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.

VCS

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

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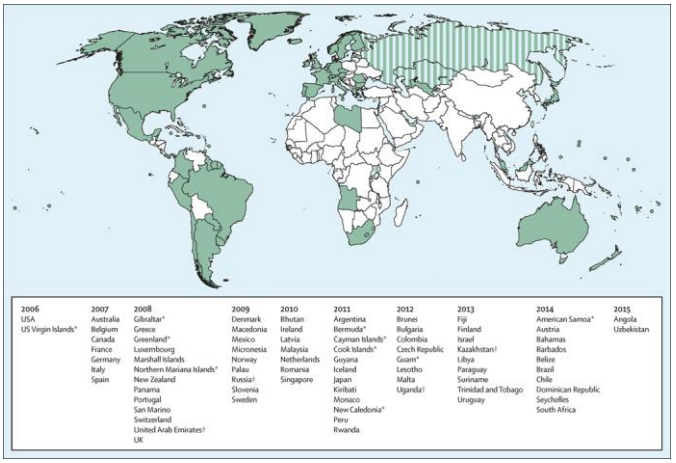
OVERVIEW

- 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

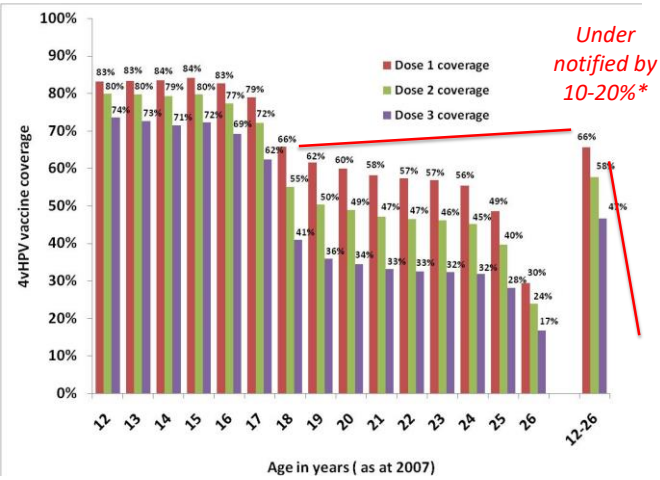


Bruni L et al. The Lancet Global Health 2016 4, e453-e463

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

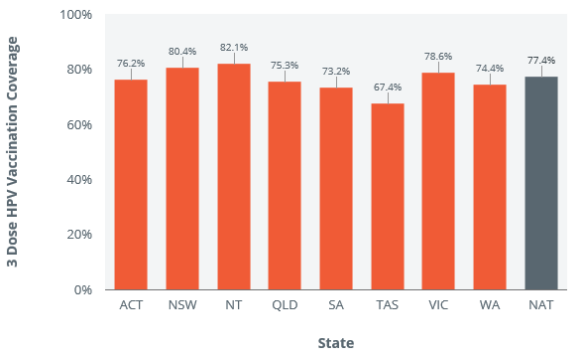


As held at Sept 2011. Excludes consumers who have opted off. * Brotherton JML, et al. Vaccine 2014;32: 592– 597.

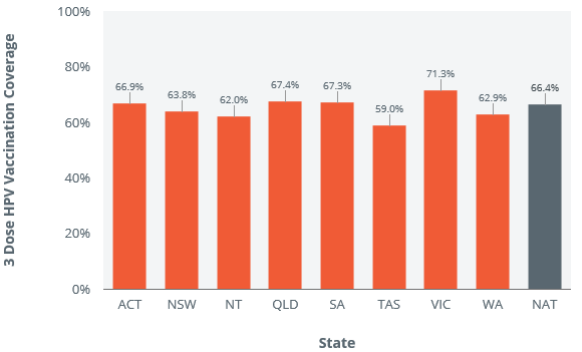
National HPV Vaccination Program Register

Coverage data

National (Australia) HPV 3 dose vaccination coverage for females turning 15 years of age in 2015



National (Australia) HPV 3 dose vaccination coverage for males turning 15 years of age in 2015



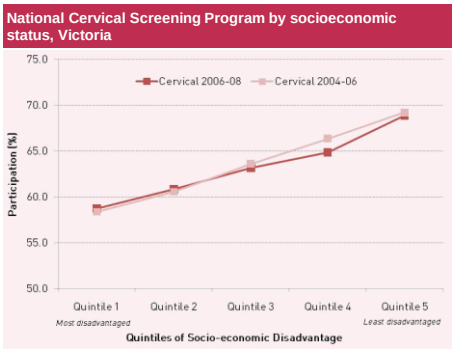
Source: www.hpvregister.org.au/research/coverage-data

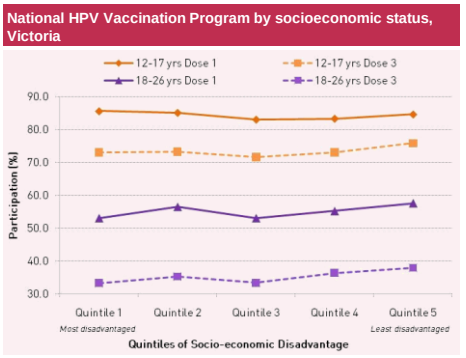
National HPV Vaccination Program Register

Equity in screening vs vaccination

- Victoria, Australia
- (Barbaro et al *Med J Aust* 2012; 196 (7): 445)
- National data similar (Barbaro & Brotherton, *Aust N Z J Public Health*. 2014; 38: 419–423)

www.hpvregister.org.au/research/coverage-data





National HPV Vaccination Program Register

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

National HPV Vaccination Program Register

The vaccines are very safe*

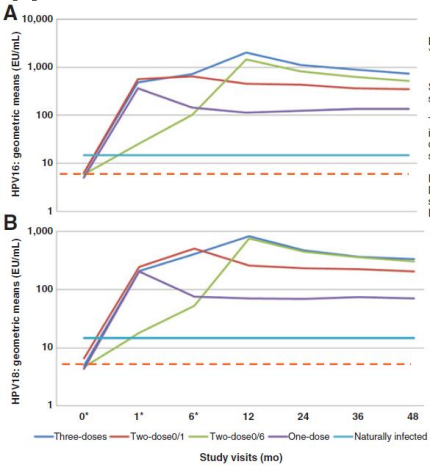
- Global distribution >232 million doses
  - 4vHPV 178 million, 2vHPV 54.4 million (to end 2014)
- Reviewed frequently by GACVS (WHO) – summary 2014
  - http://www.who.int/vaccine_safety/committee/topics/hpv/GACVS_Statement_HPV_12_Mar_2014.pdf?ua=1
- Population based assessments of thromboembolic, autoimmune, neurological diseases show no increased risk following vaccination
  - Arnheim-Dalstrom *BMJ* 2013, Scheller et al *JAMA* 2015, Chao et al, *J Intern Med* 2012, Gee et al *Vaccine* 2011, Grimaldi-Bensauda *J Intern Med* 2014
- No evidence of harm if inadvertently administered in pregnancy
  - Goss MA Obstet Gynecol. 2014, Dana et al Obstet Gynecol 2009, Garland et al Obstet Gynecol 2009, Moro Vaccine 2015, Angelo Pharmacoepidemiol Drug Saf 2014

* See safety review summary - Macartney K et al, *Drug Safety* 2013;36(6):393-412.

