The National Cervical Screening Program: On the Cusp of Change

A/Prof Marion Saville

I am Co-Principal Investigator on the Compass trial which has received equipment and funding contribution from Roche Molecular Systems.

IN THIS TALK

• National HPV Vaccination Program
  – Coverage
  – Impact
  – Future

• Renewal of the National Cervical Screening Program
  – Rationale
  – Safety
  – Practical Implications

• The Compass trial
  – Why
  – Design
  – Progress
OVERVIEW

- Where are we now?
  - Coverage in females
  - Coverage in males
  - What have we learnt
- Where might we be going?
  - Two dose schedules
  - Nine valent vaccine

National HPV Vaccination Program

- 4vHPV vaccine 3 dose course prevents infection and disease (CIN, cervical, anogenital cancers and genital warts) due to HPV types 16/18/6/11
- 2007-2009: catch up females aged 12-26
- 2009-present: routine school based vax girls (1st yr high school – usual age 12-13)
- 2013-2014: catch up program males at school age 12-15 (+ some GP delivery)
- 2015: routine school based vax boys and girls (1st yr high school – usual age 12-13)
National notified coverage female catch up


Coverage data

Source: www.hpvregister.org.au/research/coverage-data
Equity in screening vs vaccination

• Victoria, Australia
• (Barbaro et al Med J Aust 2012; 196 (7): 445)

National HPV Vaccination Program by socioeconomic status, Victoria

National Cervical Screening Program by socioeconomic status, Victoria

Vaccine knowledge we now have...

• The vaccines are very safe
• The vaccines are very immunogenic
• The vaccines are very effective
  – In the real world as well as in trials
  – At creating herd immunity
  – In males and in sites other than the cervix
  – With some cross protective effects against non-targeted HPV types
  – At available prices, in most settings, they are cost-effective
  – Although not therapeutic, they can prevent secondary disease/'recurrence' in those with previous disease

www.hpvregister.org.au/research/coverage-data
The vaccines are very safe*

- Global distribution >232 million doses
  - 4vHPV 178 million, 2vHPV 54.4 million (to end 2014)
- Reviewed frequently by GACVS (WHO) – summary 2014
- Population based assessments of thromboembolic, autoimmune, neurological diseases show no increased risk following vaccination
- No evidence of harm if inadvertently administered in pregnancy


The vaccines are very immunogenic

- High level antibodies sustained for ~ decade*
- Evidence of sustained high level antibody after 1 dose 2vHPV vaccine and associated VE
- Is the immune response more like that to a whole virus than a subunit vaccine??

* Roteli-Martins 2012 Hum Vac Immunother; Nygard et al EUROGIN 2013
** Schiller J, Lowy D JID 2015
The vaccines are very effective: in the real world

Fall in cervical HPV prevalence in young women 18-24yrs

- Overall 0.22 (95%CI 0.16–0.31) p<0.0001
- Fully vaccinated 0.07 (95%CI 0.04–0.14) p<0.0001
- Unvaccinated 0.65 (95%CI 0.43–0.96) p=0.03


![Graph showing fall in cervical HPV prevalence in young women](image)

Decline in pre-cancer now impacting up to 30 years

Figure 1: Trends in prevalence rates of high grade histologically confirmed cervical abnormalities (CIN2+) diagnosed in Victorian women, Australia, by age group, 2000-2015
Updated from Brotherton et al.: MJA 2016. Source VCCR
Population HPV vaccine effectiveness for cervical histological outcome, by age in 2007, for completed vaccine course

![Graph](image)

Adj VE CIN3+ 47.5%
(22.7%-64.4%)

The vaccines are very effective...

