Protocol for Compass:
A randomised controlled trial of primary HPV vs. cytology screening for cervical cancer in HPV-unvaccinated and vaccinated women in Australia

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Karen Canfell,[1*] Philip Castle,[1] Michael Caruana,[1] Val Gebski,[2] Jessica Darlington-Brown,[1] Stella Heley,[3,] Julia Brotherton,[3] Marion Saville[3]

1 Cancer Research Division, The Cancer Council NSW, Sydney, Australia (current affiliation)
2 NHMRC Clinical Trials Centre, University of Sydney, Australia
3 Victorian Cytology Service Ltd, Carlton, VIC 3053, Australia
*Corresponding author

Email addresses:
KC: karen.canfell@nswcc.org.au
PC: castle.philip@gmail.com
VG: Val@ctc.usyd.edu.au
MC: michael.caruana@nswcc.org.au
JDB: jessica.db@nswcc.org.au
SH: sheley@vcs.org.au
JB: jbrother@vcs.org.au
MS: msaville@vcs.org.au

BACKGROUND

Current status of cervical screening in Australia

The National Cervical Screening Program (NCSP) in Australia has resulted in substantial reductions in cervical cancer incidence and mortality since its inception in 1991.[1] The program recommends screening with conventional cytology every 2 years for sexually active women aged 18-20 to 69 years and achieves relatively high 2-yearly and 3-yearly participation rates.[1] Despite the considerable success of the program, a number of issues prompted recent consideration of changes to the screening recommendations. The recommended 2-yearly screening interval and relatively wide age range of screened women means that screening is conducted more intensively in Australia than in most developed countries[2] and the National Health and Medical Research Council recommended a review of the screening interval in 2006.[3] The International Agency for Research on Cancer (IARC) has recommended that for cytological screening, the optimal screening interval is 3 years in women aged 25-49 years, and 5-years in women aged 50-64 years.[4] The IARC recommendations are based on a body of international evidence that suggests that little benefit is gained by screening women more frequently; thus these intervals for screening represent the best balance of harms and benefits of cytological screening.

Another major driver for changing the cervical screening program in Australia has been the implementation of the National HPV Vaccination Program. A universal access school-based vaccination program in females using quadrivalent HPV 16/18/6/11 vaccine commenced in April 2007, with community-based catch-up vaccination to 26 years implemented to end-2009. Vaccines based on HPV16/18 virus-like particles have been shown to be highly effective in preventing persistent HPV infection and the development of precancerous cervical intraepithelial neoplasia (CIN) in females naïve to HPV vaccine types.[5, 6] The implementation of the National HPV Vaccination Program in Australia was performed early in the international context; it has one of the widest reported age ranges for publicly funded catch-up vaccination; one of the higher levels of vaccination coverage reported in any country to date (approximately 73% in 12-13 year old girls11 and ~30-50% in the older catch-up cohorts aged 20-26 years in 2007)[7-9] and one of the youngest ages of starting screening.[10] Therefore, Australia is the first setting in the world in which large numbers of vaccinated women are participating in population-based cervical screening, which will still be necessary because current HPV vaccines provide only partial protection against cervical cancer. A large number of studies have now documented the effects of the vaccination program in substantially reducing vaccine-included type-specific infections, anogenital warts, and high grade abnormalities (CIN2+) in young women in Australia.

Vaccination has been demonstrated not to affect the clearance of pre-existing HPV infections.[11] Therefore, women positive for a specific oncogenic HPV type should be considered to be at similar risk of developing a precancerous lesion in the future, irrespective of their prior vaccination status. Thus, using HPV testing for the presence of any oncogenic type allows for the simplification of screening recommendations in the post-vaccination era. This is an important consideration because the vaccination status of the population targeted for screening will vary over time as more vaccinated cohort reach screening age.

Primary HPV screening

Primary HPV testing has been reviewed and endorsed as a primary screening method by the International Agency for Research on Cancer.[4] Evidence from overseas clinical studies suggests that the introduction of HPV screening would allow a further extension of the screening interval of up to 5-7 years, and in recent years a significant body of evidence has emerged to support this from a number of international randomised controlled trials on primary HPV testing.[12-15] The findings show that compared to cytology, primary HPV testing has an increased sensitivity for high grade precancerous disease (cervical intraepithelial neoplasia grade 2 or above; CIN2+) which, in an initial round of screening results in increased detection of high grade abnormalities with consequently reduced rates of precancerous disease or invasive cancer (CIN3+), in follow-up screening rounds. A number of longitudinal observational studies have also reported lower rates of CIN3+ in HPV-negative compared to cytology-negative women over time. For example, an analysis of pooled data in the Joint European Cohort Study found that the cumulative rate of CIN3+ in HPV-negative women at 6 years after HPV testing was 0.27% (95%CI:0.12-0.45%); compared to the rate at 3 years for women who were cytology negative at baseline, which was 0.51% (95%CI:0.23-0.77).[16] Recently, a major meta-analysis of data from four large European trials, involving pooled data on 276,000 women, found that

as screening intervals increased beyond 2-3 years, HPV testing resulted in up to 60% increased protection against invasive cervical cancer, compared to cytology-based screening.[15]

A number of clinically positioned technologies for HPV testing are available. The technology which was used in first tranche of international randomised controlled trials was Qiagen's Hybrid Capture 2 (HC2) (QIAGEN N.V, Netherlands), which returns a positive result if any oncogenic HPV type is detected. However, a new generation of alternative HPV testing platforms have emerged in recent years which have the ability to perform partial genotyping i.e. to stratify outputs for HPV positive samples with respect to whether the highest risk HPV types [16/18 and potentially additional types] are present, versus other oncogenic types. This new generation of technologies includes a partial genotyping version of HC2, as well as COBAS 4800 (Roche Molecular Systems, Pleasanton, CA), RealTime PCR (Abbott Molecular, Des Plaines, IL), OncoClarity (Becton Dickinson, Franklin Lakes, NJ), and Aptima (Hologic, Bedford, MA). A major randomised trial of HPV screening using the Cobas system in the USA, ('ATHENA')[17] underpinned the 2014 FDA approval of this test for primary screening in women aged over 25 years.

Various options for the management of HPV positive women have been proposed, including cytological triage, partial genotyping with direct referral of women with HPV16/18 to colposcopy, and the use of dual-stained cytology for the overexpression of the molecular markers cyclin-dependent kinase inhibitor p16INK4a (p16) and Ki-67.[18] Partial genotyping, potentially in conjunction with the other approaches, appears a highly promising strategy which could allow high volume clinical testing with further risk stratification, allowing the differential (more aggressive) management of women exposed to the HPV types most often found in cervical cancer.[19]

In a HPV 16/18 vaccinated population, the current strategy of partial genotyping with HPV 16 and 18 is specifically designed to detect vaccine-included types. In regards to partial genotyping the focus of Compass is on the approach used for the renewed National Cervical Screening Program in Australia, which is supported by an extensive review of the evidence and modelling of long term outcomes.[20]

Renewal of Australia's National Cervical Screening Program

Several factors, including the NHMRC recommendation to review the frequent cervical screening interval in Australia, the availability of LBC options, the emerging body of international evidence on the efficacy of primary HPV screening, and the advent of HPV vaccination, prompted a major review of the National Cervical Screening Program. This review, known as 'Renewal', was announced in November 2011, and is being conducted in two phases – evaluation and implementation. The changes considered in Renewal involved a complete review of screening and triage technologies (considering manually and image-read LBC and primary HPV screening); increasing the interval of screening; and changing the age of starting screening to 25 years.

The evaluation phase involved a review by the Medical Services Advisory Committee (MSAC) which incorporated an extensive systematic review of the literature and effectiveness and economic modelling in Australian context.[21] On the basis of the findings of the review, in April 2014, MSAC recommended that Australia should replace its 2-yearly cytology screening program with 5-yearly primary HPV screening with partial genotyping for HPV16/18 and direct referral of women with these infections to colposcopy. In addition it was recommended that screening starts at 25 years instead of the current 18-20 years in sexually active women, and that women continue to screen until their early 70's, when they can be discharged from screening if an exit test is clear. Women with symptoms (including pain or bleeding) can have a cervical test at any age.[22]

Renewal has now entered an implementation phase, with full roll-out of the changes originally targeted for May 2017. However, there are a number of challenges in implementation, including instituting appropriate laboratory process for large volume HPV testing, instituting new registry invitation and reminder processes for 5-yearly screening starting at age 25 years, instituting pre-qualification and quality assurances processes for new HPV technologies, finalising the clinical management algorithms and guidelines for HPV positive women and women at other points of the diagnosis and treatment pathways in the context of HPV screening, and safety monitoring of the changes. All of these will be informed by establishing a sentinel cohort for the national program changes prior to 2017, via the women recruited to the Compass trial. The implementation of the Renewed National Cervical Screening Program Australian has been delayed from 1st May 2017 until 1st December 2017. This provides the opportunity to accelerate recruitment of the vaccinated cohort by expanding the trial from Victoria across Australia.

Compass Pilot Study

A pilot study for Compass, involving 5,000 women recruited from 2013-2014, has been performed. The objectives of the pilot study were to assess (1) participant acceptance of the randomisation process and use of longer routine screening intervals; (2) confirm the operational feasibility of laboratory processing procedures for two alternative HPV test platforms (Qiagen HC2 and Roche Cobas 4800); (3) to assess test positivity rates for the primary screening test in each arm; and (4) to estimate the sensitivity and specificity of dual-stained cytology testing in women positive for HPV.

Women in the pilot study were randomised at a 1:2:2 allocation ratio to (i) 3-yearly image-read LBC screening with HPV triage testing of low grade smears; or (ii) 6-yearly primary HPV screening with partial genotyping and direct referral of 16/18 positive to colposcopy, with LBC triage testing for other oncogenic types; or (iii) 6-yearly primary HPV screening with partial genotyping and direct referral of 16/18 positive to colposcopy, with dual-stained cytology testing for other oncogenic types. For objective (4) a dual-stained cytology sub-study was conducted wherein all women with HPV–positive findings and a random sample of HPV-negatives (who had colposcopy the exclude the presence of disease) had dual-stained cytology testing performed.

