported to the study central office. This location routinely receives results of pap smears and colposcopy and contains appropriate security. The results of Metro Vancouver pathology will be obtained from the division of pathology, BCCA, which undertakes pathologic interpretation of all colposcopic biopsies performed at the Vancouver colposcopy centre. Results of pathology from Victoria will be received from the Royal Jubilee Hospital Pathology laboratory. Linked files in the database will use the SIN as identifier. SINs will be generated sequentially at entry to the study and will be generated by algebraic formulae with no two study numbers differing by only a single digit to reduce potential entry errors. The study database will produce regular reports indicating accrual, testing and other study performance parameters.
6.1 Primary Outcome Measures:
1) Histologically confirmed incident ≥CIN2 detected at 2 years in both the control arm and in the safety-check arm. If the number of women with ≥CIN2 in the safety-check group is significantly above 0.8 times that in the control arm at the 2 year screen, then the trial will be terminated and the 4-year intervention arm called for its exit screen.
2) Histologically confirmed cumulative incident ≥CIN3 detected up to and including 4 years in both the control arm and in the intervention arm (or at some earlier time if data from the safety check group triggers an earlier exit screen) as a surrogate marker for eventual reductions in the incidence of cervical cancer.
3) Detection of histologically confirmed ≥CIN3 in the participants allocated to 12-month retesting.
4) The total estimated cost per woman screened and the total estimated cost per quality-adjusted life-year gained for each technology.

6.2 Secondary Outcome Measure:
1) Clearance of HPV infection in women who are HPV-positive and cytology negative at recruitment.

6.3 Questionnaires:
Baseline, demographic and financial information will be collected on study participants through the use of study questionnaires (“Study Epidemiological”, and “Study Financial Implications” questionnaires, found in appendices 2 and 3). The questionnaires will capture such things as participant demographic data, simple medical and gynecologic history, income, and financial implications of initial screening, follow-up visits or colposcopy appointments. The financial questionnaire will only be administered to a subgroup of randomized subjects. Some woman may also be administered quality of life, or questionnaires assessing attitudes and perceptions surrounding HPV testing for cervical cancer screening (tools not yet identified). Subjects will have the option not to answer any or all of the questions on each questionnaire if they do not feel comfortable doing so.

7 Statistical Considerations

7.1 Sample Size:
The planned intake sample size planned is 9,140 women each, in the Control and Intervention arms. Accrual to the safety arm completed January 1st 2011 and 6,217 subjects were recruited into this arm. Total sample size is ~24,500.

Background information prior to the start of the trial: Rates of HPV infection and associated histologically proven disease in women with an HPV infection are not known accurately for the BC population. We have therefore used rates from the HART study(26) which provides these data from a population that has been subject to organized cervical screening of a very similar nature to that used in BC, with similar entry criteria, similar cytology coding system and used the same HPV test as the one proposed in this trial. In addition, we have also drawn upon prevalence rates from the CCaST trial conducted in Quebec and Newfoundland and results from a sample of BC women. Based on this data, we anticipate that 9.5% of participants will be HPV-positive at recruitment and based upon BCCA cytology data, we know that 4% of women will have abnormal cytology at recruitment. We therefore estimate that 90.5% of the arms with HPV and 96% of the cytology arm will screen negative and be
recommended for 4 year or 2 year recall as specified in the protocol. Results as of July 2011 indicate that these assumptions are being met or exceeded with 92.2% HPV negative and 96.1% cytology negative. The HART trial found rates of $\geq$CIN3 identified by cytology were $6.2 \times 10^{-3}$ with a further $1.9 \times 10^{-3}$ detected by HPV testing. Power calculations were performed using the nQuery Advisor, version 2, software package.