National HPV Vaccination Program Register

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
  - Safaeian M et al *Cancer Prev Res* 2013, Kreimer A et al *JNCI* 2011 & *Lancet Oncol* 2015
- *Is the immune response more like that to a whole virus than a subunit vaccine?***

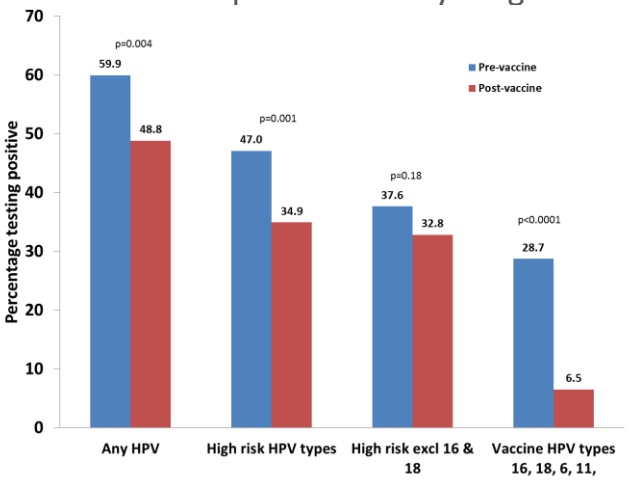


* Roteli-Martins 2012 *Hum Vacc Immunother*; Nygard et al *EUROGIN* 2013
** Schiller J, Lowy D *JID* 2015

National HPV Vaccination Program Register

The vaccines are very effective: in the real world

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



Post vaccine period

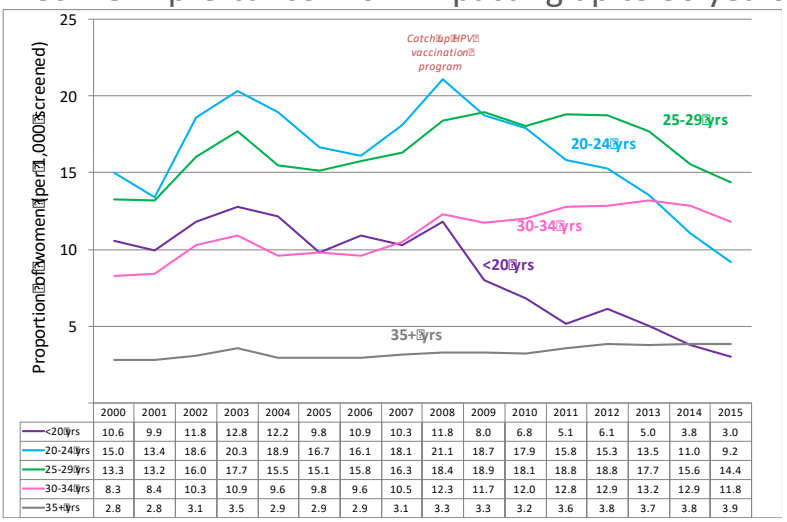
Adjusted prevalence ratio HPV6/11/16/18

- 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

Tabrizi and Brotherton et al. *Lancet Infect Dis*. 2014 Oct;14(10):958-66.

National HPV Vaccination Program Register

Decline in pre-cancer now impacting up to 30 years

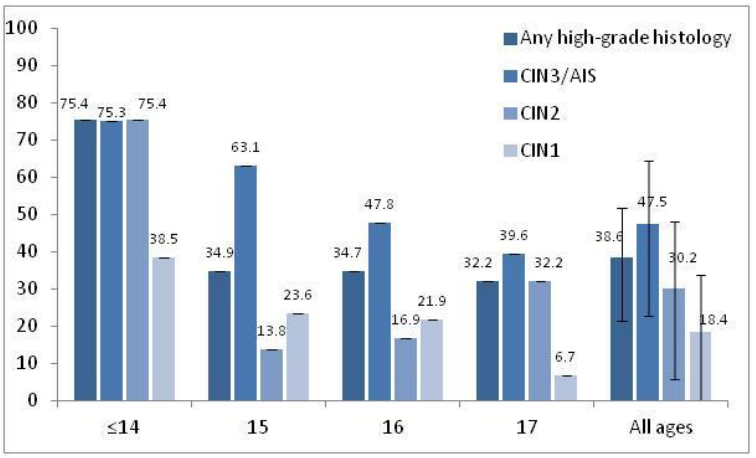


	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
<20yrs	10.6	9.9	11.8	12.8	12.2	9.8	10.9	10.3	11.8	8.0	6.8	5.1	6.1	5.0	3.8	3.0
20-24yrs	15.0	13.4	18.6	20.3	18.9	16.7	16.1	18.1	21.1	18.7	17.9	15.8	15.3	13.5	11.0	9.2
25-29yrs	13.3	13.2	16.0	17.7	15.5	15.1	15.8	16.3	18.4	18.9	18.1	18.8	18.8	17.7	15.6	14.4
30-34yrs	8.3	8.4	10.3	10.9	9.6	9.8	9.6	10.5	12.3	11.7	12.0	12.8	12.9	13.2	12.9	11.8
35+yrs	2.8	2.8	3.1	3.5	2.9	2.9	2.9	3.1	3.3	3.3	3.2	3.6	3.8	3.7	3.8	3.9

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

Victorian Cervical Cytology Registry

Population HPV vaccine effectiveness for cervical histological outcome, by age in 2007, for completed vaccine course



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

Gertig DM, Brotherton JML, Budd AC, Drennan K, Chappell G, Saville AM. . BMC Medicine 2013, 11:227 doi:10.1186/1741-7015-11-227

Victorian Cervical Cytology Registry

The vaccines are very effective…

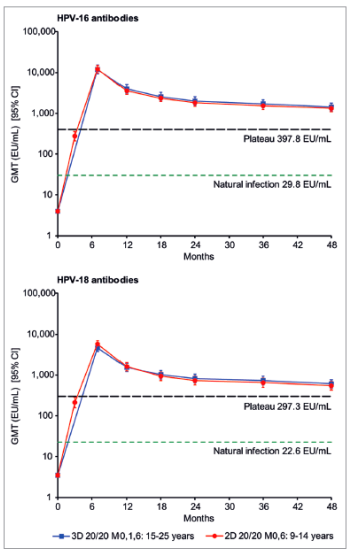
- **In males & in sites other than the cervix** (anal, oral) (Giuiliano et al *NEJM* 2011, Palefsky et al *NEJM* 2011, Kreimer et al *Lancet Oncol* 2011, Herrero et al *PLOS One* 2013)
- **With some cross protective effects** against non-targeted HPV types (Malagon et al *Lancet ID* 2012)
- At available 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)

National HPV Vaccination Program Register

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

* Brotherton et al. Curr Obs Gynecol Rep 2016



Human Vaccines & Immunotherapeutics 10:5, 1155–1165; May 2014

Figure 2. Kinetics of HPV-16 and HPV-18 antibody responses for girls aged 9–14 y in the 2D 20/20 M0,6 group and women aged 15–25 y in the 3D 20/20 M0,1,6 group (according-to-protocol month 48 immunogenicity cohort, subjects seronegative at baseline). 2D, 2-dose schedule; 3D, 3-dose schedule; 20/20, 20 µg each of HPV-16 and -18 L1 virus-like particles; 95% CI, exact 95% confidence interval; EU/mL, ELISA unit per milliliter; GMT, geometric mean antibody titer; M, month. Natural infection, GMT in subjects who had cleared a natural infection.[12] Plateau, GMT at the plateau level (month 45–50) in women aged 15–25 y (total vaccinated cohort) in a study in which sustained protection with the HPV-16/18 AS04-adjuvanted vaccine has been shown (i.e., 397.8 EU/mL for HPV-16 and 297.3 EU/mL for HPV-18).[13]

National HPV Vaccination Program Register

Nine valent HPV vaccine

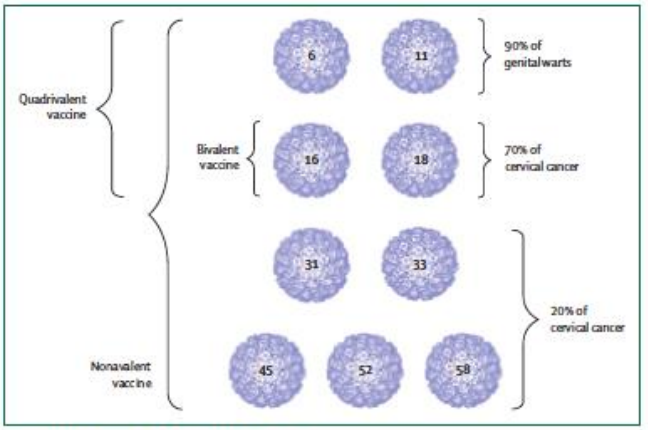


Figure 2: HPV VLP types in the nonavalent VLP vaccine
VLPs in the bivalent, quadravalent, and the nonavalent vaccines are shown with the proportion of neoplasistic disease attributed to each group. HPV=human papillomavirus. VLP=virus-like particle.