- **In males & in sites other than the cervix** (anal, oral) (Giuliano et al *NEJM* 2011, Palefsky et al *NEJM* 2011, Kreimer et al *Lancet Oncol* 2011, Herrero et al *PLOS One* 2013)

- **With some cross protective effects** against non-targeted HPV types (Malagon et al *Lancet ID* 2012)

- At available prices, in most settings, **they are cost-effective** (Fesenfeld et al *Vaccine* 2013, Canfell et al, *Vaccine* 2012)

- Although not therapeutic, they can **prevent secondary disease/recurrence** in those with previous disease (Joura et al *BMJ* 2012, Kang et al *Gynecol Onc* 2013, Hildesheim et al 2015, Garland et al *Int J Canc* 2016)
Two dose schedules

- Two doses spaced >6 months apart in those aged < 15 years as immunogenic as 3 in adults
  - Dobson S et al JAMA 2013, Romanowski B et al. Human Vaccin Immunother 2014
- Approved for use as 2 dose schedule by WHO in 2014
- Countries which have adopted two dose schedules include
  - Switzerland (2012), parts of Canada (Quebec and BC early users with dose 3 at month 60 if required), from 2014 the UK, South Africa, France, Spain, Austria, The Netherlands and Chile.
  - By 2016, 65% of vaccinating countries using two dose schedule.*
  - Approved in US Oct 2016 for 9vHPV vaccine

Nine valent HPV vaccine

Figure 2: HPV VLP types in the nine valent VLP vaccine
VLPs in the bivalent, quadrivalent, and the nonvalent vaccines are shown with the proportion of neoplastic lesions attributed to each group. VLPs, virus-like particle.


Nine valent HPV vaccine

Fig. 1. Primary objectives of the study.

A. Luxenburg et al. / Contemporary Clinical Trials 42 (2015) 18–25
Table 2. Effect of 9vHPV Vaccine on the Incidence of Cervical, Vulvar, and Vaginal Disease and of Persistent HPV-Related Infection.¹

<table>
<thead>
<tr>
<th>End Point</th>
<th>9vHPV Vaccine (N=7099)</th>
<th>qHPV Vaccine (N=7105)</th>
<th>Risk Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cases/1000 person-yr</td>
<td>cases/1000 person-yr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>no/total no.</td>
<td>no/total no.</td>
<td></td>
</tr>
<tr>
<td>Related to HPV-31, 33, 45, 52, or 58</td>
<td>1/6016</td>
<td>0.1</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30/6017</td>
<td>96.7 (80.9 to 99.8)</td>
</tr>
<tr>
<td>Related to HPV-6, 11, 16, or 18</td>
<td>1/5883</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3/5888</td>
<td>66.6 (-203.0 to 98.7)</td>
</tr>
<tr>
<td>High-grade cervical epithelial neoplasia, adenocarcinoma in situ, and cervical cancer</td>
<td>1/5948</td>
<td>0.1</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>27/5943</td>
<td>96.3 (79.5 to 99.8)</td>
</tr>
<tr>
<td>Related to HPV-6, 11, 16, or 18</td>
<td>1/5823</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1/5822</td>
<td>-0.4 (-0.9 to 97.4)</td>
</tr>
<tr>
<td>Persistent infection ≥6 months’ duration</td>
<td>35/5939</td>
<td>2.1</td>
<td>52.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>810/5935</td>
<td>96.0 (94.4 to 97.2)</td>
</tr>
<tr>
<td>Related to HPV-6, 11, 16, or 18</td>
<td>59/5812</td>
<td>3.6</td>
<td>50.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80/5830</td>
<td>26.4 (-4.3 to 47.5)</td>
</tr>
</tbody>
</table>