In the comparison at 2 years (safety check) both cytology results and $\geq$CIN2 (identified by cytology) will be compared between the two arms undergoing cytology screening at that time. Initially it was anticipated that recruitment to the safety arm would occur until 11,000 subjects were accrued. Following the protocol change taking affect on January 1st 2011 it is anticipated 6,000 subjects will be accrued to this arm so that over 5,000 subjects will be have negative HPV (safety arm) or a similar number have negative cytology (control arm). Making the conservative assumption that 5,000 subjects per arm (safety and cytology) will be available for safety analysis the size and power of the study comparisons have been recalculated using the planned threshold of safety rate (CIN2+) < 0.8 \times control rate. A calculation was performed for the original anticipated sample size first as follows. The Pocock boundary points were calculated for the standardized test statistic comparing the rate in the safety arm to $k^* \times$control rate. The points were transformed to be appropriate for the standardized test static where $k^*$ is replaced by 0.8. $k^*$ was chosen to provide Pocock boundary points so that the probability of crossing the boundary was 0.9 when the safety arm rate was $= 0.8 \times$ control rate where the rate of CIN2+ in the control arm was assumed to be 0.01. The value of $k^*$ was found by trial and error using a simulation approach (5,000 replication of the sample size). This calculation assumed Pocock boundaries based upon comparisons at 500, 1000, 1500, 2,500, 5,000 and 10,000 subjects available for testing in each of the arms. The resulting value of $k^*$ was 0.645. The calculation was then repeated dropping the comparison at 10,000 subjects and adjusting the boundary point for the 5,000 comparison empirically so that the probability of crossing the boundary was maintained at 0.9 for the case where the safety arm rate was $= 0.8 \times$ control rate. This requirement has the effect of maintaining the probability of crossing the boundary if the safety rate is equal to the safety criterion. It was then possible to compare these two strategies (accrual to 11,000 subjects in safety arm versus accrual to 6,000 subjects) for different assumed values of the true rate in the safety arm. Literature review suggests that the most likely rate is $0.3 \times$ rate of CIN2+ in the control arm (which was assumed to be 0.01). Under this circumstance the probability of stopping the trial is estimated to be 0.0064 under the full accrual arm and 0.0098 in the new sampling plan for the safety arm. This difference in these probabilities is small and we conclude that the reduced sample size will be able to provide the originally planned level of safety with little increased probability (0.0034) of inappropriate stopping.

The original protocol did not establish an efficacy target but the provided estimated power of efficacy effects to identify the adequacy of the sample size determined from the original safety analysis based upon the decision to have equal numbers of women randomized to each arm. The assumptions and calculations were as follows: Comparisons will be made at 4 years and comparison will be based on the joint HPV and cytology exit screen results. In the cytology arm results from HART indicate an anticipated rate of $\geq$CIN3 of $8.1 \times 10^{-3}$. Assuming a cumulative loss rate 19% (10% loss per 2 years) then there would be 8,550 and 8,060 subjects in the cytology and HPV arms respectively. There would be a power of 84% to detect an 60% increase in the rate of $\geq$CIN3 and a 89% power to detect a
decrease of 50% in the rate with \( \alpha = 0.05 \) (2-sided). Thus the originally anticipated sample size provided powers in excess of 80% but not of 90% to test the alternate hypotheses. Recalculation requiring power to be at least 80% for either comparison indicates that a minimum of 9,140 women would be required per arm in the intervention and control arms. On the basis of this recalculation the sample size is 9,140 per arm for the intervention and control arms.

7.2 Statistical Analysis:
The primary analysis will be a comparison of cytology or \( \geq \text{CIN3} \) between the study arms at different time points. Rates of diseases development will be calculated using the person-years method for the different study intervals and plotted using the method of Kaplan and Meier. Rates will be calculated by age within subgroups within the study.

Tests of significance between study arms will be based on chi-square statistics. Analysis will also be performed using logistic regression to permit control of potential confounding factors since for some comparisons, balance may not be assured by randomization. The primary comparison of disease rates between test negative groups (at entry screen) will not control for potential confounding factors since they are not balanced by randomization and the tests may select for different characteristics. However controlled analyses will be performed to determine the extent to which any difference is explicable by potential confounders (principally age).