Schiller & Muller. *Next generation prophylactic human papillomavirus vaccines*. Lancet Oncol. 2015 May;16(5):e217 - e225

Nine valent HPV vaccine

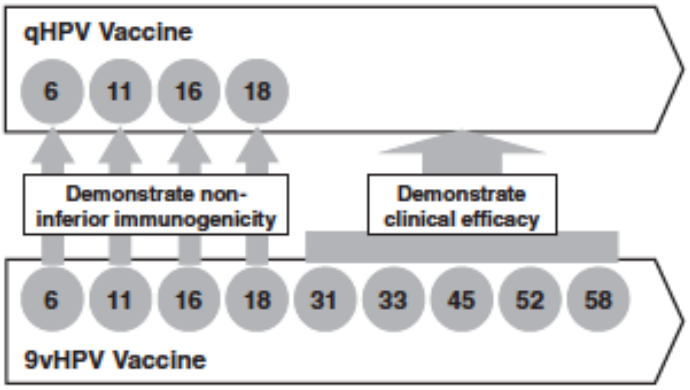


Fig. 1. Primary objectives of the study.

A. Luxembourg et al. / Contemporary Clinical Trials 42 (2015) 18–25

National HPV Vaccination Program Register

PER PROTOCOL POPULATION

Table 2. Effect of 9vHPV Vaccine on the Incidence of Cervical, Vulvar, and Vaginal Disease and of Persistent HPV-Related Infection.*

End Point	9vHPV Vaccine (N=7099)		qHPV Vaccine (N=7105)		Risk Reduction (95% CI)
	no./total no.	*cases/1000 person-yr*	*no./total no.*	*cases/1000 person-yr*	
Per-protocol efficacy population					
High-grade cervical, vulvar, and vaginal disease†					
Related to HPV-31, 33, 45, 52, or 58	1/6016	0.1	30/6,017	1.6	96.7 (80.9 to 99.8)
Related to HPV-6, 11, 16, or 18	1/5883	0.1	3/5898	0.2	66.6 (−203.0 to 98.7)
High-grade cervical epithelial neoplasia, adenocarcinoma in situ, and cervical cancer					
Related to HPV-31, 33, 45, 52, or 58	1/5948	0.1	27/5943	1.5	96.3 (79.5 to 99.8)
Related to HPV-6, 11, 16, or 18	1/5823	0.1	1/5832	0.1	−0.4 (≤ −999 to 97.4)
Persistent infection ≥6 months' duration¶					
Related to HPV-31, 33, 45, 52, or 58	35/5939	2.1	810/5953	52.4	96.0 (94.4 to 97.2)
Related to HPV-6, 11, 16, or 18	59/5812	3.6	80/5830	5.0	26.4 (−4.3 to 47.5)

Joura EA et al N Engl J Med 2015;372:711-23

National HPV Vaccination Program Register

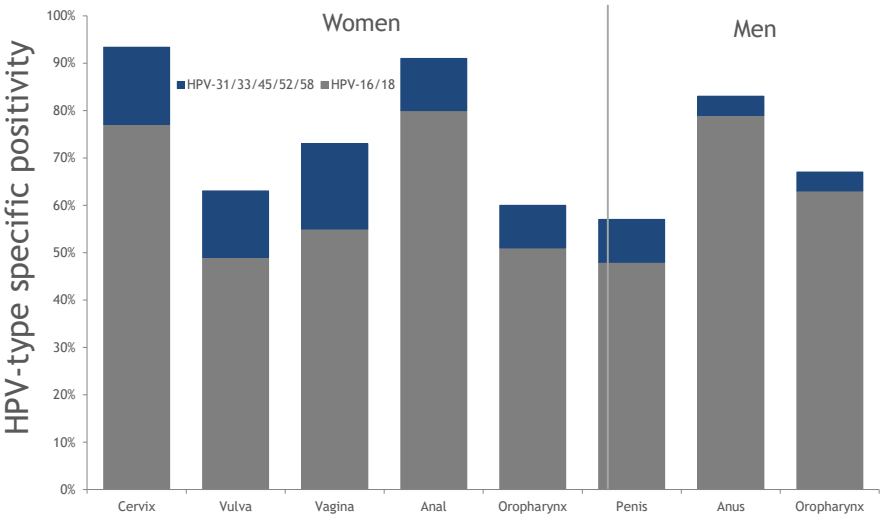
Table 4. Adverse Events.*

Event	9vHPV Vaccine (N=7071)	qHPV Vaccine (N=7078)
	no. of participants (%)	
Participants with one or more adverse events†	6640 (93.9)	6419 (90.7)
Injection-site event‡	6414 (90.7)	6012 (84.9)
Pain§	6356 (89.9)	5910 (83.5)
Mild	3754 (53.1)	4043 (57.1)
Moderate	2300 (32.5)	1682 (23.8)
Severe	302 (4.3)	185 (2.6)
Swelling	2830 (40.0)	2035 (28.8)
Mild: 0 to ≤2.5 cm	1958 (27.7)	1594 (22.5)
Moderate: >2.5 cm to ≤5.0 cm	597 (8.4)	332 (4.7)
Severe: >5.0 cm	272 (3.8)	109 (1.5)
Unknown	3 (0)	0 (0)
Erythema	2407 (34.0)	1810 (25.6)
Mild: 0 to ≤2.5 cm	1921 (27.2)	1555 (22.0)
Moderate: >2.5 cm to ≤5.0 cm	370 (5.2)	197 (2.8)
Severe: >5 cm	114 (1.6)	57 (0.8)
Unknown	2 (0)	1 (0)
Pruritus§	388 (5.5)	282 (4.0)
Mild	301 (4.3)	223 (3.2)
Moderate	80 (1.1)	56 (0.8)
Severe	7 (0.1)	3 (0)
Systemic event¶	3948 (55.8)	3883 (54.9)
Any vaccine-related systemic event	2086 (29.5)	1929 (27.3)
Headache	1031 (14.6)	969 (13.7)
Pyrexia	357 (5.0)	301 (4.3)
Nausea	311 (4.4)	261 (3.7)
Dizziness	211 (3.0)	197 (2.8)
Fatigue	166 (2.3)	150 (2.1)
Serious event	233 (3.3)	183 (2.6)
Vaccine-related event	2 (0)	2 (0)
Death‖	5 (0.1)	5 (0.1)
Discontinuation due to adverse event**	8 (0.1)	4 (0.1)
Vaccine-related event	5 (0.1)	3 (0)
Serious event	3 (0)	1 (0)
Serious vaccine-related event	1 (0)	0 (0)

Joura EA et al N Engl J Med 2015;372:711-23

4- and 9-valent HPV vaccine

Potential for cancer prevention



Slide courtesy of Marc Brisson

Ref: 1) Saraiya, JNCI 2015

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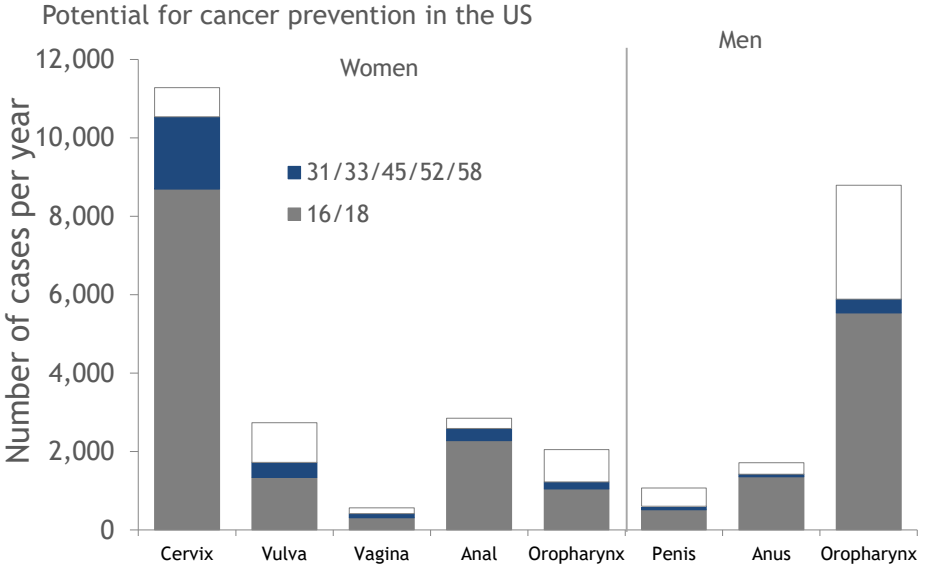
4- and 9-valent HPV vaccine