The Compass pilot study was performed at the Victorian Cytology Service (VCS), which also houses the Victorian Cervical Cytology Register (VCCR) (and now also the South Australian Cytology Registry) and the National HPV Vaccination Program Register (NHVPR). Recruitment was carried out in 47 primary practice and community clinics across Victoria. LBC samples were collected and randomised at VCS Pathology; screening invitation and reminder letters were sent via the VCCR. Human research ethical committee approval was obtained from the Alfred Hospital Ethics Committee and the Royal Australian College of General Practitioners National Research Ethics Evaluation Committee. A trial Scientific Advisory Committee (SAC) and Independent Safety Monitoring Committee (IDSMC) were established and their Terms of Reference agreed and ratified.

The successful completion of the recruitment phase of the pilot study has meant that fully operational systems for trial recruitment, primary practitioner training, information and materials for women and practitioners, randomisation, registry invitation and reminder letters, and laboratory processing, and data cleaning and analysis have now been established. Preliminary findings from the pilot study were presented to the trial SAC in May 2014, IDSMC in October 2014, and at the EUROGIN2015 and HPV2015 international meetings. In brief, the findings indicate that the laboratory and referral procedures are practical and that women can be successfully enrolled into a trial of this nature, with the overall recruitment rate over 50%.

The test positivity rates in each arm of the pilot study have been used to inform the sample size calculations for the main trial. Several changes to the protocol from the pilot to the Compass main trial were proposed by the co-principal investigators and discussed with the SAC in May 2015. These changes reflect both the experience gained through the pilot study and changes in the landscape as a result of the ongoing Renewal processes. The main changes are as follows:

- The screening interval for HPV was reduced from 6 to 5 years to reflect the final recommendations for primary HPV screening in Renewal announced in April 2014 (the Renewal evaluation originally considered both 5-yearly and 6-yearly options). In order to maintain 'synchronisation' of follow-up between HPV and cytology aims in the trial, the LBC screening interval for the main trial was also reduced to 2.5 years; this is very similar to the timing of the reminder letters sent in the current program at 27 months.
- In order to simplify the randomisation process, and in line with the primary and secondary objectives of the main trial, the randomisation process has been modified so that women are initially randomised at a 1:2 randomisation allocation ratio to either LBC or primary HPV screening (relating to the primary objective to assess performance of these primary screening tests). For women randomised to HPV screening, who are positive for another oncogenic type (not 16/18), a second-stage randomisation occurs at a 1:1 allocation ratio for triage testing using either LBC or dual stained cytology (relating the secondary objective to assess the comparative sensitivity and specificity of these tests used at this point of the pathway after primary HPV testing).

- No ‘verification’ colposcopy will be performed in screen-negative women – in the pilot study 5% of women were referred for verification colposcopy but this component of the study was difficult to implement, compliance with referral was poor, and the sample attending non-representative.
- The pilot study, by its nature, benefited by being ‘open’ - with the findings available on an ongoing basis to the investigators. However, in line with best practice for RCTs, analysis related to the trial primary endpoint will be conducted only as pre-specified.

The final analysis of the pilot study baseline screening round is complete, preliminary findings were presented at HPV2015 in Lisbon in September 2015 and The Australian Society of Cytology Annual Scientific Meeting in Brisbane in October 2015. Results from the pilot were published in September 2017 [23].

COMPASS MAIN TRIAL METHODS AND DESIGN

PRIMARY ENDPOINT, OBJECTIVES AND POWER AND SAMPLE SIZE CALCULATIONS

Participants in Arm A (LBC cytology screening) will experience three screening rounds in the trial - Round 1 at baseline, Round 2 at 2.5 years, and Round 3 at 5 years. Participants in Arm B (HPV screening) will experience 2 screening rounds in the trial – Round 1 at baseline, and Round 2 at 5 years.

A 10% sample of HPV negative women in each strata of Arm B will be recalled at 2.5 years for cytology testing, for safety monitoring purposes (in order to allow safety monitoring data to be accrued earlier as the trial progresses, the initial randomization to safety monitoring will be increased to 20% of all women recruited from early-mid 2016 until sufficient women to result in an average 10% ratio randomised to safety monitoring have been recruited in each strata). The women recruited for safety monitoring are additional to the women recruited for the analysis of primary outcomes; i.e. this group will not be included in the analysis for the primary endpoint.

All women presenting for cervical screening or follow-up will be enrolled in the trial. All women will be randomized but if under current follow-up will be assigned to the appropriate management branch of the arm to which they are assigned. This approach is in line with Compass providing a sentinel experience for the National Cervical Screening Program transition in 2017, in which all women will need to transition to management under new pathways. A total of 36,300 women in the birth cohorts not offered vaccination and 84,700 women in the cohorts offered vaccination, who are presenting for routine screening, will be recruited, along with additional women to bring the total number recruited to 121,000 (with the additional women representing those presenting for routine follow-up (approximately 5%) and those recruited for a safety monitoring sample (10% of HPV screen negative participants presenting for routine screening)). The sample size requirements for the trial are based on assessment of the cumulative proportion of CIN3+ (including CIN3 and invasive cervical cancer) in women who were screen-negative at baseline.

Primary Outcome

Cumulative CIN3+ (Cervical Intraepithelial Neoplasia Grade 3 or invasive cervical cancer)
The primary outcome will be cumulative CIN3+ at 5 years following a 5-year HPV exit testing round in both arms, in women randomised to the HPV arm vs. women randomised to the LBC arm, adjusted for censoring after CIN2+ treatment.

For the primary outcome, intention to treat analysis will be performed with closed loop testing for non-inferiority and superiority if non-inferiority is declared. Assuming a total average CIN3+ rate in the LBC arm (across unvaccinated and vaccinated women) of 0.6%, and an absolute non-inferiority margin of 0.22%, the trial will have >90% power with 97.5% confidence to detect non-inferiority for the HPV arm, allowing for a 10% non-compliance rate. This sample is adequately powered to detect this margin should the LBC rates be higher than the assumed 0.6%.

The sample size requirements for the trial are based on assessment of the cumulative proportion of CIN3+ (including CIN3 and invasive cervical cancer) in women who were screen-negative at baseline. A major impact of this study will be the value of extended screening intervals in patients who are screen-negative at baseline. Logistically, it would be difficult to randomise patients after baseline screening and as such, the cumulative 5-year CIN3+ rates in baseline screen-negative patients may no longer be strictly comparative. However, this is a critical scientific question and so the trial is powered for this secondary outcome: the cumulative proportion of CIN3+ (including CIN3 and invasive cervical cancer) in screen-negative women, adjusted for censoring after CIN2+ treatment

Secondary Outcomes

The secondary outcomes are listed below. These will be assessed separately in each recruitment strata, i.e. in women not offered publicly-funded vaccination (born on or before 30th June 1980) and in those women offered vaccination (born on or after 1st July 1980):

1. Cumulative CIN3+ in baseline screen-negative women (ITT)
   Cumulative CIN3+ in women presenting for routine screening randomised to the HPV arm who were HPV-negative at baseline, vs. CIN3+ in those randomised to the LBC arm and who were LBC-negative at baseline, adjusted for censoring after CIN2+ treatment and stratified by recruitment group (date of birth >=July 1st 1980 and <1st July 1980). Intention to treat analysis will be performed with closed loop testing for non-inferiority and superiority if non-inferiority is declared.

2. Cumulative CIN3+ in baseline screen-negative women (per protocol)
   Cumulative CIN3+ in women presenting for routine screening randomised to the HPV arm who were HPV-negative at baseline, vs. CIN3+ in those randomised to the LBC arm and who were LBC-negative at baseline and at 2.5 years, adjusted for censoring after CIN2+ treatment and stratified by recruitment group (date of birth >=July 1st 1980 and <1st July 1980). Per-protocol analysis will be performed in women screened and followed up within a defined tolerance period according to protocol recommendations.

3. Cumulative CIN2+ in baseline screen-negative women (ITT)
   Cumulative CIN2+ in women randomised to the HPV arm who were HPV-negative at baseline, vs. CIN2+ in women who were randomised to the LBC arm and were LBC-negative at baseline, adjusted for censoring after CIN2+ treatment and stratified by recruitment group (date of birth >=July 1st 1980 and <1st July 1980).

4. Baseline CIN2+ and CIN3+
   Cross-sectional outcomes for CIN 2+ and CIN3+ detection in each arm, stratified by recruitment group (date of birth >=July 1st 1980 and <1st July 1980).

5. CIN2+ in women randomised to HPV testing at baseline with other oncogenic HPV
   CIN2+ in women randomised to HPV testing at baseline who have other HPV (not 16/18), stratified by recruitment group (date of birth >=July 1st 1980 and <1st July 1980).

6. CIN2+ and CIN3+ in women who have an abnormal test result at baseline
   CIN2+ and CIN3+ in women who have an abnormal test result at baseline, adjusted for censoring after CIN2+ treatment and stratified by recruitment group (date of birth >=July 1st 1980 and <1st July 1980).

7. CIN2+ and CIN3+ in women who were in follow-management for a previous abnormality at baselineCIN2+ and CIN3+ in women who were in follow-management for a previous abnormality at baseline, adjusted for censoring after CIN2+ treatment and stratified by recruitment group (date of birth >=July 1st 1980 and <1st July 1980).

Supplementary Outcomes

Compass will also be a vehicle for other sub-studies and will have the following further objectives:

1. To create a Biobank by collecting and storing samples for retrospective testing to assess the cross-sectional sensitivity, specificity, and positive and negative predictive values (PPV and NPV) of a number of alternate HPV test assays not used for primary screening or management in the study, potentially including PCR-based oncogenic HPV test technologies, signal amplified technologies, alternate systems for HPV16/18 partial typing, and mRNA tests for the expression of the HPV oncogenes E6 and E7.

2. COMPASS PLUS. In a sub-study of women, to collect data to support calculation of health state utilities (quality of life estimates) using a multivariate attribution method involving a self-administered questionnaire in a subsample of women from each study arm, who will be followed longitudinally through the study. (An additional consent process will be developed and additional ethical approval will be sought for this sub-study).