Safety comparisons are based on the standardized statistic for the difference in the rate of CIN2+ in the safety arm at 2 years and \( 0.8 \times \) rate of CIN2+ in control arm at the same time. Comparisons will be made at accruals of 500, 1,000, 1,500, 2,500 and 5,000 returned subjects per arm who are screening negative at baseline. The derivation of the Pocock boundary points is described in the sample size section. The boundary points for the standardized statistic were found to be 1.51, 1.12, 0.82, 0.36 and -1.28.

7.3 Health Economics Assessment:
Changes to any large scale public health intervention require robust health economic analyses to clearly illustrate the economic repercussions of the proposed changes. This trial includes a cost-effectiveness evaluation of screening using HPV testing with cytology triage of women having a positive result, compared to screening with LBC alone, and to the routine Pap smears as currently practiced in the BCCSP. The evaluation will be undertaken as an integral component of the RCT to allow for the prospective collection of high-quality cost data, and the direct incorporation of the trial outcome data into the analysis. It will be conducted using 2 alternative perspectives, that of the PHSA, and a societal perspective, following established guidelines(37). The former includes only direct costs borne by the PHSA, whilst the latter includes both direct and indirect costs (such as travel and time costs incurred by women and family members in attending screening tests). Direct costs will be estimated through a combination of routine utilization data sources, published price tariffs, and interviews with/surveys of clinical, laboratory and administrative staff. Indirect costs will be estimated through surveys of the trial participants, who will be asked about time and travel costs, out-of-pocket medical expenditures, time off work, etc.

Incremental cost-effectiveness ratios (ICERs) for the cost per case of cervical cancer detected will be estimated for each arm using outcomes data from the trial. Sensitivity analysis will be performed to test key assumptions, and cost-effectiveness acceptability curves will be used to examine uncertainty.
in ICER estimates\cite{38}. However, since these ICERs are based on intermediate measures of health outcomes (cervical cancer cases detected), simulation modelling techniques will also be used to estimate the cost per Quality Adjusted Life Year (QALY) gained for each arm of the trial\cite{39}. This will allow analysis of the long-term impact of HPV testing on morbidity and mortality compared to current practice. Data from the trial will be augmented with existing BCCA cervical cancer datasets to model long-term costs and mortality associated with each arm. QALY estimates will be derived from the literature and patient surveys at the BCCA (using established utility instruments such as the EQ-5D or HUI-III). Sensitivity analysis will be performed to test assumptions about the discount rate, and cost-effectiveness acceptability curves generated.

8 Subject Compliance and Loss to Follow-up

Within the context of the proposed trial, compliance with the initial intervention will not be an issue because the intervention is obtaining a sample of cervical cells in the same fashion as a routine Pap smear and this is completed at the time of recruitment.

Loss to follow-up within the BCCSP is monitored on an annual basis. Figures for 2003 show that there was a 10\% loss to follow-up at 24 months within the screening program\cite{3}. Mechanisms have been implemented into the study to minimize non-compliance, and or unscheduled screening by study participants. These include the following:

1) The trial staff will be composed of adequate and experienced recruitment clerks (RCs) throughout the duration of the trial who will be dedicated to maintaining contact with the trial participants and ensuring that they attend screening appointments only when they are scheduled to do so according to the protocol. The staff will also maintain open lines of communication with the FP office staff to offer support and answer questions.

2) A dedicated website has been established to provide information to both participants and FPs participating in the trial (www.bccancer.bc.ca/hpvfocal). A variety of useful information is found on the website including information about the study, Pap smears, cervical cancer, HPV infection and HPV testing, in addition to contact information for the study staff, information for FP collaborators, and a list of all collaborators. The website will be updated as necessary throughout the conduct of the trial.

3) All FPs participating in the trial are requested to attend an orientation/education session together with annual update meetings at which the importance of maintaining screening schedule compliance will be stressed.

4) An event driven study database has been established for the trial where participants’ follow-up schedule will be available and adhered to.

5) All women participating in the trial will be identified as study participants in their medical charts at the FP clinic. If a woman requests a Pap smear, it is normal clinical practice for the MOA to check her chart (electronic or hard copy) and women who are not scheduled for screening per study protocol procedures will be informed of this and instructed to wait to be reminded to book their appointment for their next study required screening visit per protocol schedule.