Potential for cancer prevention in the US



Slide courtesy of Marc Brisson

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

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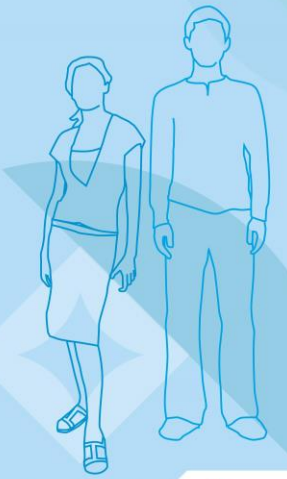
CONCLUSIONS

- 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

National HPV Vaccination Program Register

Renewal of the National Cervical Screening Program

- Rationale
- Safety
- Practical Implications



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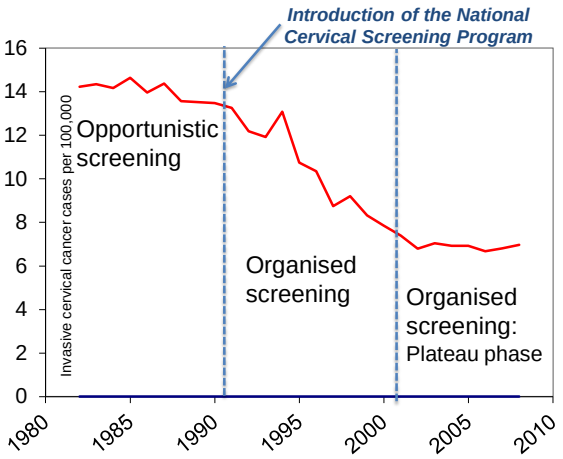
1991 NCSP Policy:

- 2-yearly (Pap test)
- 18 to 69 years[1]
- Registry reminder

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

- 50% reduction in incidence & deaths



[1]*NHMRC Australia, Guidelines for Cervical Screening 2005.*
[2]*Australian Institute of Health and Welfare 2014, 2011-2012.*

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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**.

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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

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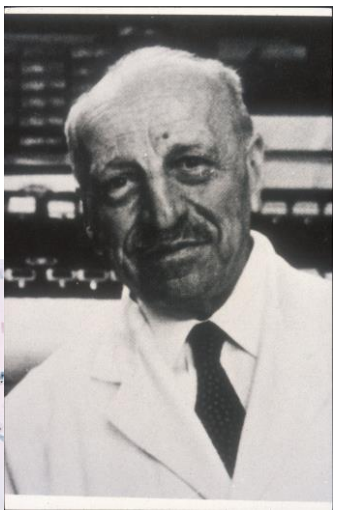
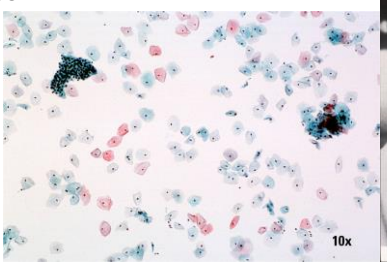
George Papanicolaou

- 1928- Pap test developed
- 1943- Diagnosis of uterine cancer by the vaginal smear
- 1948- American Cancer Society
- "Pap smear is a valuable test"





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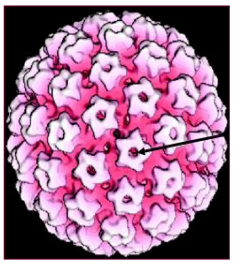
Harald zur Hausen

1982

- Demonstrated that HPV was the cause of cervical cancer

2008

- Nobel Prize in Medicine



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Ian Frazer AC

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

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Australian Government
Medical Services Advisory Committee

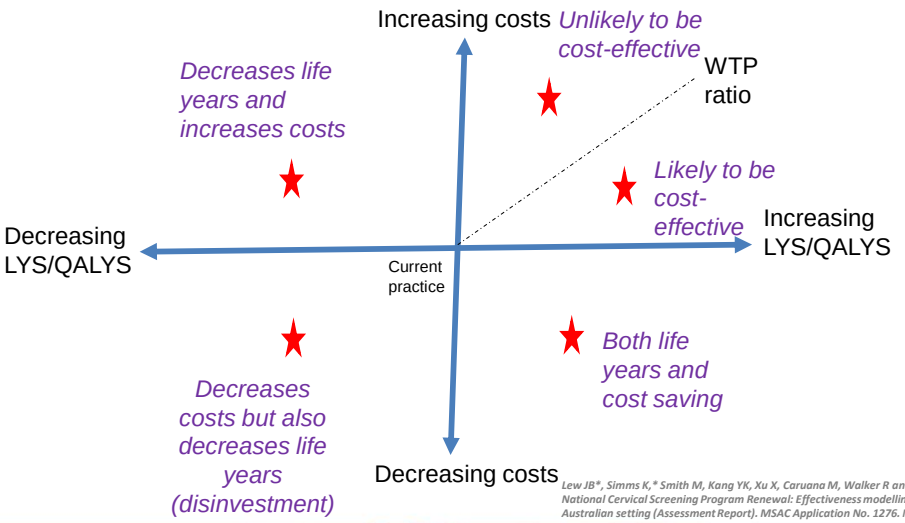
MSAC Outcomes

Application No. 1276 – Renewal of the National Cervical Screening Program

Sponsor/Applicant/s: **Standing Committee on Screening**

Date of MSAC consideration: **MSAC 61st Meeting, 3-4 April 2014**

Cost-effectiveness plane



Lew JB, Simms K,* Smith M, Kang YK, Xu X, Caruana M, Walker R and Canfell K. (*Joint first authors) National Cervical Screening Program Renewal: Effectiveness modelling and economic evaluation in the Australian setting (Assessment Report). MSAC Application No. 1276. November 2013.*