3. Perform analysis assuming progressively less strict per-protocol adherence criteria for cumulative CIN3+ in women presenting for routine screening randomised to the HPV arm who were HPV-negative at baseline, vs. CIN3+ in those randomised to the LBC arm and who were LBC-negative at baseline, adjusted for censoring after CIN2+ treatment and stratified by recruitment group (date of birth >=July 1st 1980 and <1st July 1980).

4. In a subgroup we will also perform specific analysis of the proportion of women that adhere to their screening records, and assess factors associated with adherence

5. As a measure of the harms of alternative screening approaches, we will assess colposcopy referral rates and treatment rates, which will enable us at the end of the trial to calculate measures for number-needed-to-colposcopy and number-needed-to-treat to prevent each CIN3+.

PARTICIPANTS

Eligibility Criteria

Eligible women will be aged 25-69, presenting for cervical screening or routine follow-up (early repeat screening test or post-treatment surveillance test) at participating Primary Health Care Clinics (PHCC) in Australia. Women with a history of cytological or histological abnormalities or who have been treated for high grade CIN in the past will be eligible as will those presenting for an early repeat screening test following unsatisfactory cytology reports, providing that the current visit is for the purpose of routine follow-up. Women undergoing monitoring (i.e. routine follow-up) for low grade and high grade cervical pre cancer will be eligible for participation in the trial. Only women who are willing and able to provide informed consent will participate in the trial.

Inclusion Criteria

- Australian female resident aged 25-69 years
- Either:
    - Attending for routine screening
    - History of cytological or histological abnormalities or who have been treated for high grade CIN in the past and presenting for a routine follow-up test
    - Presenting for an early repeat screening test following unsatisfactory cytology report
    - Previously enrolled in the Compass Pilot but discharged to routine screening.

Exclusion Criteria

- Previous total hysterectomy (uterus and cervix)
- The presence of symptoms for which cervical cancer must be excluded
- Currently undergoing treatment for cervical cancer
- Currently enrolled in the Compass Pilot Study.

Women who are pregnant, or who become pregnant during the trial will be eligible for enrolment. They will be managed according to trial protocol. Any subsequent colposcopy will be managed as per the 2005 NHMRC guidelines for pregnant women.

Recruitment has initially been carried out in the state of Victoria. As of mid-2017 recruitment will be carried out across Australia. This is feasible as, in addition to Ltd operating the VCCR and the South Australia Cervical Screening Register on behalf of the South Australia government VCS has the capacity to manage follow-up of women from across Australia in the Compass trial utilising the Compass Register. It should be noted that recruitment outside of Victoria will be confined to the younger strata (i.e. women age-eligible for HPV vaccination aged at least 25 and born on or after 1st July 1980) since recruitment of the older cohort was met in early 2016. To allow for recruitment to begin outside of Victoria, VCS Ltd has made necessary changes to the trial resources including the information sheet and consent from.

STUDY DESIGN

Coordinating Centres and Study Investigators

The coordinating centres will be the Cancer Research Division at the CCNSW, Sydney, and the Victorian Cytology Service (VCS) Ltd. which includes VCS Pathology, the Victorian Cervical Cytology Registry (VCCR), the South Australian Cervix Screening Registry (SACS Registry – located at VCS Ltd) and the National HPV Program Register (NHVPR), Melbourne, Australia.

VCS Pathology is an accredited, government funded pathology laboratory, reporting around 280,000 cervical cytology tests per year. This represents approximately half the cervical smears taken annually in Victoria. VCS Pathology places a strong emphasis on practitioner liaison. VCS Pathology has the capability to perform image analysis cytology and dual-stained cytology for molecular progression marker analysis. Recruitment and laboratory work will be coordinated and performed at VCS Pathology.

The Cancer Research Division at CCNSW, which will coordinate Compass activities, is involved in a number of projects in cervical cancer modelling and epidemiology. The group performed the effectiveness modelling and economic evaluation for the Medical Services Advisory Committee's review of the Renewal of the National Cervical Screening Program. The group leads a number of other projects including the New Zealand Women and HPV study, studies of cervical cancer patterns of care in Australia and Canada, and cervical screening behaviour in migrant women in NSW, Australia. It is also the provider of the Independent Monitoring Reports for the New Zealand National Cervical Screening Program. Ethics approvals, protocol development and data analysis will be coordinated and conducted at CCNSW.

The investigative team will involve a number of individuals from VCS Ltd., CCNSW and the University of Sydney's Clinical Trials Centre, in addition to a number of other key individuals with specific expertise.

Intervention and comparator

The screening and management pathways for the two study arms are shown in Figures 1 and 2 and are defined as follows:

- Active control - Arm A: 2.5 yearly image read cytology screening with reflex HPV triage testing for low grade smears;
- Intervention - Arm B: Five-yearly HPV screening with types 16/18 genotyping and secondary randomisation of intermediate risk women testing positive for other oncogenic HPV infection to either image read cytology screening or dual-stained (DS) cytology testing (with p16/Ki67).

Randomisation

Compass is a two armed randomised controlled trial of image read cytology screening versus primary HPV DNA testing in Australian women aged 25-69, at the time of entry into the trial. The trial will have a parallel group design, with randomisation to one of two arms at a 1:2 (cytology:HPV) allocation ratio, with secondary randomisation of women with other oncogenic HPV type infections in the HPV arm to either LBC or dual-stained cytology at a 1:1 allocation ratio. In addition, 10% of women in the HPV screening arm who test negative will be recalled at 2.5 years for LBC for safety monitoring purposes.

Upon receipt and logging of the sample at VCS Pathology, individual subject allocation to one of the study arms will be performed using a computer-generated randomisation sequence in a 1:2 ratio, stratified by age at recruitment (DOB <1st July 1980 and DOB ≥≥ 1st July 1980) (indicating whether or not offered HPV vaccination in the publicly-funded program). Secondary randomisation at a 1:1 ratio will be performed on samples which are allocated to study arm B (HPV DNA testing) and which are found to be other oncogenic HPV positive (not HPV 16/18) – this group will be randomised to receive either an LBC or dual-stained cytology triage test. A total of 10% of women in the HPV study arm will have early recall (at 2.5 years) for LBC testing for safety monitoring, should their primary HPV test result be negative.

Neither the participant nor the practitioner will be aware of subject allocation at the time of the recruitment visit and cervical sampling. Allocation will not be concealed in the laboratory (for reasons of practicality). The study allocation and test results will be communicated to the practitioner by means of a standard laboratory reporting form which will include the appropriate follow-up recommendation.

The randomisation schedule and process will be the responsibility of the NHMRC Clinical Trials Centre which has extensive experience in developing and managing the randomisation procedure for clinical trials.

Data Analysis Plan

Pre-specified analyses will be conducted at four time points. These will be done separately for each recruitment strata, as appropriate given the timing for when recruitment for each strata matures, and are as follows:

1. **BASELINE and 12-month follow-up analysis**
   Cross-sectional analysis of results from the baseline and 12-month follow-up screening rounds, including test positivity rates, colposcopy referral rates and CIN2+ and CIN3+ detection rates (*Secondary Objectives 4 and 5*).

2. **2.5 YEAR SCREENING ROUND ANALYSIS (Arm A)**
   Cross-sectional analysis of CIN2+ and CIN3+ rates at the 2.5-year screening round (Arm A).

3. **2.5 Year SAFETY MONITORING ANALYSIS (Arm B)**
   Cross-sectional analysis of CIN2+ and CIN3+ rates at the 2.5-year Safety Monitoring analysis (Arm B).

4. **5 YEAR FOLLOW-UP** Following completion of trial follow-up at 5.5 years.
   At this point follow-up will be completed from all screening rounds, allowing for 6 months in order to obtain final histological outcomes. Longitudinal analyses will be conducted according to the primary and secondary objectives listed above.

Safety and trial stopping guidelines

In addition to the pre-specified analyses, stopping guidelines will act as a trigger for Independent Data and Safety Monitoring Committee (IDSMC) review, at which point full clinical history of individual cases may be reviewed (if the IDSMC determines it is appropriate) before a decision is made about stopping the trial.

Since cytology in the trial control arm (Arm A) is not performed according to current practice, we will also monitor events in this arm as well as the HPV intervention arms. The stopping guidelines assumed that the age-distribution of the participants in the Compass is equivalent to that observed in the general cervical screening population in Victoria. All calculations take into account the 1:2 recruitment ratio for the two study arms (cytology: HPV). Refer to the IDSMC Terms of Reference (included as an attachment) for more detail.

RECRUITMENT AND CLINICAL MANAGEMENT

Consent

Potential participants will be identified by their health care practitioner when they attend for a routine cervical screening at an Australian PHCP. Recruiting practitioners will be debriefed on how to obtain informed consent from women and the VCS liaison physicians will regularly liaise with them throughout the duration of the trial to ensure compliance with the study protocol. Participating recruiting practitioners will be provided with a Compass Trials Details document to read and sign (attached). In addition, they will be provided with the following documentation (prior to commencing recruitment):

A. Medical Practitioner Information Sheet setting out the background to the Compass Trial.
B. Participant Information Sheet explaining the nature of the trial, which is to be provided to each woman prior to seeking her consent to participate (attached).
C. Cytology Request Form/ Participant Consent Form to be completed and signed by each woman prior to enrolling her in the trial (attached).
D. Monitoring, Handling & Recording of Adverse Events Procedure (attached).
E. Protocol for the collection of cervical screening samples for the Compass Trial

Participating practitioners will be provided with a document outlining the trial eligibility criteria. The practitioner will decide whether the woman is able to make informed consent and if so, invite them to participate in the trial. Eligible women will be given an information sheet to read and if they choose to participate will be provided with a consent form to read and sign. If a woman chooses to participate she will have a routine cervical sample collected using an LBC vial. The LBC sample vial will be labelled with the woman's name and date of birth, placed in a sample bag, along with the consent form, and returned to a centralised processing laboratory, at VCS Pathology.

Regardless of where they live in Australia women will have their cervical cytology sample and pathology/consent form sent to VCS Pathology for testing and processing.