6) If a conventional Pap smear is received at the CPRLL for a trial participant, the clinician submitting the Pap smear will be contacted and reminded and or notified of patient trial participation so it can be determined if the Pap smear was taken in error or for investigation of symptoms. Where possible, Pap
smears taken in error will be discarded, following instruction from the clinician who obtained the Pap smear.
As a result of these efforts, we should have a lower dropout rate than the BCCSP, although we have still allowed for a 20% loss to follow-up over the 4 years of the trial.

9 Interim Analysis and Trial Management

9.1 Data Monitoring:
A fully independent Data and Safety Monitoring Board (DSMB) has been appointed and will receive regular reports providing the following for each trial arm:

- Recruitment numbers and proportion of expected total recruitment
- Rates for all classifications of cytology stratified by age
- HPV prevalence stratified by age
- Rates of referral to colposcopy
- Rates of biopsy
- Rates for all histological classifications
- Cumulative rates of ≥CIN2 and CIS and invasive cancer (by histopathology).
- Computations of differences in rates between the three arms including measures of statistical significance

Initial safety analysis will occur as described in the section on statistical analysis and in the section on sample size. Briefly results (CIN2+) will be analysed at 2 years among subjects screen negative at baseline screening in the control and safety arms. Comparisons will be made using modified Pocock boundaries for standardized statistic comparing two weighted proportions at 500, 1,000, 1,500, 2,500 and 5,000 subjects per arm. Data will be blinded as to study arm although the DSMB can vote to have the data unblinded at any time. Any cases of cancer occurring between screening rounds will be immediately reported to the DSMB as they are identified.

The DSMB is external to the study and is chaired by Dr Anthony Miller (Ontario) with the following members: Dr. Joan Murphy (Ontario), Dr Alberto Severini (Winnipeg) and Dr Stephen Walter (Hamilton). The committee will receive regular reports detailing recruitment, compliance to protocol, cytology, HPV, colposcopy and histology findings and the committee will meet annually to review results. When the data is available, they will review the results of the 2 year safety-check arm and compare these to the control arm as indicated in the trial protocol. The chair will be notified of any findings of invasive cervical cancer occurring between screening rounds prior to the completion of the trial.

9.2 Stopping Rules:
In order to provide an additional measure of security for HPV-negative women randomized to the 4-year intervention arm, rates of histologically confirmed ≥CIN2 arising during the 2-year screen of the control and safety-check arms will be compared and if the rate in the safety-check arm is significantly higher than 80% of the rate in the control arm the trial will be stopped. Since accrual will occur over a prolonged period and randomization to all three arms will be undertaken simultaneously all individuals in the experimental arm will be more than two years post-screen when all women randomized to the safety arm will have returned for their two year exit screen. Thus it will be
necessary to undertake interim analyses of results from the safety arm (and the control arm) as they become available. Consequently 5 looks at the data are planned at the following numbers of returned patients per arm 500, 1,000, 1,500, 2,500 and 5,000. The Pocock sequential boundary points will be used based upon a standardized z-score statistic in which the comparison is between the rate in the safety arm and 0.8 times the rates in the control arm at the 2 year return visit. Details of the calculation of the boundary points are provided in the sample size section. A full meeting of the DSMB will be convened to fully assess any situation and decide upon the continuance of the trial. In addition, should any case of invasive cancer be detected or occur in the interval between screens in any arm, a full meeting of the DSMB will be convened to fully assess the situation. Full documentation of all cases of invasive cervical cancer detected will be supplied to the DSMB.

9.3 Trial Management:
Day to day management of the trial is being undertaken by the Study Management Committee composed of key members of the investigative team. The Management committee meets biweekly during the trial and at whatever additional times are required to ensure its successful completion. In addition, the Steering Committee (composed of all trial investigators and essential collaborators) meet quarterly (in person or teleconference) and otherwise will communicate as necessary by email and telephone. Steering Committee members are responsible for overseeing the conduct of the trial, for upholding and modifying study procedures as needed, addressing challenges with protocol implementation, formulating the analysis plan, reviewing and interpreting the data, and preparing the manuscript.