Table 3. Adverse Events.²

<table>
<thead>
<tr>
<th>Event</th>
<th>9vHPV Vaccine (N=7091)</th>
<th>qHPV Vaccine (N=7108)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of participants (%)</td>
<td>no. of participants (%)</td>
</tr>
<tr>
<td>Participants with one or more adverse events†</td>
<td>6840 (95.3)</td>
<td>5449 (90.7)</td>
</tr>
<tr>
<td>Injection-site event‡</td>
<td>6414 (90.7)</td>
<td>6002 (94.9)</td>
</tr>
<tr>
<td>Purp</td>
<td>4556 (65.9)</td>
<td>5010 (83.5)</td>
</tr>
<tr>
<td>Mild</td>
<td>1374 (19.3)</td>
<td>1485 (24.3)</td>
</tr>
<tr>
<td>Moderate</td>
<td>2200 (31.5)</td>
<td>2482 (40.8)</td>
</tr>
<tr>
<td>Severe</td>
<td>302 (4.3)</td>
<td>385 (6.4)</td>
</tr>
<tr>
<td>Swelling</td>
<td>2203 (3.1)</td>
<td>2015 (3.3)</td>
</tr>
<tr>
<td>Malignant ≥0.1 cm to ≤2.5 cm</td>
<td>1958 (27.7)</td>
<td>1594 (22.5)</td>
</tr>
<tr>
<td>Malignant &gt;2.5 cm to ≤5.0 cm</td>
<td>597 (8.4)</td>
<td>332 (4.7)</td>
</tr>
<tr>
<td>Severe &gt;5.0 cm</td>
<td>272 (3.9)</td>
<td>109 (1.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2407 (34.0)</td>
<td>1810 (28.0)</td>
</tr>
<tr>
<td>Malignant ≥0.1 cm to ≤2.5 cm</td>
<td>1921 (27.2)</td>
<td>1555 (22.0)</td>
</tr>
<tr>
<td>Malignant &gt;2.5 cm to ≤5.0 cm</td>
<td>370 (5.2)</td>
<td>197 (3.0)</td>
</tr>
<tr>
<td>Severe &gt;5.0 cm</td>
<td>114 (1.6)</td>
<td>37 (0.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (0)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>386 (5.5)</td>
<td>281 (4.0)</td>
</tr>
<tr>
<td>Mild</td>
<td>301 (4.3)</td>
<td>223 (3.2)</td>
</tr>
<tr>
<td>Moderate</td>
<td>80 (1.1)</td>
<td>56 (0.8)</td>
</tr>
<tr>
<td>Severe</td>
<td>7 (0.1)</td>
<td>3 (0)</td>
</tr>
<tr>
<td>Systemic event</td>
<td>3498 (53.8)</td>
<td>3833 (54.9)</td>
</tr>
<tr>
<td>Any vaccine-related systemic event</td>
<td>2086 (29.3)</td>
<td>1929 (27.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>101 (1.4)</td>
<td>94 (1.3)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>357 (5.0)</td>
<td>301 (4.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>351 (4.9)</td>
<td>261 (3.7)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>211 (3.0)</td>
<td>197 (2.8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>166 (2.3)</td>
<td>155 (2.1)</td>
</tr>
<tr>
<td>Serious event</td>
<td>233 (3.3)</td>
<td>383 (5.4)</td>
</tr>
<tr>
<td>Vaccine-related event</td>
<td>2 (0)</td>
<td>2 (0)</td>
</tr>
<tr>
<td>Death</td>
<td>5 (0.1)</td>
<td>5 (0.1)</td>
</tr>
<tr>
<td>Discontinuation due to adverse event***</td>
<td>8 (0.1)</td>
<td>2 (0.0)</td>
</tr>
<tr>
<td>Vaccine-related event</td>
<td>5 (0.1)</td>
<td>3 (0)</td>
</tr>
<tr>
<td>Serious event</td>
<td>3 (0)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Serious vaccine-related event</td>
<td>1 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

4- and 9-valent HPV vaccine
Potential for cancer prevention

Slide courtesy of Marc Brisson

Ref: 1) Jemal JNCI 2013; 2) Saraiya, JNCI 2015

4- and 9-valent HPV vaccine
Potential for cancer prevention in the US

Slide courtesy of Marc Brisson

Ref: 1) Jemal JNCI 2013; 2) Saraiya, JNCI 2015
CONCLUSIONS

• HPV vaccination has been a major success for Australia
• In coming years we expect to see an profound impact on the incidence of cervical and other cancers
• A two dose 9 valent HPV vaccination schedule is effective and likely to be cost effective

Renewal of the National Cervical Screening Program

• Rationale
• Safety
• Practical Implications
1991 NCSP Policy:
- 2-yearly (Pap test)
- 18 to 69 years
- Registry reminder

- Participation:
  - 2-yearly 58%
  - 5-yearly 83%

- 50% reduction in incidence & deaths

WHAT IS THE AIM OF RENEWAL?

- Ensure the success of the program continues
- All women, HPV vaccinated and unvaccinated......
- Access to a cervical screening program based on current evidence and best practice.
WHY?