- Additional consent from these women will be obtained to enable: Their cervical screening records to be transferred from their local Pap test register to the Compass register, hosted by VCS Ltd.
- Any subsequent cervical screening records to be stored on the Compass Register.
- The Compass investigators to opt participants out of receiving correspondence from their local Pap test register on their behalf
- These women to be followed on the Compass Register for the duration of the trial, including reminding participants when their next cervical screening test is due.
- The transfer of their complete screening record to the National Cancer Screening Register at the conclusion of the trial for ongoing follow-up unless they choose to opt off the NCSR.

Screening and triage test technologies

The following technologies have been selected for use in the trial. All devices used in the trial will be listed on the Australian Register of Therapeutic Goods (ARTG) and will be used within their listed approved use. However, during the course of the trial, alternative products may potentially be used, as appropriate, if they fulfil these criteria and if they are successfully pre-qualified at the VCS in accordance with NATA laboratory requirements, and if they satisfy the Quality Assurance Processes currently being established for new

technologies to be used in the Renewal National Cervical Screening Program (since alternate ARTG-listed LBC medium and HPV test technologies are available).

Specimen Collection Technology: Samples in the trial will be collected using a liquid-based sample medium. The technology to be used will be PreserveCyt/ThinPrep (Hologic Inc, Bedford MA) (included on the ARTG)).

Image read LBC technology: The Hologic Thinprep Imaging (TPI) System will be used for image read analysis (included on the ARTG).

HPV DNA testing technology: Primary HPV DNA testing will be performed using the COBAS 4800 HPV Test (Roche Molecular Systems Inc., Pleasanton, CA) (listed on the ARTG) and incorporating:

- Cobas 4800 System, Sample Preparation Kit: c4800 SMPL PREP
- Cobas 4800 System, Amplification/Detection Kit: c4800 HPV AMP/DET
- Cobas 4800 System, Preparation Kit: c4800 LIQ CYT
- Cobas 4800 System, Wash Buffer Kit: c4800 WB

Dual-stained cytology (DS). Analysis of dual stained cytology for p16/Ki-67 markers in the trial will involve use of the CINtec® PLUS kit (VENTANA MEDICAL SYSTEMS, INC., AZ) (this in-vitro diagnostic medical device is included on the ARTG).

Laboratory, Reporting and Follow-up Processes

All cytology and HPV DNA testing will be performed by trained pathologists, scientists and laboratory technicians at VCS Pathology. Molecular tests and preparation of cytology samples will be performed according to the relevant manufacturer's recommendations. Cytology examinations will be reported according to standard internal procedures. Any unsatisfactory test result will be repeated, according to manufacturer's instructions. Pre-aliquots will be taken before sample testing for future testing with different HPV testing technology. Histology results will be reported according to standard internal procedures by NATA-accredited laboratories.

The laboratory report issued to the practitioner, from VCS Pathology, will specify an overall cervical screening result (low/ intermediate or higher risk for cervical cancer or precursors), the primary test performed and its result, any reflex test performed and its result and finally a recommendation for clinical follow-up that takes account of the woman's screening history and the current results (according to the flowcharts in Figures 1 and 2). A purse-sized reminder card will be included with the laboratory test result. This card will have the date of next test and a reminder to the practitioner that an LBC sample needs to be collected. As per routine practice, it will be the responsibility of the referring practitioner to forward the test result slip to participating women.

Women will be followed up through the Compass Register, operated by VCS Ltd. The Compass Register will routinely follow up cervical abnormalities through reporting of cervical cytology and histology; questionnaires to doctors and Pap test providers; phone calls to doctors; and letters and registered letters to women.

Recruitment post-Renewed National Cervical Screening Program

Conventional cervical cytology (the Pap smear) has been used in Australia for 25 years, the success of the program is demonstrated by annual incidence and mortality rates for cervical cancer that are now amongst the lowest in the world. The Renewal of the National Cervical Screening Program to introduce HPV screening in Australia in place of the Pap test is based on the best available current evidence, and is anticipated to further reduce the incidence of cervical cancer. The trial arms in Compass are reflective of the longstanding program (Arm A) and the renewed program (Arm B), and both methods for cervical screening have been established to be safe and effective.

Although Arm A in Compass is based on the current program (pre-December 2017), it uses LBC (not conventional cytology) screening followed by partial genotyping-based HPV triage for women with abnormal cytology, which is expected to be more effective than the current triage process in the national cytology-based program (which involves repeat cytology only without HPV-based triage testing). Therefore, in Compass, 'Arm A' represents best practice triaging for cytology screening.

Following the transition to the Renewed Cervical screening program, the Compass trial will continue to recruit women until the recruitment target of 121,000 women is met. Compass will continue to recruit participants in the same manner, however the as the standard recommendations for screening in Australia will change from cytology to HPV testing, women being invited to participate in the trial will need to be advised of this.

Although long term improvements in program performance are anticipated with the new program, these gains are based on participation in one or other program for a cohort's entire screening lifetime. Women in Arm A will have two LBCs instead of one HPV test and then transition to routine 5-yearly HPV tests.

Therefore, women recruited to Compass and randomized to cytology after the transition will:

(i) Receive 'best practice' cytology/triaging for abnormal cytology;
(ii) Receive 2 cytology tests vs one HPV test before the 5-yearly HPV exit test;
(iii) Transition to routine 5-yearly HVP screening after exit testing.

The consent form and information sheet have been updated to reflect the changes in current practice to ensure that women are fully aware that they have consented to potentially being randomized to LBC based screening.

Hysterectomy

Women who are enrolled in Compass and have a total hysterectomy (cervix removed) during the trial will be managed according to the NCSP guidelines (2016 Guidelines) [24] and will not receive any additional correspondence from the VCS or VCCR. Trial data from these women will continue to be provided to CCNSW and they will be censored at the appropriate time point during data analysis.

Immune deficient women, including those who are infected with Human-Immunodeficiency Virus (HIV)

Women who are enrolled in Compass and are either immune deficient or become immune deficient (as defined in the 2016 Guidelines), during the trial will be managed according to the 2016 Guidelines. They will continue to be enrolled and followed up via the Compass trial and will receive follow-up by the Compass Register as per the 2016 Guidelines [24].

Other clinical circumstances

Women with any particular combination of clinical circumstances not articulated in the trial protocol will followed in accordance with the National Cervical Screening Program, Guidelines (2016) [24].

Histopathology

For women referred for diagnostic evaluation, histological analysis will be performed as is routinely done by the pathology laboratory used by the colposcopist. As per normal clinical processes, the pathologist providing the original report will be aware of the findings of the screening and triage tests and other relevant clinical information. There is some variation in regards to the use of p16 staining in routine pathology. However, there are efforts underway to standardise this reporting in Australia.[i] All clinical management will be based on the results of routine clinical analysis. A second histopathology analysis will be performed, both with and without p16 immunohistochemistry testing, by an independent quality control (QC) panel comprising three non-local expert pathologists who will not be aware of the study arm, the referral pathway to histology, or screening or triage test results. The trial outcomes will be reported against all three reference standards (local histology, and QC histology with and without p16 testing). However, it should be noted that the main endpoint for analysis remain histologically-confirmed CIN3+ (i.e. not including reclassified CIN2 who are p16 immunohistochemistry positive). In addition, a QC reference standard which does not include p16 assessment will also to provide an additional unbiased assessment of the performance of dual-stained cytology as a triage test (p16/ki67) of HPV-positive women for the related secondary endpoints.

QC review will be performed on all biopsies taken on women who are in the trial, with discordant results defined as a result for which the colposcopy directed biopsy does not correlate with the LBC done at the

time of referral to colposcopy. The QC panel review will be performed in a blinded fashion and the QC pathologists will not be aware of the source of the slides. Histopathology slides reported by other labs will be requested by the investigators to be sent to VCS Pathology for the purposes of coordinating the independent review and then returned.

For women in whom the QC histopathology analysis indicates a previously undiagnosed CIN 2/3+ lesion, their primary practitioner will be made aware of the QC diagnosis. If the woman has not been referred for further evaluation or for treatment of high grade cervical precancerous disease since the biopsy in question was originally taken, the letter to the practitioner will recommend that further investigation is conducted and that treatment of a confirmed high grade lesion proceeds according to the new 2017 NCSP Guidelines [24]. In general terms, Compass participants who are treated for CIN 2+ disease will have post-treatment follow-up according to NCSP guidelines for HPV as "test of cure", and at the point of treatment will be considered to have completed trial follow-up. Following completion of test of cure these women should return to the routine screening as recommended. Although this group of women will be censored from the main trial analysis from the time of treatment, routine follow-up through the VCCR and SACSR will continue, and the data will be collated as part of the trial, for safety monitoring purposes and supplementary analyses.

Procedure for managing off-protocol women

The lab will be guided by the following principles for managing women who are "off protocol".

Both conventional cytology and LBC received: If both a conventional and LBC sample are received then the lab will process the LBC sample according the study protocol. The laboratory will then call the referring practitioner and seek their consent to not process the conventional smear. If the practitioner would like the conventional processed the lab will process conventional and LBC and report on both.

Conventional cytology received at 12-month, 24-month follow-up or at 2nd or 3rd round screening*:* In the event that a Compass participant has a conventional cytology smear collected, rather than the prescribed liquid based cytology (LBC), we will not request that practitioners recollect a LBC. Rather the sample will be read as a conventional smear and managed according to Study Arm A, regardless of what study arm the woman was originally assigned to. If the woman is in Study Arm A and screen negative she will be asked to return in 2.5 years for routine cytology screening using LBC. If the test is LSIL or HSIL, the woman is followed up according to the protocol schedule for Study Arm A.

If a woman is in Study Arm B and negative, or LSIL she will be asked to return in 12 months for a HPV DNA test. If the result is HSIL, the woman is treated as higher risk and follows the protocol schedule (as per Study Arm A) for this result.
In the event that a Practitioner collects a conventional cytology they will be contacted by the Compass Register and reminded to collect LBC samples for all Compass women.

Conventional cytology received at colposcopy: If a conventional cytology sample is returned at colposcopy the sample will be read as a conventional smear and recommendations will be reported as usual.

Woman attends for screen early*:*
If a woman has been randomised to Study Arm A, the sample will be processed, and will be followed-up as per the protocol schedule for Study Arm A.
If a woman has been randomised to Study Arm B, and attends for an early re-screen, and the test result is negative (low-risk), follow-up will be according to the previous Compass test result.