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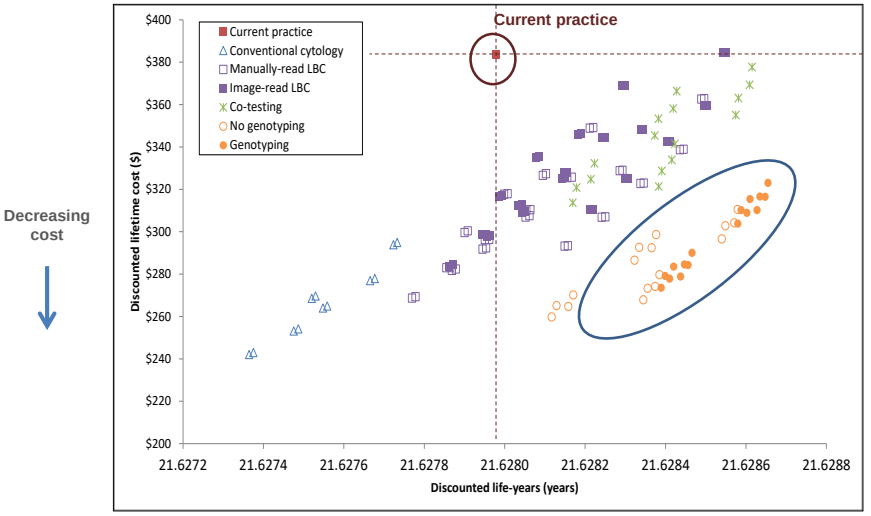
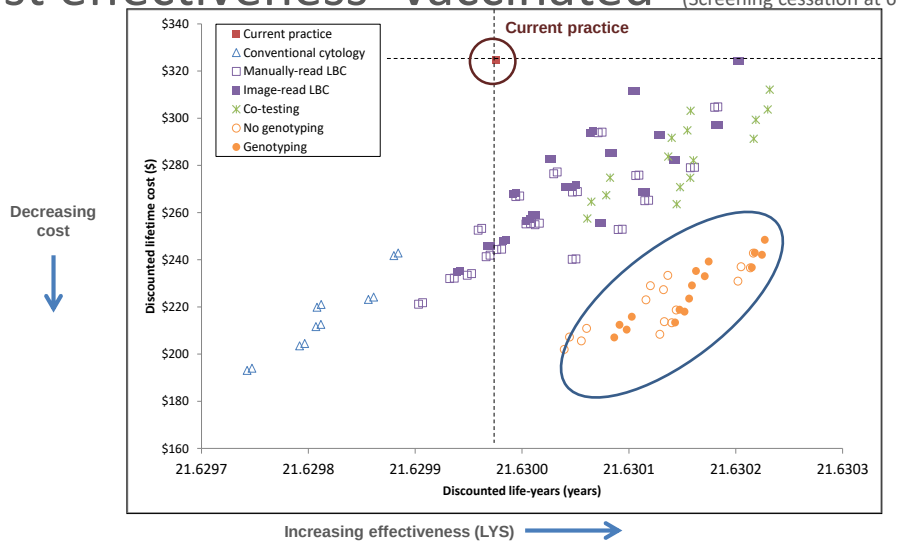
Cost effectiveness- unvaccinated (Screening cessation at 65 years)



Cost effectiveness- vaccinated (Screening cessation at 65 years)



Started - Girls 2007, Boys 2013 Current participation rate >70%

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

RENEWAL – 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: 1ST MAY 2017

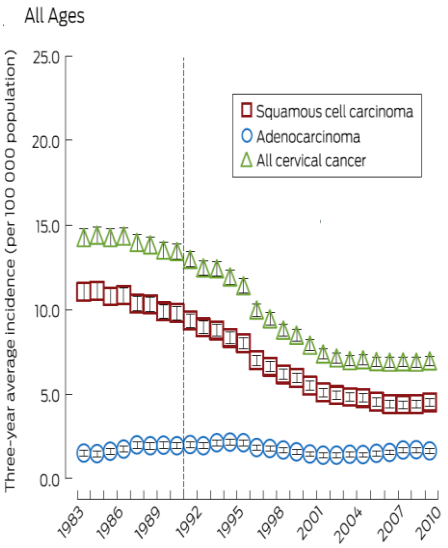
- New - screening test HPV
- New - screening interval 5 years
- New - starting age 25 years
- New - finishing age 74 years
- New - self-collection
- New - National Cancer Screening Register

NEW CHALLENGES

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

Is it safe?

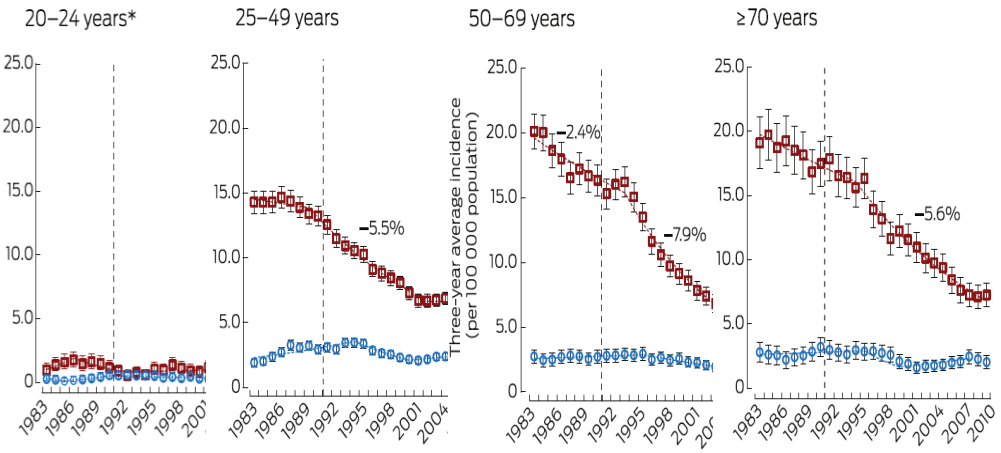
Three-year average cervical cancer incidence (with 95% CIs), by all ages and histological type, 1982-2010



M.Smith, K. Canfell: Med J Aust 2016; 205(8): 359-64

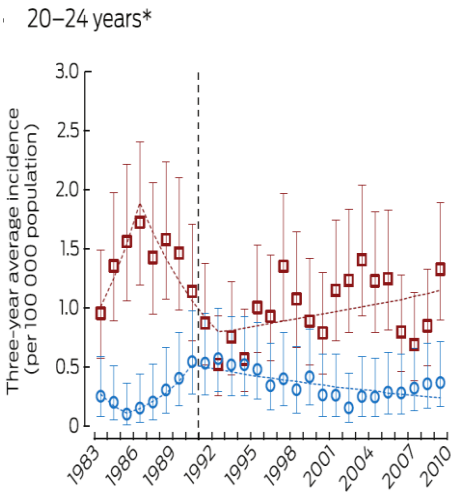
VCS

Three-year average cervical cancer incidence (with 95% CIs), by age and histological type, 1982-2010



VCS

Three-year average cervical cancer incidence (with 95% CIs), by age and histological type, 1982-201



M.Smith, K. Canfell: Med J Aust 2016; 205(8): 359-64

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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

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Why has the screening interval been extended from two years to five years?

Is it safe?

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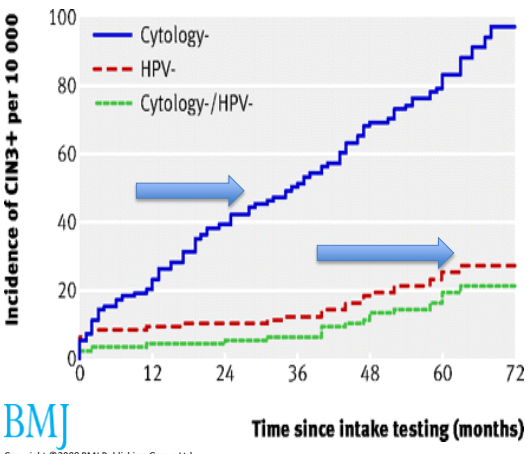
Primary HPV screening

Longitudinal results for screen-negative women



Low risk

Dillner, J. et al. Joint European Cohort Analysis. BMJ 2008;337:a1754

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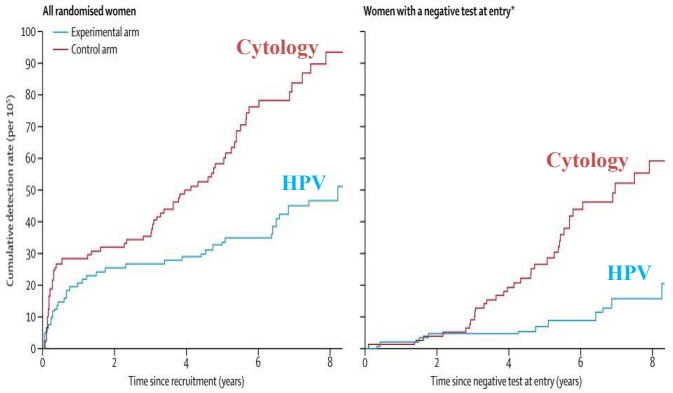
Primary HPV screening:

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"

Ronco et al, Lancet 2014

Effectiveness and Safety

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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 provid**e
  - detailed instructions
  - appropriate consumables
  - so that the sample satisfies requirements both of the HPV test and LBC, should this be required.