• New knowledge on the development of cervical cancer.
• New evidence for cervical cancer prevention and screening
  – New technologies
    • liquid-based technology
    • computer assisted image analysis
    • HPV tests
• 2007 - National HPV Vaccination Program (girls)
• 2013 - National HPV Vaccination Program (girls + boys)

• Current NCSP is intensive compared to other countries

George Papanicolaou

• 1928- Pap test developed
• 1943- Diagnosis of uterine cancer by the vaginal smear
• 1948- American Cancer Society
• “Pap smear is a valuable test”
Harald zur Hausen

1982
• Demonstrated that HPV was the cause of cervical cancer

2008
• Nobel Prize in Medicine

Ian Frazer AC

• 1991-2005 Developed the first vaccine for HPV
• 2007/2013 National HPV Vaccination Program – girls/boys
Cost-effectiveness plane

- Decreasing LYS/QALYS and Increasing costs: Likely to be cost-effective
- Decreasing LYS/QALYS and Decreasing costs: Both life years and cost saving (disinvestment)
- Increasing LYS/QALYS and Increasing costs: Unlikely to be cost-effective
- Increasing LYS/QALYS and Decreasing costs: Decreases life years and increases costs

Current practice
Cost effectiveness - unvaccinated  
(Screening cessation at 65 years)

Cost effectiveness - vaccinated  
(Screening cessation at 65 years)
MSAC RECOMMENDATIONS

Cervical Screening Test (CST)

- HPV test with partial genotyping (16/18)
- Reflex Liquid Based Cytology (LBC) triage
- Five year screening interval
- Start at age 25 years
- Exit at 70–74 years
- All sexually active women-HPV vaccinated or not
- Self collection: never-screened and under-screened
- Invitation & reminders to screen: National Register

RENWAL – GOOD NEWS FOR WOMEN

Primary HPV screening program will lead to:

Up to 30%

Fewer cases of cervical cancer

Fewer deaths from cervical cancer
NCSP: 1¹ˢᵗ⁰¹ MAY 2017

- New - screening test: HPV
- New - screening interval: 5 years
- New - starting age: 25 years
- New - finishing age: 74 years
- New - self-collection
- New - National Cancer Screening Register

NEW CHALLENGES

Why has the recommended age for commencing screening been raised to 25 years?

Is it safe?
Three-year average cervical cancer incidence (with 95% CIs), by all ages and histological type, 1982-2010

Three-year average cervical cancer incidence (with 95% CIs), by age and histological type, 1982-2010
SAFETY OF NOT SCREENING WOMEN (< 25 years)

25 years of screening women under 25 years of age
  • no impact on incidence of cervical cancer in this age group

Systematic literature review
  • No evidence for screening effectiveness in other countries

Very low incidence of cervical cancer in these women
  • Expected to decline further due to HPV vaccination

IARC recommendation
  • Do not screen women under age 25 years
Why has the screening interval been extended from two years to five years?

Is it safe?

Primary HPV screening
Longitudinal results for screen-negative women
Primary HPV screening:
Pooled data on invasive cervical cancer outcomes from four European trials - 176,000 women

“At longer intervals HPV-based screening provides 60—70% greater protection against invasive cervical carcinomas compared with cytology”

WHAT DOES THIS MEAN FOR YOU?

What sample should you collect for a cervical screening test?

• **Liquid based cervical specimen only**
  • Conventional Pap smear no longer accepted !!

• **Laboratories will provide**
  • detailed instructions
  • appropriate consumables
  • so that the sample satisfies requirements both of the HPV test and LBC, should this be required.
WHAT DOES THIS MEAN FOR YOU?

- Will still need a speculum vaginal examination
- Will be invited to have a screening test every 5 years
- A sample will be taken from her cervix and sent to lab
  - If cytology needed – no additional visit to GP/provider
- Women will receive results from their GP/provider
  - active communication
- Test results: kept by National Cancer Screening Registry

RENEWAL NCSP

Steering Committee for the Renewal Implementation Project (SCRIP)

Implementation Project Plan

- MBS items
- National Cancer Screening Register
- Workforce + Practice Change
- Quality and Safety
- Communication, Education and Information
NATIONAL CANCER SCREENING REGISTER

- Linked to HPV register
- Used to issue invitations/reminders
- Full history from vaccination-diagnosis
- Colposcopy and pathology data
  - Monitoring and service improvement

One woman = One record

Endorsed by NHMRC
9th June 2005

Implemented
3rd July 2006
THE 2016 GUIDELINES

WHAT WAS INCLUDED?