A study office has been established within the BCCA. This office is managed by a Study Manager having experience in the management of clinical trials, and who is responsible for the day-to-day operation of the trial. The Study Manager will have a staff of full-time Study Clerks and coordinators for the duration of the trial. Study centre staff will be responsible for obtaining verbal informed consent, answering participant and FP office staff questions about the trial, ensuring participants are followed-up, and attend follow-up appointments appropriately, collecting and entering data etc. In addition, the study team will include a Data Manager, Health Records Analyst and a Statistical Analyst.

10 Ethical Issues

This study will be conducted in accordance with the Ethical Conduct for Research Involving Humans Tri-Council Policy Statement (2) http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2- eptc2/Default/ . Ethics approval has been obtained from the University of British Columbia, BC Cancer Agency Clinical Research Ethics Board. No protocol dictated procedures will be conducted without approval of an appropriate Clinical Research Ethics Board.

Consent will be obtained by the participant “verbally” via telephone after it has been determined the participant is eligible for the study, and has had the opportunity to read the Information and Consent form. The participant will then take the unsigned Information and Consent form with her to her cervical screening appointment where appropriate signatures will be obtained at that time. “FP identified” participants will read and sign the information and consent form at the FP office prior to
sample collection. Consent will not be sought from individuals who are not capable of consenting on their own behalf.

All information for this trial will be kept behind locked doors or in secure computer files. On study related documents, subjects will be identified by SIN. On interim and final reports, all data will be de-identified.
Women 25-65 years of age, Attending for routine screening

Randomize 1:1:1

HPV Testing

HPV positive
HPV negative

Cytology

HPV positive
HPV negative

Colposcopy

HPV positive and >ASC-US
HPV positive and cytology negative

Treatment based on colpo results

ASC-H or >LSIL
ASC-US
Cytology Negative

Repeat cytology at 12 months

Control Arm

Return to regular screening program and care by FP

Cytology negative

Colposcopy

Treatment based on colpo results

ASC-H or >LSIL
ASC-US
Cytology Negative

Repeat cytology at 12 months

4-Year Intervention Arm

HPV positive
HPV negative

Cytology Testing

HPV positive
HPV negative

Colposcopy

HPV positive and >ASC-US
HPV positive and cytology negative

Treatment based on cotlopo results

ASC-US
Cytology Negative

Return to regular screening program and care by FP

24 month screening with cytology

48 month exit screen: cytology and HPV testing

2-Year Safety Check arm

Women 25-65 years of age, Attending for routine screening

Randomize 1:1:1

HPV Testing

HPV positive
HPV negative

Cytology

HPV positive
HPV negative

Colposcopy

HPV positive and >ASC-US
HPV positive and cytology negative

Treatment based on colpo results

ASC-H or >LSIL
ASC-US
Cytology Negative

Repeat cytology at 12 months

48 month screen with cytology and HPV testing

4-Year Intervention Arm

HPV positive
HPV negative

Cytology Testing

HPV positive
HPV negative

Colposcopy

HPV positive and >ASC-US
HPV positive and cytology negative

Treatment based on colpo results

ASC-US
Cytology Negative

Return to regular screening program and care by FP

24 month screening with cytology

24 month comparison

Control Arm

12 month repeat protocol

Managed same as women who are ASC-US or ASC-H or >LSIL at 2 year mark in Control arm

12 month repeat protocol

Safety check & Intervention Arms: HPV & Cytology testing at 12 mos. Referred to colpo if >ASC-US OR HPV positive at 12 mos. If HPV AND cytology neg at 12 mos, return to routine screening interval for that arm.
REFERENCES

13. Matisic J.


32. Ronco G. Personal Communication.


APPENDIX 1:

A Randomized Controlled Trial of HPV Testing for Cervical Cancer Screening
“HPV FOCAL Study”:

Study Eligibility Questionnaire
Date: (will be automatically entered)