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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

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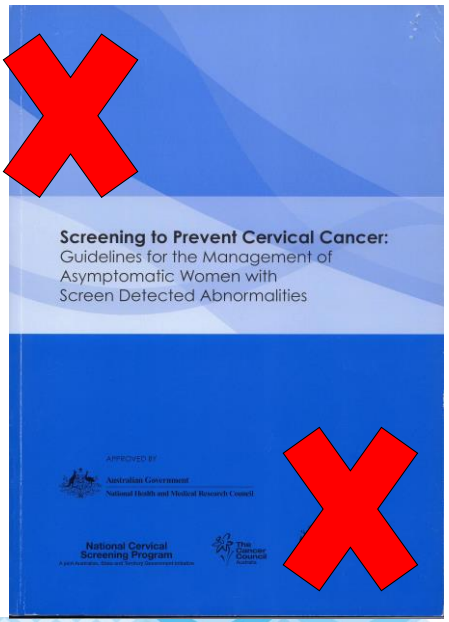
Endorsed by NHMRC

9th June 2005

Implemented

3rd July 2006



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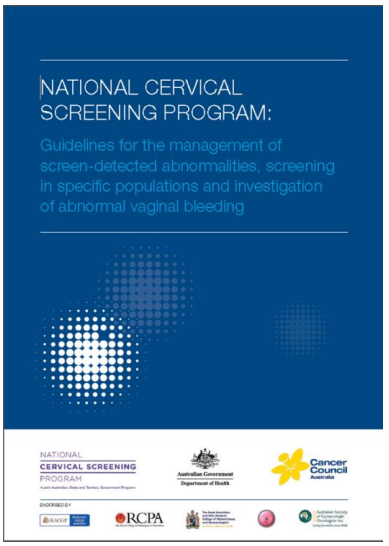
THE 2016 GUIDELINES



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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

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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 assessme**nt
  - 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

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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

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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

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

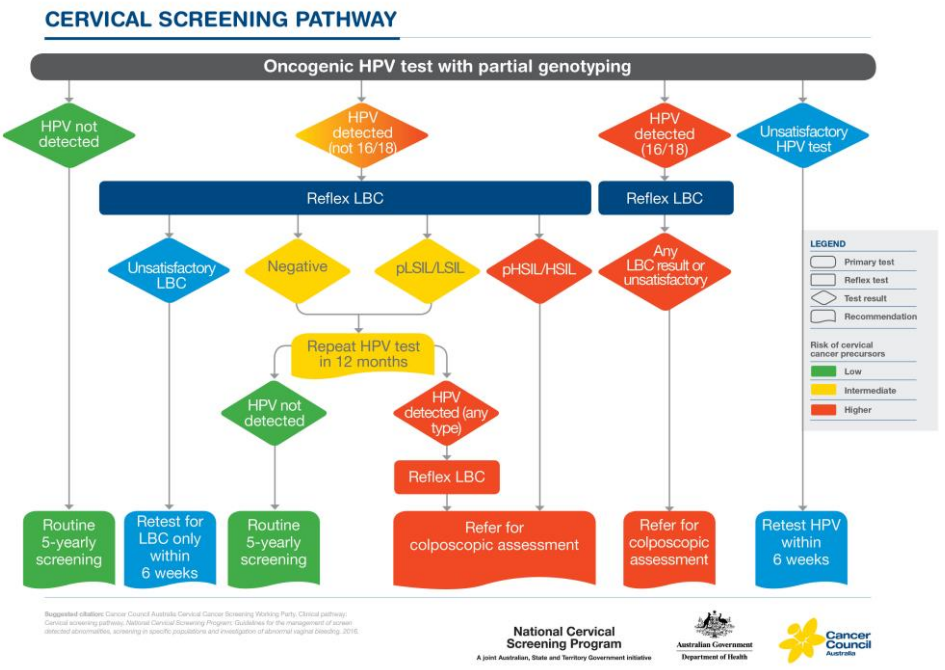
Specimen Cervical – ThinPrep

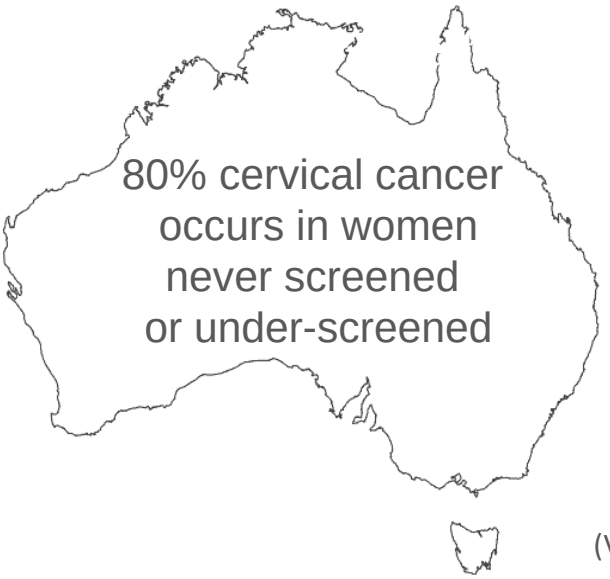
Test results PCR for oncogenic HPV and genotype

- HPV 16 – Not detected
- HPV 18 – Not detected
- HPV (not16/18) – **Detected**

Liquid based cytology (LBC) image assisted: **Unsatisfactory**

Recommendation: Repeat LBC in six weeks





(VCCR 2012)

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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

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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.**

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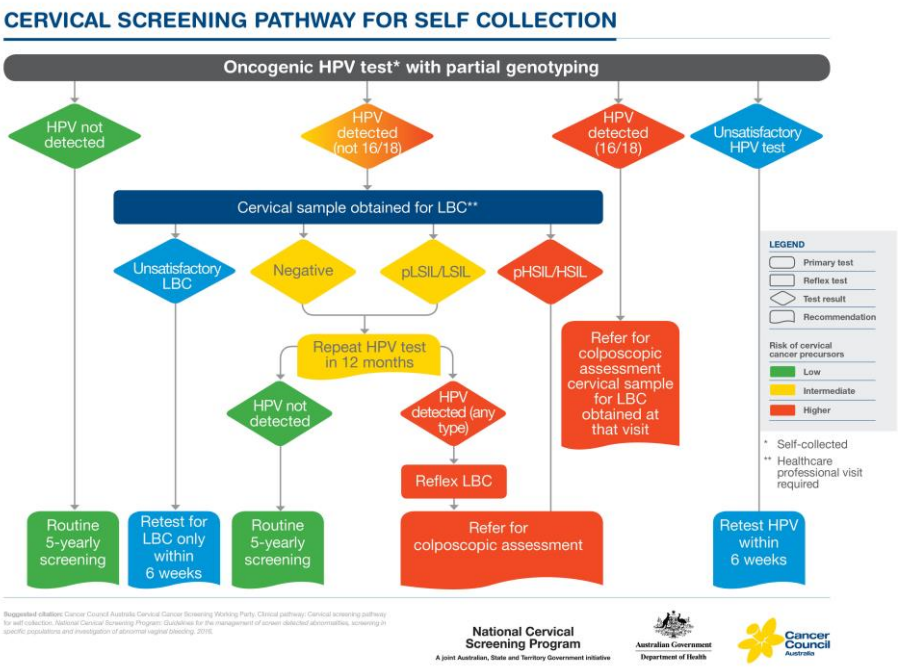
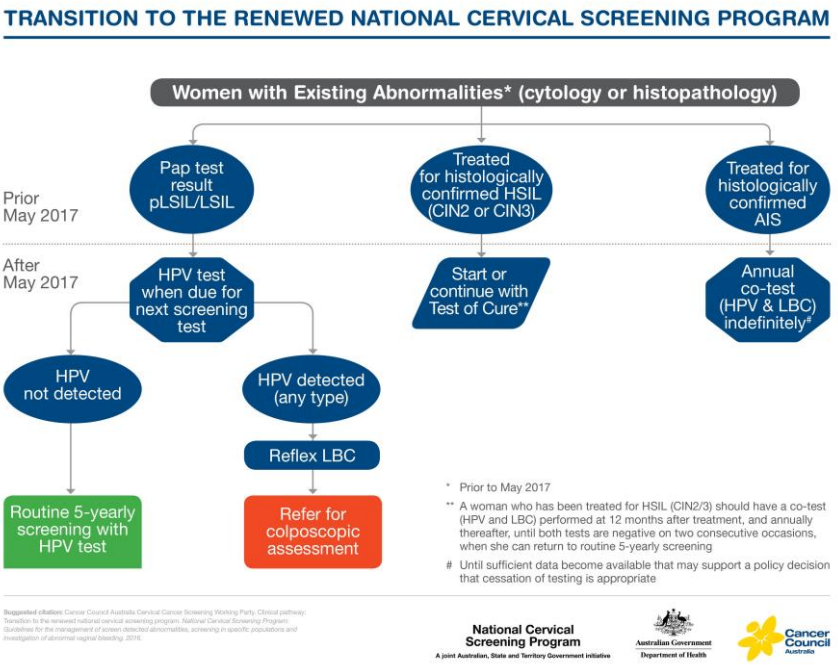
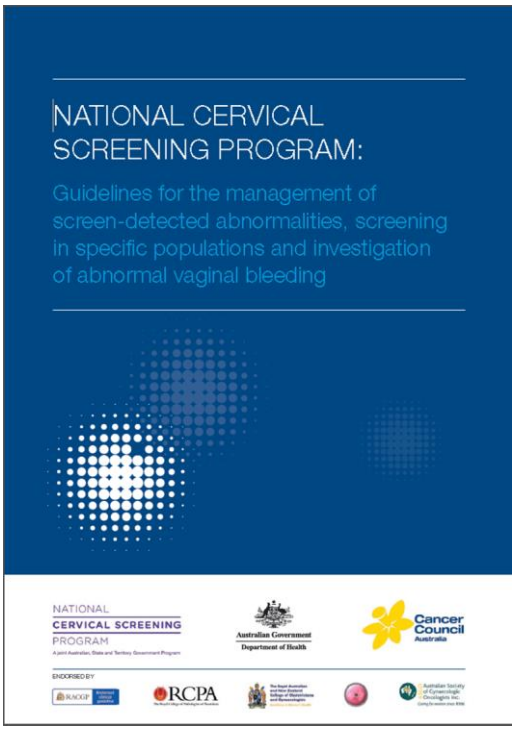