Management of screen detected abnormalities
• Clinician collected cervical samples
• Self-collected vaginal sample

Terminology

Colposcopy

Screening in specific populations
• Pregnancy, Immune-deficient, early sexual activity, DES, after hysterectomy and Aboriginal and Torres Strait Islander women

Investigation of abnormal vaginal bleeding
WHAT’S NEW

• Terminology
• Management of oncogenic HPV test results
• Specific Populations
• Transition to the renewed NCSP
• Investigation of abnormal vaginal bleeding

TERMINOLOGY: TESTS

• **HPV test**: detects HPV DNA or RNA in cervical cells contained in a liquid based cervical sample
• **Liquid Based Cytology (LBC)**: cytology performed on a liquid cervical sample and may be manual or automated
• **Reflex LBC**: cytology performed ‘automatically’ on a cervical sample in which HPV is detected

• **Co-test**: HPV test *and* LBC test ordered *together* and is used for test of cure, investigation of abnormal vaginal bleeding, after hysterectomy, DES exposed women: but *not* for routine screening
TERMINOLOGY: HISTOLOGY

Lower Anogenital Squamous Terminology (LAST)

• **HSIL**: high grade squamous intraepithelial lesion
  – Incorporates CIN2 or CIN3
• **LSIL**: low grade squamous intraepithelial lesion
  – Appearance of HPV infection in cervix
• **SISCCA**: superficially invasive squamous cell carcinoma
• **Squamous cell carcinoma**

MANAGEMENT OF ONCOGENIC HPV RESULTS

What should we expect from the lab report?

• **An overall cervical screening risk assessment**
  - Low risk
  - Higher risk
  - Intermediate risk

• **A statement of test(s) performed and the results**
  HPV test result including any LBC result

• **A recommendation for follow-up/action**
  Taking account of screening history and clinical notes
**MANAGEMENT OF ONCOGENIC HPV RESULTS**

**LOW RISK**
HPV not detected

**ACTION:** REPEAT CST in 5 YEARS

**HIGHER RISK**
HPV (16/18) detected
(with any LBC result)
OR
HPV (not 16/18) detected
(with LBC: pHSIL, HSIL or any glandular abnormality)

**ACTION:** REFER for COLPOSCOPY

**MANAGEMENT OF ONCOGENIC HPV RESULTS**

**Intermediate risk**

HPV (not 16/18) detected
(with LBC negative or pLSIL/LSIL)

**ACTION:** Follow-up HPV test in 12 months
Women at Intermediate risk

Follow-up HPV test in 12 months

At follow-up 12 month test
HPV detected (any type) with any LBC result (= persistent HPV infection)

**ACTION:** REFER for COLPOSCOPY

At follow-up 12 month test
HPV not detected

**ACTION:** REPEAT CST in 5 YEARS

---

**CERVICAL SCREENING**  LOW RISK FOR SIGNIFICANT CERVICAL ABNORMALITY

**Specimen**  Cervical – ThinPrep
**Test results**  PCR for oncogenic HPV and genotype
  • HPV 16 – Not detected
  • HPV 18 – Not detected
  • HPV (not16/18) – Not detected

**Recommendation:** Re-screen in 5 years
## Cervical Screening: Higher Risk for Significant Cervical Abnormality

**Specimen**  
Cervical – SurePath

**Test results**  
PCR for oncogenic HPV and genotype  
- HPV 16 – Not detected  
- HPV 18 – Not detected  
- HPV (not16/18) – **Detected**

Liquid based cytology (LBC) manually read:  
- **HSIL** (high-grade squamous intraepithelial lesion)  
- Endocervical component: Present