1. Do you have a problem understanding English/Mandarin?  No   Yes
2. Are you under the age of 25 or over the age of 65?        No             Yes
3. Did you have a Pap test less than 1 year ago?   No   Yes
4. Are you pregnant?   No   Yes
5. During the past 5 years, have you treatment to your cervix for abnormal findings (such as a
   LEEP, lazer therapy, cone biopsy,etc)?   No   Yes
6. Have you ever had a diagnosis of cervical cancer?   No   Yes
7. Have you had surgery to remove your cervix/uterus (a hysterectomy)?   No   Yes
8. Do you have HIV?   No   Yes
9. Are you on any immunosuppressive treatments?   No   Yes

If all 9 questions above are answered “NO”, then the woman is eligible to
participate in the study.

Consented to study participation:

Yes:_________ Date and Time:_________Duration of call:_________

Initials:_________

OR

No: __________ Date and Time: ___________
If no, reason for not participating:
HPV FOCAL Participant Contact Information: Study ID: __________

Participant name: ___________________________ Maiden Name: ___________________________

Any other surnames: ___________________________ Date of Birth: ___________________________

Participant address: ___________________________

email address: _____________________________________________

Phone#(home) ___________________ (Work): ___________________ (Cell): ___________________

Best time of day to contact: ___________________________ Best number: ___________________

Family physician: _____________________________

Have you received the HPV Vaccine?: Yes: _________________ No: ___________________

If yes: Date of first dose(month/yr): _________________ How many doses received: _________________

If No: “If you do receive the HPV vaccine at any point during your study participation, please contact us and let us know so that we can log this information.

Are you willing to be contacted in the future for research studies that may possibly evolve from this trial? Yes: _________________ No: _________________

RECORD OF CORRESPONDENCE

Return letter received (Y or N)? _________________ If Yes, date letter received: ___________________

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<th>Participant Calls to Study Centre</th>
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HPV FOCAL Study
Version 8.0
March 12, 2012
APPENDIX 2

A Randomized Controlled Trial of HPV Testing for Cervical Cancer Screening
“HPV FOCAL Study” (FULL EPIQ. No longer administered as of Jan 2010)

Please take the time to answer the following questions as honestly as possible. Any information you provide will be kept strictly confidential. Answers will only be used for study purposes. Your name, and all other personal identifiers will not be associated with this questionnaire. PLEASE NOTE THIS IS DOUBLE SIDED

BAR CODE: ____________________  SID:________________________

DEMOGRAPHICS

1. Date of birth: ___/___/___ (day/month/year)  Age: (automatically calculated from DOB)

2. Current marital status:
   - Married
   - Single
   - Unmarried, but living with a partner
   - Divorced/Separated
   - Widowed

3. Which ethnic or cultural group(s) did your ancestors belong to? (eg. French, Scottish, Chinese, East Indian). (mark all that apply)
   - Aboriginal (eg. North American Indian, Metis, Inuit)
   - Arab
   - Black
   - British/Irish/Scottish/Welsh
   - Chinese
   - Eastern Europe (eg. Hungary, Poland, Russia, Ukraine)
   - Filipino
   - French
   - Japanese
   - Korean
   - Latin American
   - Northern European (eg. Denmark, Finland, Iceland, Sweden)
   - South Asian (eg. India, Pakistan, Sri Lanka)
   - South East Asian (eg. Vietnam, Cambodia, Malaysia)
   - Southern European (eg. Greece, Italy, Portugal, Spain)
   - West Asian (eg. Iran, Afghan, etc)
   - Western European (eg. Austria, Belgium, Germany, Holland)
   - Other (please specify) ____________________
Employment and Education

4. Are you currently working? □ Yes □ No
5. Are you on disability? □ Yes □ No
6. Are you on social assistance? □ Yes □ No
7. What is your occupation? ____________________________
8. What is the highest level of schooling you have attained?
   - □ No Formal Education
   - □ Elementary school
   - □ High School (complete)
   - □ High School (incomplete)
   - □ Trade certificate/diploma from vocational school or apprenticeship training
   - □ College
   - □ University (undergraduate)
   - □ University (masters level or higher)