‘290 pages’

Wiki Platform

PDF



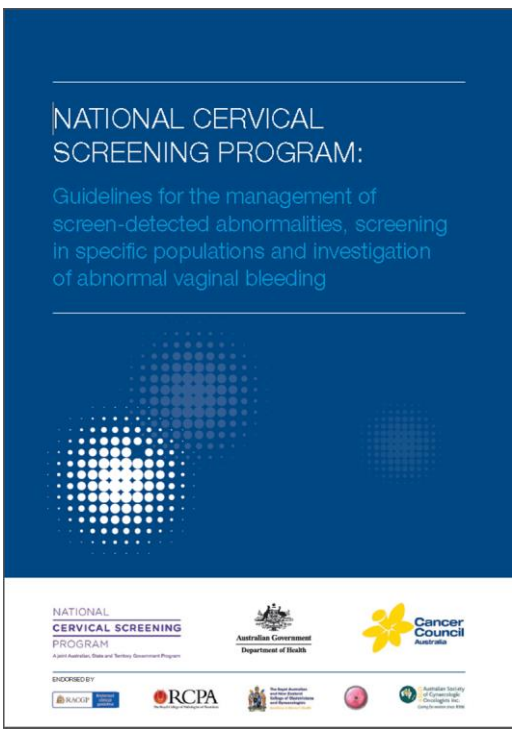
Benefits of wiki-based guidelines

- **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

Cancer Council

ENDORSED BY

- RACGP
- RANZCOG
- RCPA
- ASCCP
- ASGO



MAIN CHANGES FROM MAY 2017

NOW	MAY 2017
• Pap Smear	• HPV Test
• 2 Yearly	• 5 Yearly
• Start 18 Years	• Start 25 Years
• End 69 Years	• End 70-74 Years
• Reminders	• Invitations/Reminders
	• Self Collection

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Screening history of Victorian women diagnosed with cervical cancer for the period 1 January 2013 to 31 December 2013.

	Invasive squamous cell carcinoma		Other invasive cervical cancer[6]		Invasive sub-total		Micro-invasive		Total (Invasive and micro-invasive)	
Screening history	Number	%	Number	%	Number	%	Number	%	Number	%
A. Never screened	24	37%	20	34%	44	35%	25	54%	69	41%
Never screened, recorded on VCCR[1]	*23*	*35%*	*9*	*15%*	*32*	*26%*	*6*	*13%*	*38*	*22%*
Never screened, estimated to not be recorded on VCCR[2]	*1*	*2%*	*11*	*19%*	*12*	*10%*	*19*	*41%*	*31*	*18%*
B. Lapsed screeners	24	37%	25	42%	49	40%	11	24%	60	35%
Lapsed screener, > 2.5 years	*1*	*2%*	*5*	*8%*	*6*	*5%*	*5*	*11%*	*11*	*6%*
Lapsed screener, > 3.5 years	*1*	*2%*	*6*	*10%*	*7*	*6%*	*2*	*4%*	*9*	*5%*
Lapsed screener, > 5.5 years	*11*	*17%*	*7*	*12%*	*18*	*15%*	*1*	*2%*	*19*	*11%*
Lapsed screener, > 10 years	*9*	*14%*	*3*	*5%*	*12*	*10%*	*3*	*7%*	*15*	*9%*
Lapsed screener, > 18 months[3]	*2*	*3%*	*4*	*7%*	*6*	*5%*	*0*	*0%*	*6*	*4%*
C. Adequately screened (last screen within 2.5 years)	2	3%	7	12%	9	7%	6	13%	15	9%
D. Delayed diagnosis	11	17%	3	5%	14	11%	3	7%	17	10%
E. Not eligible[4]	3	5%	3	5%	6	5%	1	2%	7	4%
F. Other[5]	1	2%	1	2%	2	2%	0	0%	2	1%
Grand Total	65	100%	59	100%	124	100%	46	100%	170	100%

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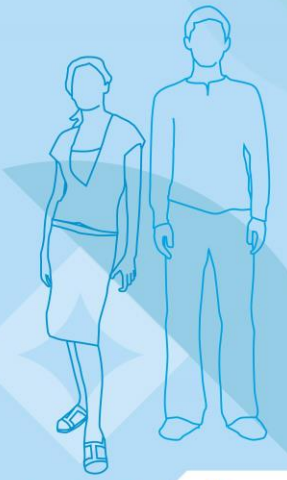
Until 1st May 2017
Business as usual !