**Recommendation:** Referral for colposcopic assessment

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## Cervical Screening: Intermediate Risk for Significant Cervical Abnormality

**Specimen**  
Cervical – SurePath

**Test results**  
PCR for oncogenic HPV and genotype  
- HPV 16 – Not detected  
- HPV 18 – Not detected  
- HPV (not16/18) – **Detected**

Liquid based cytology (LBC) manually read:  
- There is no evidence of a squamous intraepithelial lesion or malignancy  
- Endocervical component: Present

**Recommendation:** Repeat HPV test in 12 months
CERVICAL SCREENING  UNSATISFACTORY

Specimen  Cervical – ThinPrep
Test results  PCR for oncogenic HPV and genotype
  • HPV 16 – Not detected
  • HPV 18 – Not detected
  • HPV (not 16/18) – Detected
Liquid based cytology (LBC) image assisted: Unsatisfactory

Recommendation: Repeat LBC in six weeks

CERVICAL SCREENING PATHWAY

Oncogenic HPV test with partial genotyping

- HPV not detected
- HPV detected not 16/18
- HPV detected 16/18
- Unsatisfactory HPV test

Reflex LBC
- Unsatisfactory LBC
- Negative
- p16 IHC
- p16ISH
- Any LBC result or unsatisfactory

Repeat HPV test in 12 months
- HPV not detected
- HPV detected any type

Reflex LBC
- Refer for colposcopic assessment

Routine 5 yearly screening
- Refer for LBC only within 8 weeks

Routine 5 yearly screening
- Refer for LBC

Revised 5 yearly screening
- Refer for colposcopic assessment

 HPV within 8 weeks
80% cervical cancer occurs in women never screened or under-screened

(VCCR 2012)

MSAC RECOMMENDATION

Self collection of vaginal sample for HPV test

– Under screened and never screened women only
– Facilitated by a health professional
– Or on behalf of a medical practitioner
– Who also offers routine cervical screening
HPV SELF-COLLECTION

• Increased participation rate for never and under-screened

• Not as effective as health professional collected sample
• More effective than the current Pap test
• Accuracy varies for different sampling devices, HPV tests
• Less cost effective than routine pathway.
• If HPV+ve will need separate visit for LBC sample

• Only available to under or never screeners.
TRANSITION TO THE RENEWED NATIONAL CERVICAL SCREENING PROGRAM

Women with Existing Abnormalities* (cytology or histopathology)

Prior
May 2017

Pap test result
pLSIL/LSIL

Treated for histologically confirmed HSSL
(CIN2 or CIN3)

Treated for histologically confirmed AIS

After
May 2017

HPV test when due for next screening test

HPV not detected

HPV detected (any type)

Reflex LBC

Start or continue with "Test of Cure***"

Annual co-test (HPV & LBC) indefinitely

Routine 5-yearly screening with HPV test

Refer for colposcopic assessment

* Prior to May 2017

** A woman who has been treated for HSSL (CIN2) should have a co-test (HPV and LBC) performed at 12 months after treatment, and annually thereafter, until both tests are negative on two consecutive occasions, when she can return to routine 5-yearly screening

*** Until sufficient data become available that may support a policy decision that cessation of testing is appropriate

‘290 pages’
Wiki Platform
PDF
Benefits of wiki-based guidelines

• **Easy to navigate**
  – links and hyperlinks

• **Easy to update**
  – when new evidence becomes available

• **Infrastructure in place**
  – run literature updates for systematic reviews
  – screen new literature online

ENDORSED BY

• RACGP
• RANZCOG
• RCPA
• ASCCP
• ASGO
MAIN CHANGES FROM MAY 2017

<table>
<thead>
<tr>
<th>NOW</th>
<th>MAY 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pap Smear</td>
<td>HPV Test</td>
</tr>
<tr>
<td>2 Yearly</td>
<td>5 Yearly</td>
</tr>
<tr>
<td>Start 18 Years</td>
<td>Start 25 Years</td>
</tr>
<tr>
<td>End 69 Years</td>
<td>End 70-74 Years</td>
</tr>
<tr>
<td>Reminders</td>
<td>Invitations/Reminders</td>
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<tr>
<td></td>
<td>Self Collection</td>
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Screening history of Victorian women diagnosed with cervical cancer for the period 1 January 2013 to 31 December 2013.
Until 1\textsuperscript{st} May 2017
Business as usual!