If the cytology test is abnormal (LSIL or HSIL), the woman will be followed-up according to the protocol schedule for Study Arm A (intermediate and higher risk categories).

Opting-out of the trial

Participants will be informed at the time of consent that they will have the right to opt-out of the trial at any point. Participants will be able to opt-out of the trial by either calling VCS Pathology, the VCCR (Compass Hotline), the recruiting primary health care clinic or the relevant Human Research Ethics Committee (HREC). Instructions to the women on the participant information sheet will provide the study hotline as the primary suggested mechanism to opt out. Once a woman chooses to opt out of the trial, her details on VCS Pathology database (CIS) will be updated to reflect this and her Compass study flag will be changed to an opt-out flag. A similar opt-out of trial flag will be marked at the Compass Register. These women will subsequently be followed up by their local Pap test register consistent with National Cervical Screening Policy at the time.

Biobanking

Women will consent to residual samples to be stored for later retrospective testing for research purposes with one of more alternative test technologies. Residual samples in LBC vials will be stored for a minimum of 1-3 months according to usual laboratory practices (in case repeat testing is required for any reason) and may be retained longer, or at a later time, cell pellets may be spun down and frozen as whole cells. This will allow for later assessment of DNA, RNA or protein biomarkers. Samples will be labelled with a unique ID and stored in a secure freezer located at VCS Pathology or at another appropriate site for which appropriate contractual and governance arrangements for storage are in place. This will create a biobank resource, comprising population-based samples for which linkage to the results of histopathology analysis, screening test history, trial outcomes and other data will be performed. This resource will allow for future assessment of differences between true and false positive rates between different HPV test technologies, partial typing systems, and progression markers. The parallel testing using alternate technologies will not be used to manage women and will be performed retrospectively. The results of these tests will not be made available to women or their doctors (i.e. the results of testing will be 'concealed'). It is anticipated that separate funding will eventually be sought for testing Biobank samples. Residual samples that have been anonymised may be exported internationally for further HPV testing and research and development purposes. Separate ethics approval will be obtained prior to testing these samples using any technologies not specified in this protocol.

Future contact with participants to enable further research

At the time of consent in the clinic, women consent to the possibility of being contacted in the future to enable further research. As one example, we will seek further ethical approval to approach a random selection of participants from each study arm and representing each main management pathway in the trial to participate in a longitudinal study of health state utilities, or quality-of life aspects related to their screening experience. These women will be sent a short, self-administered questionnaire. The protocol and related participant materials for this or any other future sub-study will be submitted for ethical review.

Use of trial data based analysis by Aboriginal Torres Strait Islander Status (ATSI)

The Compass Register has the ability to record a woman's Indigenous status (ATSI status) if this is provided on the pathology request form and subsequently to the register. Many practitioners undertaking routine cervical screening collect this information in order to support program design that meets the needs of all Australian women. The Compass Investigators will have access to this de-identified information and do intend to perform analysis by Aboriginality to determine the extent to which the findings from Compass are generalizable to Aboriginal and Torres Strait Islander women. Such analysis will only be performed on de-identified information once approval has been obtained from the Aboriginal Health Research Ethics Committee (AHREC). No results based on ATSI analysis will be published without prior consultation with appropriate Indigenous groups, for example the Aboriginal Health Council of South Australia.

Use of trial data for cost-effectiveness or simulation modelling

Analysis of trial data will be used to inform and update existing epidemiologic and cost-effectiveness models at CCNSW, in order to perform a modelled prediction of the lifetime outcomes associated with each screening and management strategy and also to assess outcomes and cost-effectiveness of a range of variations to the study protocol. Such models may also be used in a range of other epidemiologic and economic evaluations. The data used in these modelled evaluations will be de-identified.

The data used for modelling will include costing data, test positive and negative rates, compliance rates, trial analysis results and all available other trial results. These findings will be used to inform future modelled analysis, performed as part of NHMRC grants and other research projects undertaken by co-Principal investigator, Prof Karen Canfell's research group at Cancer Council NSW.

Compass PLUS

A sub-study will be conducted in the main trial among women 25-49 years old (n=~30,000) to evaluate the psychological impact of primary HPV screening and to obtain utilities for QALY estimates. Please refer to the COMPASS PLUS sub-study protocol for further information.

USE OF TRIAL DATA FOR SAFETY MONITORING FOR THE RENEWED NATIONAL CANCER SCREENING PROGRAM

As part of the 2015-16 Commonwealth Budget the Australian Government has accepted the Medical Services Advisory Committee (MSAC) recommendation to replace the two yearly Pap test with a five yearly primary HPV screening test and has committed funds to support this change. Medicare Benefits Schedule (MBS) items for cervical screening and follow-up management of positive test results will change on 1st December 2017.

Following the MSAC recommendations and their acceptance by the Australian Government, Cancer Council Australia was commissioned and funded by the Department of Health Australia to review and updated the existing 2005 evidence based NHMRC endorsed guidelines: Screening to Prevent Cervical Cancer: Guidelines for the Management of Women with Screen Detected Abnormalities, with the assistance of an expert clinical management guidelines working party and technical support from the Cancer Screening Group at Cancer Council NSW.

These new 2016 Clinical Management Guidelines: Guidelines for the management of screen-detected abnormalities, screening in specific populations and investigation of abnormal vaginal bleeding (CCA, Australia, 2016) offer guidance to health professionals and women as to best practice in the clinical management of women with positive oncogenic HPV test results and abnormalities detected on subsequent LBC. These guidelines address the current epidemiology of cervical cancer in Australia , the benefits and harms of cervical screening, the natural history of cervical HPV infection, the terminology for HPV testing, LBC, cervical histopathology and colposcopy, management of older women and those undergoing exit testing, management of women with positive oncogenic HPV test results, colposcopy, management of histologically confirmed squamous and glandular abnormalities, screening in specific populations, screening for women who are transitioning from the old into the new program, psychosocial issues and economic issues.

The renewal Quality and Safety Monitoring Committee (QSMC) terms of reference specifies that the QSMC will provide advice to the Department of Health on safety and quality aspects of the National Cervical Screening Program (NCSP) cervical screening pathway and any new statistical analyses that will be required to monitor the safety of the renewed National Cervical Screening Program including that of the 2016 Clinical Management Guidelines.

The Safety monitoring protocols will monitor the safety of women participating in the renewed NCSP will assist to:

1. Reassure women they are at low risk of developing cervical cancer during the routine five yearly screening intervals;
2. Monitor the performance of the screening test to ensure it is performing as expected;
3. Monitor the safety of the 2016 Cancer Council Australia's Clinical Management Guideline recommendations for women at intermediate risk and higher risk of developing cervical cancer;

4. Ensure the ongoing success of the renewed NCSP which aims to reduce the incidence and mortality of cervical cancer.

Pending Department of Health Approval, Compass data will be used for analysis in the safety monitoring of the renewed program.

SAFETY MONITORING, QUALITY ASSURANCE AND STUDY MONITORING

Safety Monitoring

An Independent Data Safety and Monitoring Committee (IDSMC) has been configured to monitor the safety of participants in the main trial and the Pilot study. The Terms of Reference for the IDSMC can be found as an attachment to this protocol.

During the study, the investigators, practitioners and other site staff will be responsible for detecting and documenting events meeting the criteria and definition of an Adverse Event (AE) or serious adverse event (SAE). The adverse event reporting protocol is attached.

It will be the responsibility of all study personnel to record an AE/SAE when it occurs. Study personnel include investigators, study coordinators, participating medical practitioners, Victorian Cytology Service staff and CCNSW staff.

Adverse Events and Serious Adverse Events (as defined in the attached document) shall be handled and reported according to VCS's internal procedures, and in compliance with any applicable national and international laws, regulations, and guidelines. VCS shall report all Adverse Events in a timely correct manner to local authorities according to national laws, regulations and guidelines.

Study Monitoring and Quality Assurance

Compass will be conducted in compliance with the approved scientific protocol and in line with the National Statement on Ethical Conduct in Human Research, NHMRC 2007. No deviation from the protocol will be executed without the prior review and approval of the lead HREC. Any unanticipated necessary deviation from protocol will be immediately reported to the leading HREC according to its standard policies and procedures.

VCS Ltd has well established documented policies and procedures to cover operations in both technical and non-technical areas of VCS Pathology, VCCR and the NHVPR VCS Pathology is a specialist gynaecological pathology laboratory which fully complies with AS ISO 15189:2009, NATA and NPAAC standards relevant to its scope of activities. VCS Pathology maintains a comprehensive quality system. Compass data, files and SOPs will be monitored regularly, and reviewed annually, by the project coordinator to ensure the trial procedures comply with the approved Protocol and HREC requirements.

VCS Ltd. Operational Quality Assurance and Control

The VCS policy on Management of Health and Personal Information and the VCS Code of Conduct apply across the Service, although individual department procedures may contain additional specific information and instructions where appropriate. The Quality Assurance Committee (QAC), a sub-committee of the board of directors of VCS Ltd, meets monthly to review scientific and operational quality assurance activities.

Laboratory Quality Assurance

VCS Pathology employs only appropriately qualified or experienced staff for laboratory roles and also provides formal training for Medical Laboratory Scientists. Training needs are identified at least annually.

Safety Monitoring Arm

At the point of allocation to the safety monitoring arm (for the 10% of women selected from the HPV arm for safety monitoring) women will be notified via the lab report that they should have a repeat LBC test at 2.5 years. Invitation letters to re-attend screening will be issued to participants at appropriate times (three months prior to the scheduled re-screening interval). Reminder letters (or email/text) will be issued to participants who do not attend within 3 months and a second reminder letter will be sent at 6 months. Follow-up of any abnormalities detected in safety monitoring will be according to study Arm A (Figure 1).

DATA LINKAGE, SECURITY AND STORAGE

Data linkage

Initial screening test results and follow-up data for the Compass trial will be retained as part of routine data processes for the Compass Register.