Lifestyle

9. Have you ever smoked cigarettes regularly, (1 cigarette or more every day for 1 year or more)?
   □ Yes □ No If No, go to question 12
10. At what age did you start smoking? _______________
11. Do you still smoke?
   □ Yes □ No If No, at what age did you stop? Age: _____ years

Medical, Gynecologic and Obstetric History

12. At what age did you get your first period? ________
13. When did you have your last menstrual period? _____ / _____ month year
14. How would you categorize your periods?
   □ Regular □ Irregular □ Infrequent □ Absent
15. Have you undergone menopause yet?
   □ Yes □ No □ I don’t know
   If No OR if you don’t know, go to question 17
16. At what age did menopause start? ________________
17. Are you currently taking hormone replacement therapy (not contraception) prescribed by a doctor (in the form of pills, patch, cream or gel) for menopause?

☑ Yes ☐ No ☐ I don’t know

18. If yes, how long have you been taking them? __________________________

19. How old were you the first time you had sexual intercourse (vaginal) with a male partner?

Age: ________ years

☐ I have never had sexual intercourse with a male
If Never, go to question 22

20. What is the number of male partners with whom you have ever had sexual intercourse (vaginal)?

☐ 0 ☐ 1-50
☐ 1-250
☐ 6-100
☐ 11-500
☐ 51-99
☐ >99

21. What is the number of male partners with whom you have had sexual intercourse (vaginal) in the past 6 months?

☐ 0 ☐ 1-50
☐ 1-250
☐ 6-100
☐ 11-500
☐ 51-99
☐ >99

22. Have you ever used any of the following methods of birth control? (mark all that apply)

☑ Condoms (male) ☐ Condoms (female)
☑ Contraceptive Cream ☐ Contraceptive Film
☑ Contraceptive Foam ☐ Contraceptive Jelly
☑ Contraceptive Patch ☑ Contraceptive Vaginal Suppository
☑ Contraceptive Sponge ☐ Contraceptive Sponge Suppository
☑ Diaphragm ☐ Withdrawal
☑ Implant (Norplant) ☐ Other (specify) __________________________
☑ Injection (Depo-Provera) ☐ Oral Contraceptive

☐ Intrauterine Device (IUD) ☐ Hormonal Intrauterine Device
☐ Hysterectomy (uterus removed) ☑ Male Sterilization (vasectomy)
☐ Morning After Pill ☐ Oral Contraceptive (the pill)
☐ Rhythm ☐ Tubal Ligation (tubes tied)
☐ None ☐ Other (specify) __________________________
23. What method(s) of birth control are you currently using? *(mark all that apply)*

- Condoms (male)
- Condoms (female)
- Contraceptive Cream
- Contraceptive Film
- Contraceptive Foam
- Contraceptive Jelly
- Contraceptive Patch
- Contraceptive Sponge
- Contraceptive Vaginal Suppository
- Diaphragm
- Implant (Norplant)
- Injection (Depo-Provera)
- Intrauterine Device (IUD)
- Hormonal Intrauterine Device
- Hysterectomy (uterus removed)
- Male Sterilization (vasectomy)
- Morning After Pill
- Oral Contraceptive (the pill)
- Rhythm
- Tubal Ligation (tubes tied)
- Withdrawal
- None
- Other (specify) __________________________

24. If you have ever been on oral contraceptives (the pill), how long (in years) have taken the pill (total number of years, even if you stopped and restarted taking them at any point in time)? ________ years

25. Are you currently pregnant?

- Yes
- No
- I don't know

26. Have you been pregnant before?

- Yes  
  If Yes, go to next question
- No  
  If No, go to question 30

27. How many times (including premature births, full-term births, stillbirths, ectopic pregnancies, miscarriages and abortions) have you been pregnant? ________ times

28. How many times have you given birth? ________ times

29. How old were you when you became pregnant for the first time?  
   Age: ________ years

### Socioeconomic Status

30. What is your usual yearly gross (before taxes) household income?

- < $10,000
- $10,000 to $19,999
- $20,000 to $29,999
- $30,000 to $39,999
- $40,000 to $49,999
- $50,000 to $59,999
- $60,000 to $69,999
- $70,000 to $79,999
- $80,000 to $89,999
- $90,000 to $99,999
- $100,000 to $124,999
- $125,000 to $149,999
- > $150,000
### APPENDIX 3