MORE INFORMATION

www.cancerscreening.gov.au
Or
Cervicalrenewal@health.gov.au
THE COMPASS TRIAL, AN UPDATE

IN THIS SECTION

• Revisit why the trial is being undertaken and how it relates to renewal of the NCSP
• Update recruitment progress
• Discuss the response from recruiting practitioners
• Present our analysis plan, including safety monitoring strategy
  – When we expect to be reporting results
STUDY OUTLINE

Large scale RCT of 5-yearly HPV testing vs. 2.5 yearly liquid-based cytology (LBC) screening in Victoria, Australia

• Dual stain (p16/Ki67) compared with LBC as the triage test for women positive for HPV (not 16/18)

WHY ANOTHER RCT OF PRIMARY HPV SCREENING?

• Evaluating primary HPV screening in an extensively vaccinated population
  – Previous trials have been conducted prior to the implementation of HPV vaccination

• Applying updated testing technology
  – Allowing separate identification of HPV 16 and 18
  – And thus enhanced management of women who test positive for these types, to match their increased level of risk

• Examining the optimal management of women positive for HPV(not 16/18)
  – Comparing LBC and dual stain as triage tests in this context
WHY ANOTHER RCT OF PRIMARY HPV SCREENING

- Specific evaluation of safety, effectiveness and costs in Australian context
- Pragmatic trial/demonstration of concept
p16/Ki-67 Dual Stained Cytology

Research

Predicts Outcomes

Empirical Evidence

Modelling
DESIGNED AS A SENTINEL EXPERIENCE OF THE RENEWED NCSP

• Has enabled the development and refinement of processes and resources to support
  – Education of women
  – Education of practitioners
  – Laboratory testing and reporting, including the development of combined screening reports
  – Registry follow-up

PILOT STUDY

• 5,000 women aged 25 to 64
• Recruitment from Oct 2013 - Nov 2014
• Three arms: women randomised 1:2:2 to cytology: HPV: HPV screening
• Baseline screening round completed, including 6 month follow-up for histology outcomes
  – These results presented at ASC meeting in 2015 and currently under review with journal
• 12 month follow-up round completed, including 6 month follow-up for histology outcomes
  – Analyses not yet complete
MAIN TRIAL

- 121,000 women aged 25 to 69
  - 36,300 in the “older” unvaccinated cohort
  - 84,700 in the young vaccine eligible cohort
- Recruitment commenced Jan 2015
- As at October 2016 a total of 56,414 women recruited

Total Main Trail Recruitment as at 14th October 2016 = 56,414
LIKE US ON FACEBOOK!

“It’s inspirational that so many Victorian women and health professionals are actively involved in this research and are contributing to our understanding of cancer screening…”

Todd Harper CEO Cancer Council Victoria
Attend a one hour interactive education session (practice visit or webinar) covering
- current evidence on new cervical cancer screening technologies
- a detailed discussion about the future NCSP and
- the Compass trial

Recruit a minimum number of patients
- with informed consent and
- follow up according to trial recommendations

Complete and return Evaluation and Self Reflection Activity

*40 QI&CPD Category 1 points. Women’s health points apply
5 LEARNING OBJECTIVES FOR QI&CPD FOR RACGP AND THE COMPASS TRIAL.

541 GPs have completed this activity the remaining 11 are practice nurses who have competed the forms.

QUOTES FROM GPS

“Women Love it”
“patients are more likely to have (their) children vaccinated”
“less unsatisfactory samples since starting compass”
More quotes from GPs
“good to translate basic science into tangible benefits for patients”
“feels good to be ahead of the game”
“some patients have come specifically to be involved with the trial”
“Patients more satisfied with a greater explanation of cervical screening”
“I believe that this sort of partnership will enhance screening as women will understand the science underlying the screening process, rather than be put off by the unpleasant examination”