Participants will also be followed-up via linkage to a number of other routinely collected datasets. Data linkage will be undertaken with informed consent of participants; only de-identified data will be available to the study investigators involved in the analysis of linked data. Data custodian and ethical approval will be sought to link the trial data for each participant to the National HPV Vaccination Program Register to obtain information on vaccination status, doses delivered and timing of vaccination.

Because the trial will inherently form part of the woman's cervical screening record, individual participant results and personal information, collected as part of the trial, will be held on the databases of the VCS Pathology, VCCR and SACSR, as would normally be the case for any woman participating in the National Cervical Screening Program. In the screening program, all cervical cytology, histology and HPV test results are routinely forwarded to VCCR and SACSR from the reporting laboratory, along with personal information for the purposes of reminders and follow-up, unless a woman chooses to opt-off. If a woman does not have a record at VCS Pathology, VCCR or SACSR a new one will be created and linked with trial data.

Data transfer from State and Territory Pap test registries to the Compass Register

Upon receipt of the consent form and sample from participating women, VCS Pathology staff will contact their respective state or territory Pap test registry to obtain a copy of their screening history. This will include all cervical cytology, histology and HPV test results, recommendation codes and any other personal information routinely collected as part of the woman's cervical screening record.

The following data sets will be accessed:

Medicare Australia: address information as a failsafe for women otherwise lost to follow-up.
Department of Health and Ageing: *National HPV Vaccination Program Register*: Vaccination status, number of doses, date of doses and immunisation provider.
Compass Register: The Compass Register is based on the Victorian Cervical Cytology Registry. The Victorian Cytology Service is the primary research organisation and holds the Victorian Cervical Cytology Registry and the National HPV Vaccination Program Register. Information on date of birth (DOB), Local Government Area (LGA), and screening episodes and results of care delivered within the national cervical screening program will be analysed in the trial, including cytology histology, colposcopy and HPV tests.
The National Cancer Screening Register (NCSR) is expected to go live on December 1st 2017 and will progressively take over the roles of the state and territory based cervical screening registers. The NCSR will be an integral part of cancer screening service delivery providing the infrastructure for the recording, analysis and reporting of cancer screening data for participants of the National Cervical Screening Program and the National Bowel Cancer Screening Program.

At this stage information related to women enrolled in Compass will remain on the **Compass Register**, hosted by VCS. Their information will be transferred to the NCSR following the completion of their participation in the Compass trial, unless they indicate that they do not wish this to occur. The Compass register will operate on the infrastructure currently hosting the VCCR and the SACSR.
All Australian Cancer Registries: Confirmation of cervical cancer or cancer free status for all participants
All State Registry of Births, Deaths and Marriage: Confirmation of death status.

In addition to the above routinely collected data, mobile phone and email address will be used to follow-up women to participate in cervical screening according to trial protocol.
All trial data will be stored on a secure server, with access only to authorized study personnel.

Data Security and Storage

VCS Pathology: Consent forms and cytology request forms will be stored at the VCS in secure locked cabinets with access restricted to only those directly involved in the study or when required to ensure appropriate clinical management. With the consent of the participant, any remaining cytology sample will be aliquoted and stored in locked freezers at the VCS, with access restricted to only those directly involved in the study. The samples will be stored according to the VCS protocol on storage of human tissues. These samples may be used for future related research using alternative HPV testing technologies and/or testing biomarkers relating to cervical disease. Ethics approval will be obtained prior to performing these tests and individual participants will not have access to these test results as they are for research purpose only. Confidential data will also be stored in electronic format on a secure server platform supported by a range of system controls, infrastructure, and processes to ensure it is adequately protected. Access to electronic data files will be restricted to authorised users only who are directly involved in the study, via password protected computers located in VCS. All data collected and stored, including electronic data and hard copies, will be kept for an indefinite period of time, at the VCS, in accordance with the Victorian Cancer Act 1958. All VCS employees sign confidentiality agreements every 6 months.

Compass Register: will hold personal and health information of trial participants. This information will be collected from VCS Pathology which will report the Pap test or HPV test and will include name (current and previous), date of birth, addresses (current and previous), Medicare Number, indigenous status, country of birth, language spoken at home and Pap test result; health care practitioner's name, address and Provider Number, and the name and address of the laboratory reporting on the Pap test. All confidential electronic data at the Compass Register will be stored securely on their server platform, with access restricted to authorised users only who are directly involved in the study. Data will be kept for an indefinite period time in accordance with the Victorian Improving Cancer Outcomes Act (2014) and the Commonwealth Privacy Act (1988), including all subsequent amendments, unless a woman elects not to have her personal and health details recorded on the Register.

The Cancer Research Division, CCNSW: Participants will be assigned a unique study ID code at the VCS. Data will be extracted from the Compass Register located at VCS and sent to CCNSW. The first name, last name and address fields will be removed and replaced with a unique study identification number, however email address and phone number will be transferred to CCNSW to allow researchers to invite women in a sub-study (refer to the Compass-PLUS protocol). Only de-identified data will be used for the purpose of trial analysis. This data will be transferred on a regular basis from the Compass Register and stored on secure servers located at the Azure data centres in Sydney and Melbourne, with access only to authorized study personnel. A data manager/statistician at CCNSW will maintain the study database and perform statistical analysis. Data will be transferred between VCS and CCNSW either upon password protected computer disks/memory sticks in a secure mail bag or uploaded via a secure web-based portal. Access to the secure web based portal will be restricted to only those involved directly in the study. Data will be stored in electronic format on secure network computers for use during the duration of the research project. Access to electronic data files will be restricted to only to those directly involved in the study on password protected computers located at CCNSW. No personal information identifiers will be stored in the analysis file; all identifying information will be removed from the data set used for analysis and only the unique study identifier will remain. A master list linking numeric codes to identifying information will be stored at the Victorian Cytology Service and thus a woman will be able to be identified by VCS if the analysis by CCNSW determines there is a safety monitoring issue or inconsistency in the data. All CCNSW employees sign confidentiality agreements and comply with privacy policies. After project completion, electronic data will continue to be stored at the Azure data centres in Sydney and Melbourne. Data will be kept at Azure for a period of at least 7 years after the completion of the project and publication of results. After which Electronic data will be deleted from the Azure server and CCNSW network computers, and any disks containing information will be reformatted or destroyed.

After project completion: Trial data will be stored at Azure data centres in Sydney and Melbourne for a period of at least 7 years after the completion of the project and publication of results. This amount of time will allow for adequate interest, discussion and follow up surrounding study data to occur. Results will be reported in a series of papers, reports and presentations in scientific forums. Results will be published in

statistical aggregate form so that no individual subjects are identifiable directly or indirectly. Reports or published forms resulting from this study will be owned by their authors who will be members of the research team assigned to this study. The information collected for Compass will be owned by the research team and reports or published forms resulting from this study will be owned by their authors who will be members of the research team assigned to this study. Should the principal researcher cease to be engaged at CCNSW before completion of this research project, access to data will be negotiated between the researchers, the organisations and the relevant ethics committees. Should the data be retained at the CCNSW, remaining members of the research team involved in this project will take over protection of privacy of the data. Should a new principal researcher become involved in the project at CCNSW, they will be required to sign privacy and confidentiality agreements regarding their access to the study data. Data routinely collected by the Compass Register will be kept indefinitely in accordance with the Victorian Cancer Act 1958.

Publication of results

Results will be reported in a series of papers, reports and presentations in scientific forums. Results will be published in statistical aggregate form so that no individual subjects are identifiable directly or indirectly. Reports or published forms resulting from this study will be owned by their authors who will be members of the research team assigned to this study. The information collected for Compass will be owned by the research team and reports or published forms resulting from this study will be owned by their authors who will be members of the research team assigned to this study.

Governance

Ethical approval will be sought from appropriate certified Human Research Ethics Committees. A Scientific Advisory Committee will advise the investigator team on issues related to protocol, operations and any other issues brought by the investigators to the Committee. The Scientific Advisory Committee (SAC) will be chaired by Prof. Bruce Armstrong, Professor of Public Health at the University of Sydney. Final responsibility for protocol or operational decisions will be the joint responsibility of the co-PIs. Ethics approval from other HRECs will be obtain as required.

Trial Report, Registration and Protocol Availability

Reporting of trial results will be according to the CONSORT statement. The trial is registered on clinicaltrials.gov (NCT02328872).

Funding and sponsorship, competing interests

An agreement with Roche Molecular Systems and Ventana Inc USA has been negotiated for supply of HPV tests. This and any future agreement the co-principal investigators enter into with this sponsor or any other will ensure that the company has no role in design and conduct of the trial or the analysis of trial results and the decision to publish.

Insurance and Indemnification

The co-Principal investigator's institutions (Victorian Cytology Service Ltd., and Cancer Council NSW) will maintain such insurances to provide indemnity for their officers, employees and agents from and against all actions, claims, demands, costs or expenses (including legal costs on a solicitor and own client basis) made, sustained, brought or prosecuted or in any manner based upon, or occasioned by or attributable to, any injury to any person (including death) or loss of or damage to property which arise from, or as a result of, conducting the Compass trial. Practitioners involved in the trial will be required to inform their medical indemnity insurance provider that they are recruiting participants for clinical trial and update their policy where required. The Investigators will inform the leading medico-indemnity providers in Australia of the trial.

Compass Investigator Details and Role

CO-PRINCIPAL INVESTIGATORS

Professor Karen Canfell, *D.Phil. (PhD)* ***(co-PI)***

Role: Along with A/Prof Marion Saville, Prof Canfell is co-PI for the trial and together they developed the rationale for the trial. Prof Canfell conceived the initial concept of the trial led the development of the trial protocol including the statistical design. Prof Canfell will lead the statistical analysis and write-up of results.

Bio: Professor Karen Canfell leads the Cancer Screening Group at the Cancer Research Division Cancer Council NSW (CNSW)). The group are involved in a number of projects in prevention of cervical, colorectal and other cancers. A focus of Prof Canfell research concerns the interplay between HPV vaccination and cervical screening, both in developed countries and in lower resource settings. Her group regularly perform evaluations of new cervical screening and diagnostic technologies and pathways for government agencies in Australia, New Zealand and England; and also collaborates with the Cancer Institute of the Chinese Academy of Medical Sciences to evaluate options for cervical cancer prevention in China. Prof Canfell's group recently performed the effectiveness modelling and economic evaluation for the review of the National Cervical Screening Program in Australia.