**A Randomized Controlled Trial of HPV Testing for Cervical Cancer Screening**

**Study Financial Implications Questionnaire**

**Study #: [ ]**

#### YOUR PERSONAL FINANCIAL IMPLICATIONS CONCERNING THIS MEDICAL VISIT

1. Did you miss work to attend your medical appointment?
   - [ ] Yes
   - [ ] No
   
   If No, go to question 4

2. How many hours of work did you miss to attend your appointment? ________ hours

3. Did the number work hours you missed affect your pay or was the time granted by your employer?
   - [ ] It affected my pay
   - [ ] It was time granted by my employer

4. Estimate the total time you had to devote to this appointment, including transportation, waiting time, meeting with the doctor.
   
   ________ hours and ________ minutes

5. What means of transportation did you use to come to this appointment?
   - [ ] Private: (car) Estimate the round trip distance in kilometers: ________km
   - [ ] Public transportation (bus, skytrain, taxi)
   - [ ] Other; (Walk, Bike)

6. Quantify your expenses from this appointment.
   (Please, enter “0” if you had no expenses):
   - [ ] Parking: $ ________________
   - [ ] Public transportation: $ ________________
     Taxi: $ ________________
     Bus/SkyTrain: $ ________________
   - [ ] Babysitter: $ ________________
   - [ ] Other: (ex: meals) ________________ $ ________________

7. What is your usual yearly gross (before taxes) individual income?
   - [ ] $0 to $10,000
   - [ ] $10,000 to $19,999
   - [ ] $20,000 to $29,999
   - [ ] $30,000 to $39,999
   - [ ] $40,000 to $49,999
   - [ ] $50,000 to $59,999
   - [ ] $60,000 to $69,999
   - [ ] $70,000 to $79,999
   - [ ] $80,000 to $89,999
   - [ ] $90,000 to $99,999
   - [ ] $100,000 to $124,999
   - [ ] $125,000 to $149,999
   - [ ] > $150,000

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Please take the time to answer the following questions as honestly as possible. Any information you provide will be kept strictly confidential. Answers will only be used for study purposes. Your name, and all other personal identifiers will not be associated with this questionnaire.

PLEASE NOTE THIS IS DOUBLE SIDED

BAR CODE ___________________ STUDY ID: ____________

Date of birth: ___/___/___ (day/month/year)

23. Which ethnic or cultural group(s) did your ancestors belong to? (eg. French, Scottish, Chinese, South Asian). (mark all that apply)

- Aboriginal (eg. North American Indian, Metis, Inuit)
- Arab
- Black
- British/Irish/Scottish/Welsh
- Chinese
- Eastern Europe (eg. Hungary, Poland, Russia, Ukraine)
- Filipino
- French
- Japanese
- Korean
- Latin American
- Northern European (eg. Denmark, Finland, Iceland, Sweden)
- South Asian (eg. India, Pakistan, Sri Lanka)
- South East Asian (eg. Vietnam, Cambodia, Malaysia)
- Southern European (eg. Greece, Italy, Portugal, Spain)
- West Asian (eg. Iran, Afghan, etc)
- Western European (eg. Austria, Belgium, Germany, Holland)
- Other (please specify) ____________________________
2. What is the highest level of schooling you have attained?

- No Formal Education
- Some elementary school
- Completed elementary school
- Some High School
- Completed High School
- Trade certificate/diploma from vocational school or apprenticeship training
- College
- Some University
- Completed University (baccalaureate)
- University (masters level or higher)

3. Have you ever smoked cigarettes regularly, (1 cigarette or more every day for 1 year or more)?

- No
- Yes
If Yes, do you currently smoke?

- No
- Yes

4. What is the number of male partners with whom you have ever had sexual intercourse (vaginal)?

- 0
- 1
- 2-5
- 6-10
- 11-50
- 51-99
- >99