MORE QUOTES FROM GPS
“I have really enjoyed the change to thin preps”
“many thank me for their daughters care”
“Patients more satisfied with a greater explanation of cervical screening”
“completely changed and more confident around Cervical cancer”
“using the trial to educate patient on cervical cancer but also other gynae health”
“interesting to find older women with neg Paps but HPV positive”
Analysis plan
When can results be expected?
**ANALYSIS PLAN, BASELINE**

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Time</th>
<th>Measures of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>6 months after the last participant in a cohort is recruited.</td>
<td>Test positivity rates for primary and triage tests</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colposcopy referral rates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CIN2+ rates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CIN3+ rates</td>
</tr>
</tbody>
</table>

**ANALYSIS PLAN, 12 MONTHS**

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Time</th>
<th>Measures of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 month follow up</td>
<td>9 months after the last participant in a cohort was assigned to 12 month follow-up in the baseline screening round*</td>
<td>Test positivity rates for tests</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sensitivity and specificity for all tests.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colposcopy referral rates.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CIN2+ rates in participants in ARM B who were OHRHPV at baseline and then randomized to LBC or DS triage.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CIN3+ rates in participants in Arm B who were OHRHPV at baseline and then randomized to LBC/DS triage.</td>
</tr>
</tbody>
</table>

* Note that the 9 months includes an extra 3 months after a participant is due to for their visit and 6 months follow up.
## ANALYSIS PLAN, 2.5 YEARS LBC ARM

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Time</th>
<th>Measures of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 year screening round in Trial Arm A</td>
<td>2.5 years + 9 months after the last participant in a cohort was randomized to Study Arm A at baseline *</td>
<td>Primary (LBC) and triage (HPV) test positive rates.</td>
</tr>
</tbody>
</table>

* Note that the 9 months includes an extra 3 months after a participant is due to for their visit and 6 months follow up.

## ANALYSIS PLAN, SAFETY MONITORING HPV ARM

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Time</th>
<th>Measures of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 year screening round in Trial Arm B</td>
<td>2.5 years + 9 months after the last participant in a cohort was randomized to Study Arm B at baseline *</td>
<td>CIN2+ rates in the safety monitoring cohort</td>
</tr>
</tbody>
</table>

* Note that the 9 months includes an extra 3 months after a participant is due to for their visit and 6 months follow up.
SAFETY MONITORING

- Recall @2.5 years of a random sample of HPV-negative women in the first screening round:
  - The intent is to recruit for safety monitoring in the trial until 10% of all HPV-negative women have been allocated to safety monitoring.
  - LBC testing at the time of early recall is specified

INTERNATIONAL DATA TO INFORM EXPECTED RATE:
Longitudinal results for screen-negative women

ANALYSIS PLAN, 5 YEARS TRIAL COMPLETION

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Time</th>
<th>Measures of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 year screening round</td>
<td>5 years + 9 months after the last participant in a cohort was recruited*</td>
<td>Cumulative CN2+ after HPV exit testing</td>
</tr>
</tbody>
</table>

* Note that the 9 months includes an extra 3 months after a participant is due for their visit and 6 months follow up.

Total Main Trail Recruitment as at 14th October 2016 = 56,414
DATA ANALYSIS PLAN

CONCLUSION

- The Compass trial is being undertaken to build on existing evidence and although not formally related to Renewal, it was designed to inform transition to the renewed NCSP
- Recruitment has been progressing well but challenges remain in relation to the vaccinated cohort
- Recruiting practitioners have overwhelmingly embraced the trial with almost all saying that it has helped them to prepare for renewal
- We look forward to presenting more evidence from the trial as outlined in the analysis plan.
Acknowledgements

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• Prof Karen Canfell
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• Prof Dorota Gertig
• Dr Julia Brotherton
• Dr Stella Heley

ASSOCIATE INVESTIGATORS (MAIN TRIAL)
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• Prof Gordon Wright, Director of Anatomic Pathology Gold Coast Hospital Campus
• A/Prof Katrina Sharples, Biostatistician, Preventive & Social Medicine, Dunsedo School of Medicine, Health Sciences

Compass details:
Website www.compasstrial.org.au
Pilot Study Registration ACTRN12613001207707
Main Trial Registration: Clinicaltrials.gov NCT02328872