Prof Canfell holds a D.Phil. from the University of Oxford and an NHMRC Career Development Fellowship, and she has held a number of competitive NHMRC grants and government consulting contracts. She is regularly involved in international meetings on HPV prevention, for example as co-chair of the cost-effectiveness sessions at the International Papillomavirus Conference in 2012 and 2014, and as an invited participant in the US President's Cancer Panel Workshops on Global HPV Prevention in 2013. She recently led the review of modelled evaluations of HPV prevention in developed countries for a key WHO/ICO-sponsored monograph on HPV prevention. Prof Canfell also chairs Cancer Council Australia's Cancer Screening Advisory Committee and is a member of the Medical Services Advisory Committee's Protocol Advisory Sub-Committee.

Associate Professor Marion Saville, *MB ChB, Am Bd (Anat Path & Cytopath), FIAC, Grad Dip Med (Clin Epi)* ***(co-PI)***

Role: Along with Prof Karen Canfell, A/Prof Saville is co-PI for the trial. A/Prof Saville contributed to the development of the scientific protocol and led the development of the operational procedures at the VCS including the laboratory operations and registry follow-up systems. A/Prof Saville's role will be to manage the operational aspects of the trial carried out at the VCS as well as oversee the conduct of the trial at each of the Practitioner recruitment sites.

Bio: Associate Professor Saville is the Executive Director of VCS Limited. The service runs one of Australia's largest cervical cytology laboratories (VCS Pathology) and operates the Victorian Cervical Cytology Register (VCCR). Under A/Prof Saville's leadership VCS has established and now operates the National HPV Vaccination Programme Register (NHVPR) on behalf of the Australian Government. A/Prof Saville is a cytopathologist with special expertise in gynaecological cytology, having trained at the North western University, School of Medicine, Chicago, Illinois and with Professor Jan Silverman, then at the University of East Carolina. Her major interests now lie in cervical screening policy and planning and she completed a Graduate Diploma in Clinical Epidemiology at the University of Sydney in 2000. A/Prof Saville's research interests focus on the translation of research relevant to cervical screening into policy. She is an author on a number of related peer reviewed publications. Most recently she was a member of the Renewal Steering Committee, a group established by Australian governments to provide oversight to "Renewal" of the National Cervical Screening Programme.

OTHER CHIEF INVESTIGATORS

Dr Philip Castle, *PhD, MPH*

Role: Dr Castle has been involved in the statistical design of the trial and the development of the trial protocol. His will provide ongoing technical and statistical support to the co-PIs.

Bio: Dr. Philip Castle is a Professor in the Department of Epidemiology and Population Health at Albert Einstein College of Medicine, Bronx, N.Y., USA, the Executive Director and Co-Founder of Global Cancer Initiative (Chestertown, MD, USA), and the CEO and Co-Founder of the Global Coalition Against Cervical Cancer (Arlington, VA, USA). Previously, Dr. Castle was the Chief Scientific Officer of the American Society for Clinical Pathology (ASCP) (2011-2). He was a Senior, Tenured Investigator (2010-11) and Tenure-Track Investigator (2003-10) in the Division of Cancer Epidemiology and Genetics at the U.S. National Cancer Institute. He received his Ph.D. in Biophysics in 1995 and M.P.H. in Epidemiology in 2000 from the Johns Hopkins University. Dr. Castle's professional interests are (1) epidemiology of human papillomaviruses (HPV) and cervical/anogenital cancer; (2) science and translation of cancer prevention strategies; (3) evidence-based medicine; and (4) international health. While at the NCI, he was the lead investigator on several epidemiologic studies, including the Mississippi Delta Project, The HPV Persistence and Progression Cohort and The Guidelines Cohort at Kaiser Permanente Northern California (KPNC), the Anal Cancer Screening Study. He remains co-PI of The Guidelines Cohort at KPNC and of the Low-Cost Molecular Cervical Cancer Screening Study in China. Dr. Castle is currently conducting research in Australia, Norway, El Salvador, Brazil, Peru, Colombia, Mexico, and Rwanda. Dr. Castle has published over 250 papers on HPV and cervical cancer and has contributed articles to such prestigious journals as the New England Journal of Medicine, Lancet, Lancet Oncology.

Professor Val Gebski, *BA, MStat, honorary FRANZCR*

Role: Prof Gebski contributed to the statistical design of the trial. Previously he was a member of the Independent Data Safety Monitoring Committee (IDSMC) for the Pilot study. He will provide ongoing statistical advice to the co-PIs and Dr Caruana over the duration of the trial.

Bio: Professor Val Gebski is head of biostatistics and research methodology. He joined the CTC in 1988. He has extensive knowledge of clinical trial methodology, conduct and analysis and is the group statistician for a number of national collaborative clinical trials groups in oncology. He also has extensive experience in designing and conducting meta-analyses as well as involvement in developing terms of reference for independent data safety and monitoring committees (IDSMC), participating in (including chairing) international IDSMCs and preparing reports for these bodies. He has a BA and MStat and is an honorary Fellow of the Royal Australian and New Zealand College of Radiologists. He is involved in curriculum development and teaching in the Masters of Public Health, clinical epidemiology and medicine as well as being a co-director of the Masters of Clinical Trials (Research) being run from the CTC. He is the statistical examiner for the Royal Australian and New Zealand College of Radiologists and coordinator of the critical appraisal component of the Basic Sciences in Oncology program run by NSW Department of Health.

Dr. Michael Caruana, *B.Sc. (Hons.) (Math & Stats), D.Phil. (Math)*

Role: Dr Caruana is the trial statistician who, under the supervision A/Prof Karen Canfell and Prof Val Gebski was involved in statistical design of the trial. Dr Caruana will have an ongoing role in the trial and will perform data analysis for the study endpoints as well as routine data analysis for the Independent Data Safety Monitoring Committee (IDSMC) meetings.

Bio: Dr Caruana is currently a Research Fellow at the Cancer Research Division, Cancer Council NSW (CNSW), working with CIA A/Prof Karen Canfell in the Cancer Screening group, where he has been involved in various modelling exercises on cervical cancer screening in Australia and the UK. Dr Caruana has published 3 articles in peer-reviewed mathematical journals, co-authored a book on rough path theory and published 2 commissioned government reports. He is a CI on an NHMRC project grant which commenced in 2014, and will evaluate the cost-effectiveness of next generation 9-valent HPV vaccines and also evaluate HPV-based screening options in Australia, England and New Zealand.

A/Prof Julia Brotherton, *B Med (Hons), MPH (Hons), Grad Dip App Epi, FAFPHM, PhD*

Role: A/Prof Brotherton has contributed to the development of the trial protocol and operational processes at the Victorian Cytology Service and Victorian Cervical Cytology Registry. Dr Brotherton will be responsible for the linkage between the VCCR and the National HPV Vaccination Program Register (NHVPR).

Bio: Julia Brotherton is a public health physician and Medical Director of Australia's National HPV Vaccination Program Register. She is a medical graduate from the University of Newcastle, NSW, has a

Masters degree in Public Health and a Doctorate of Philosophy from the University of Sydney and holds a Fellowship in Public Health Medicine. For the past nine years Julia has been involved in research and policy development informing the implementation and evaluation of HPV vaccination programs in Australia. She has been a lead investigator in Australian research, which has demonstrated the world's first evidence of dramatic declines in both HPV infections and pre-cancerous cervical lesions in young women post-vaccination. She has over 90 publications to date.

Dr Stella Heley, *BA(Hons), MB BS, DipVen (Lond),FAChSHM*
Role: Dr Heley has contributed to the design of study materials and has led the enrolment of Practitioners into the trial. She will lead the ongoing enrolment of Practitioners and Clinics and act as a clinical liaison between the VCS and participants, practitioners and recruiting clinics.

Dr Stella Heley is a Sexual Health Physician and the Senior Liaison Physician at VCS. Dr Heley has spoken to hundreds of health practitioners over the years giving support to enable the best management of both the cervical screening program and sexually transmissible infections. Stella was a member of the HPV Vaccine Working Party of ATAGI (Australian Technical Advisory Group on Immunization) prior to the introduction of the HPV vaccine onto the National Immunization Program in 2007. She has written on these topics for a number of medical journals and is regularly invited to speak at medical meetings.

Associate Investigators

Mr C. David H. Wrede, ***Clinical lead for the Dysplasia service, The Royal Women's Hospital, Melbourne***
Dr Jeff Tan, ***Obstetrics and Gynaecology Royal Women's Hospital***
Ms Jessica Darlington Brown, ***Compass Clinical Trial Coordinator at Cancer Council NSW***
Dr Siobhan Bourke, ***Sexual Health Physician and Liaison Physician at VCS***
Dr Lara Roeske, ***Sexual Health Physician and Liaison Physician at VCS***
Dr Jane Collins, ***co-owner and the Clinical Director of the Clifton Hill Medical Group and Vice President of the Board of VCS***
Ms Sandy Anderson, ***Women's Health Nurse / Practice Nurse, Ballarat and District Aboriginal Cooperative***
A/Prof Sally Lord, ***Epidemiologist and Senior Research Fellow at the NHMRC Clinical Trials Centre***
Dr David Hawkes, ***Director – Molecular Biology and Biochemistry***
Ms Grace Tan, ***Director – Cytology and Histology***
Dr Wendy Pakes, ***Liaison Physician at VCS***
Dr Alexis Butler, ***Liaison Physician at VCS***
Ms Rebecca Asher, ***Biostatistician NHMRC Clinical Trials Centre***
Dr Louiza Velentzis**, Post-Doctoral Research Fellow** ***at Cancer Council NSW***
Ms Megan Smith***, Program Manager at Cancer Council NSW***
Ms Leanne Rumlee, ***Data Analyst at Cancer Council NSW***
Ms Chloe Jennett, ***Senior Research Assistant at Cancer Council NSW***

SCIENTIFIC ADVISORY COMMITTEE (SAC) MEMBERS
Chair: Professor Bruce Armstrong
Professor Jonathan Carter
Professor Rachel Skinner
Professor Suzanne Garland
Associate Professor Deborah Bateson
Professor Andrew Grulich
Dr Eduardo Franco
Ms Susan Taylor
Professor Annabelle Farnsworth *(Chair: Histopathology Review Board)*

INDEPENDENT DATA AND SAFETY MONITORING COMMITTEE (IDSMC) MEMBERS
Chair: Professor Michael Quinn,
A/Prof Penny Blomfield,
Professor Gordon Wright,
Associate Professor Katrina Sharples,

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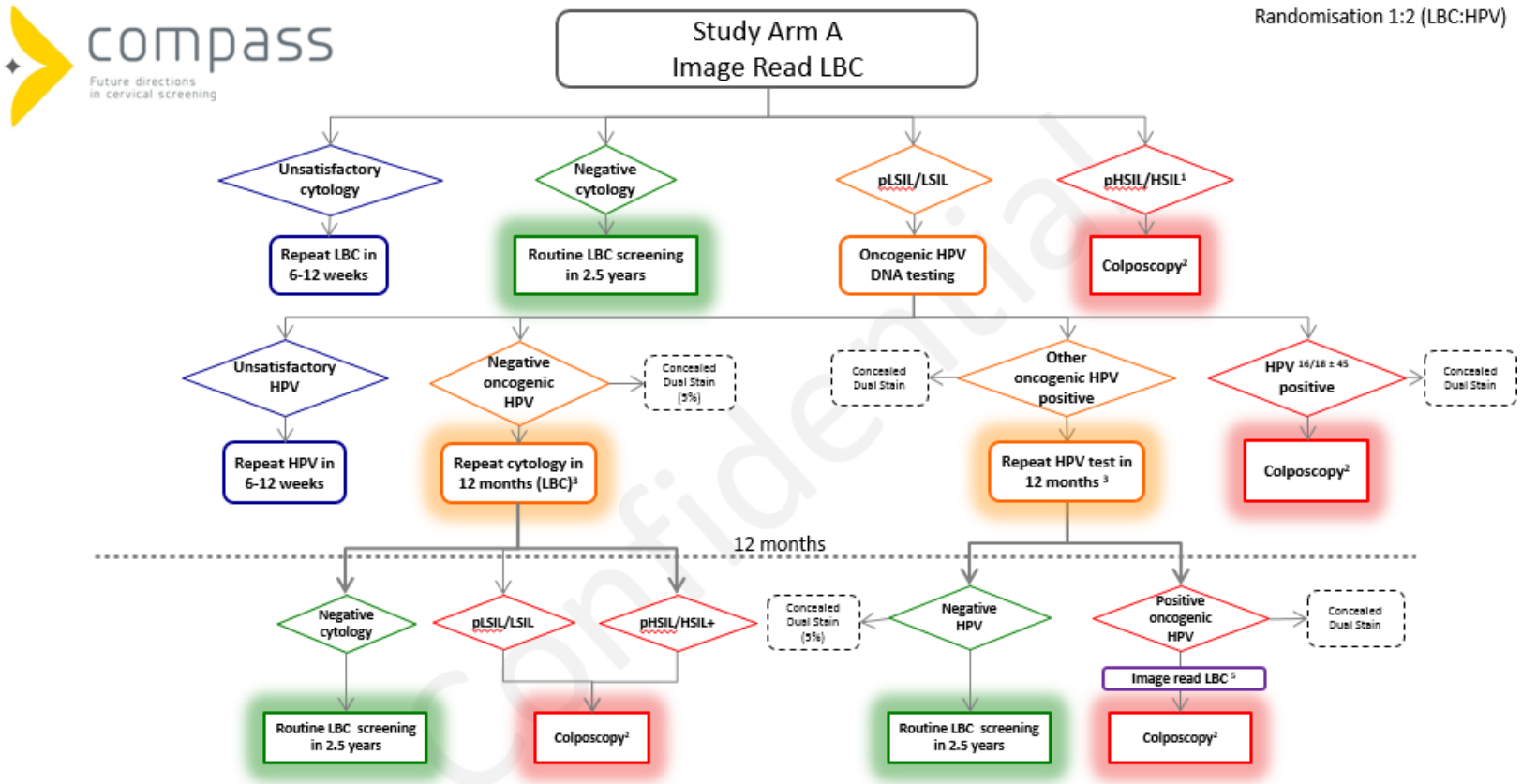
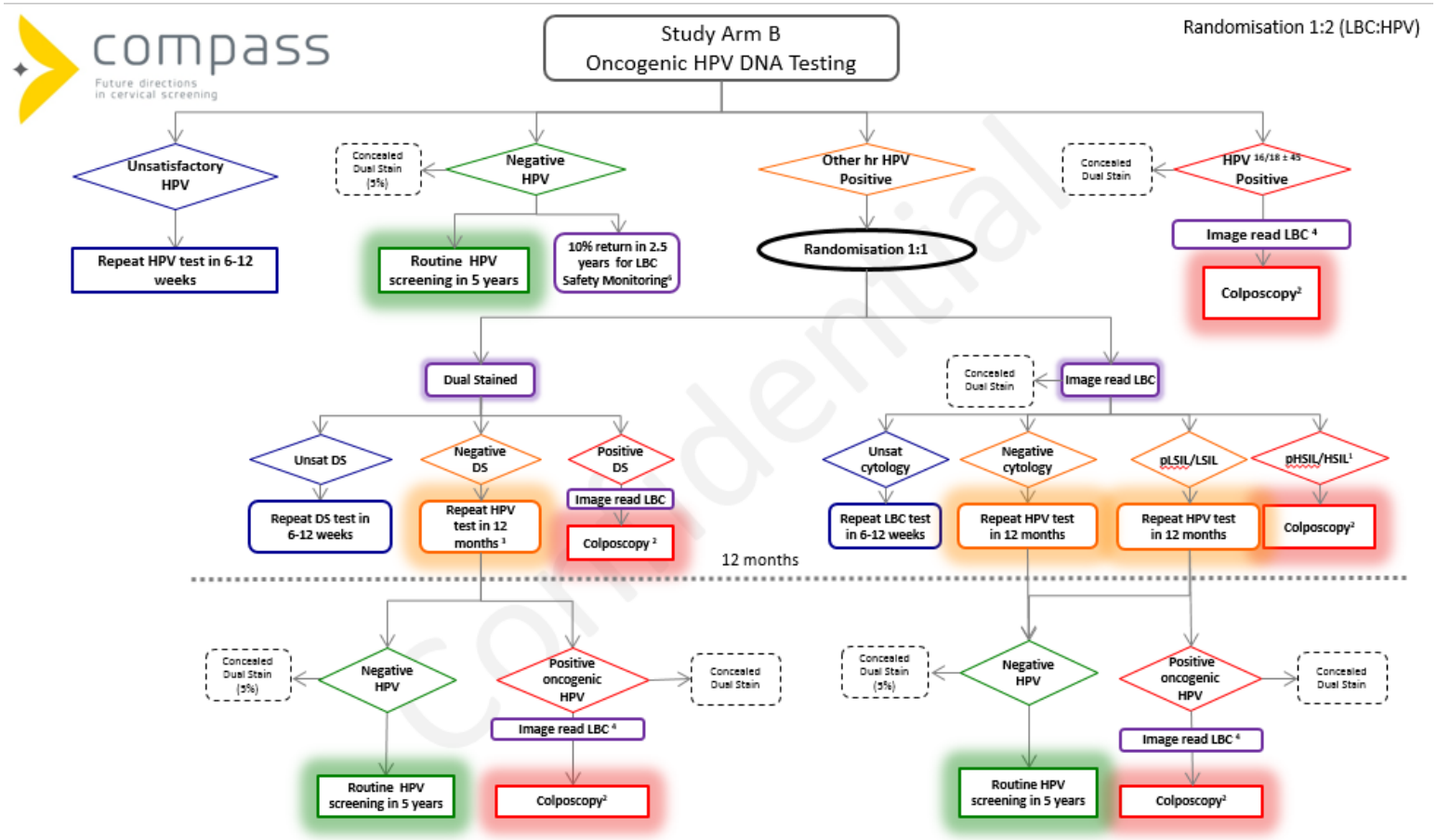


Footnotes: Study arm A

1) Includes any glandular abnormality, possible HG endocervical glandular lesions and atypical glandular cells of uncertain significance.
2) If results at colposcopy are negative/CIN 1/HPV, women require one negative follow-up tests at 12 months, using index test, before returning to routine screening (return to original study arm). If CIN 2+/AIS: treatment and follow-up according to The NCSP guidelines. Colposcopy unsatisfactory: managed by the individual specialist, informed by The NCSP guidelines (see detailed management flow charts).
3) AIS will have Annual co-test (HPV and LBC) indefinitely. Refer to the National Pathology Accreditation Advisory Council (NPAAC) draft protocol, Chapter 11 Management of Glandular Abnormalities, Flowchart 11.4 follow up after excisional treatment for AIS.
4) LBC result to assist colposcopy reading they do not feed into the recommended follow-up for women
5) Concealed DS not for management of women

Confidential



Footnotes: Study arm B

1) Includes any glandular abnormality, possible HG endocervical glandular lesions and atypical cells of uncertain significance.
2) If results at colposcopy are negative/CIN1/HPV, women require one negative follow-up tests at 12 months, using index test, before returning to routine screening (return to original study arm). If CIN 2+/AIS: treatment and follow-up according to The NCSP guidelines (see detailed management flow charts). Colposcopy unsatisfactory: managed by the individual specialist, informed by The NCSP guidelines (see detailed management flow charts).
3) AIS will have Annual co-test (HPV and LBC) indefinitely. Refer to the National Pathology Accreditation Advisory Council (NPAAC) draft protocol, Chapter 11 Management of Glandular Abnormalities, Flowchart 11.4 follow up after excisional treatment for AIS
4) LBC result to assist colposcopy reading they do not feed into the recommended follow-up for women
5) Concealed DS not for management of women
6) Configurable randomisation-may be adjusted during the trial

Version 1.3_10062016

[i] Structured reporting protocol for excisions and colposcopic biopsies performed for the diagnosis and treatment of pre-invasive cervical neoplasia, Royal Australasian College of Pathologists, 1st Edition, 2017.