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MORE INFORMATION

www.cancerscreening.gov.au

Or

Cervicalrenewal@health.gov.au

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THE COMPASS TRIAL, AN UPDATE

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Future directions
in cervical screening

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

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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)

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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

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WHY ANOTHER RCT OF PRIMARY HPV SCREENING

- Specific evaluation of safety, effectiveness and costs in Australian context
- **Pragmatic trial/demonstration of concept**

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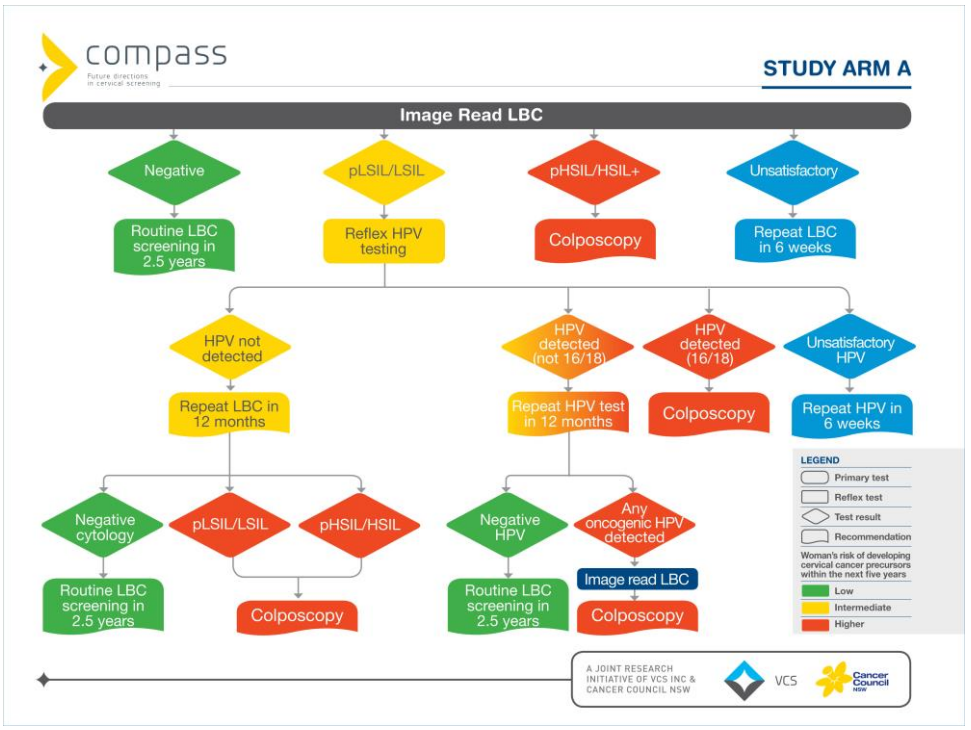

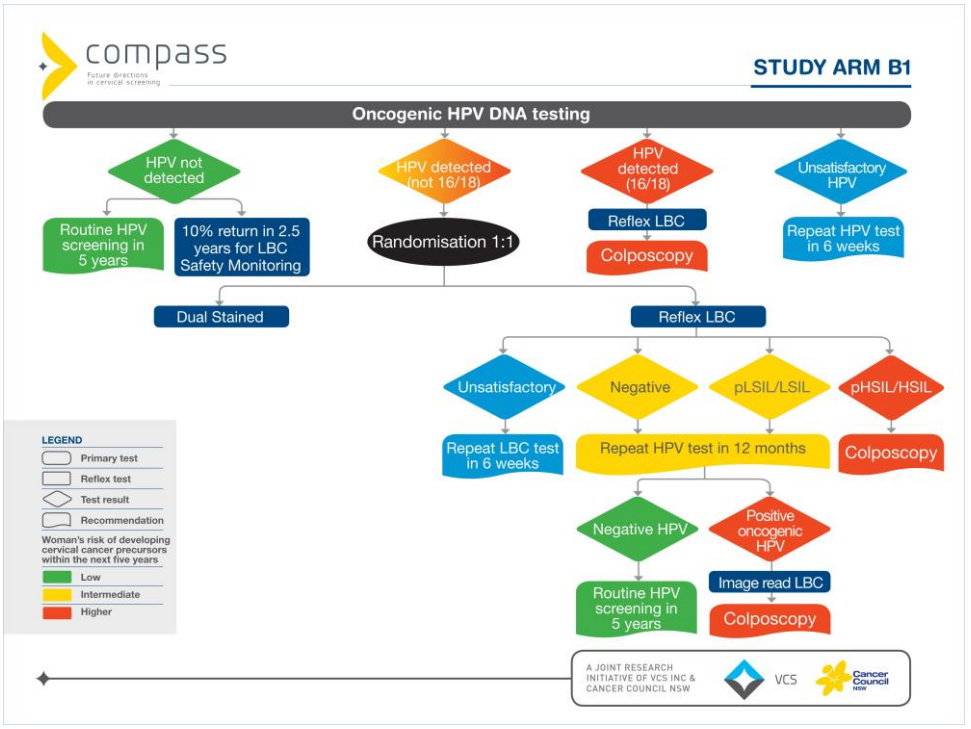
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STUDY ARM B1
Oncogenic HPV DNA testing
HPV not detected
HPV detected (not 16/18)
HPV detected (16/18)
Unsatisfactory HPV
Routine HPV screening in 5 years
10% return in 2.5 years for LBC Safety Monitoring
Randomisation 1:1
Reflex LBC
Colposcopy
Repeat HPV test in 6 weeks
Dual Stained
Reflex LBC
Unsatisfactory
Negative
pLSIL/LSIL
pHSIL/HSIL
Repeat LBC test in 6 weeks
Repeat HPV test in 12 months
Colposcopy
Negative HPV
Positive oncogenic HPV
Image read LBC
Routine HPV screening in 5 years
Colposcopy
LEGEND
Primary test
Reflex test
Test result
Recommendation
Woman's risk of developing cervical cancer precursors within the next five years
Low
Intermediate
Higher
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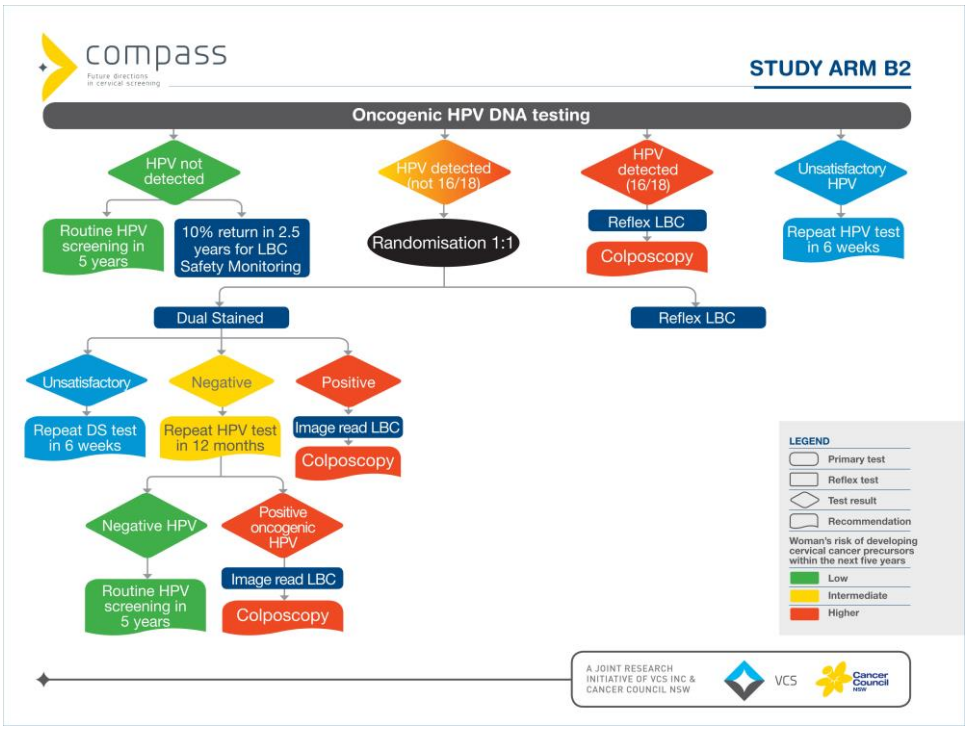
compass
Future directions in cervical screening
STUDY ARM B2
Oncogenic HPV DNA testing
HPV not detected
HPV detected (not 16/18)
HPV detected (16/18)
Unsatisfactory HPV
Routine HPV screening in 5 years
10% return in 2.5 years for LBC Safety Monitoring
Randomisation 1:1
Reflex LBC
Colposcopy
Repeat HPV test in 6 weeks
Dual Stained
Reflex LBC
Unsatisfactory
Negative
Positive
Repeat DS test in 6 weeks
Repeat HPV test in 12 months
Image read LBC
Colposcopy
Negative HPV
Positive oncogenic HPV
Image read LBC
Routine HPV screening in 5 years
Colposcopy
LEGEND
Primary test
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Woman's risk of developing cervical cancer precursors within the next five years
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Intermediate
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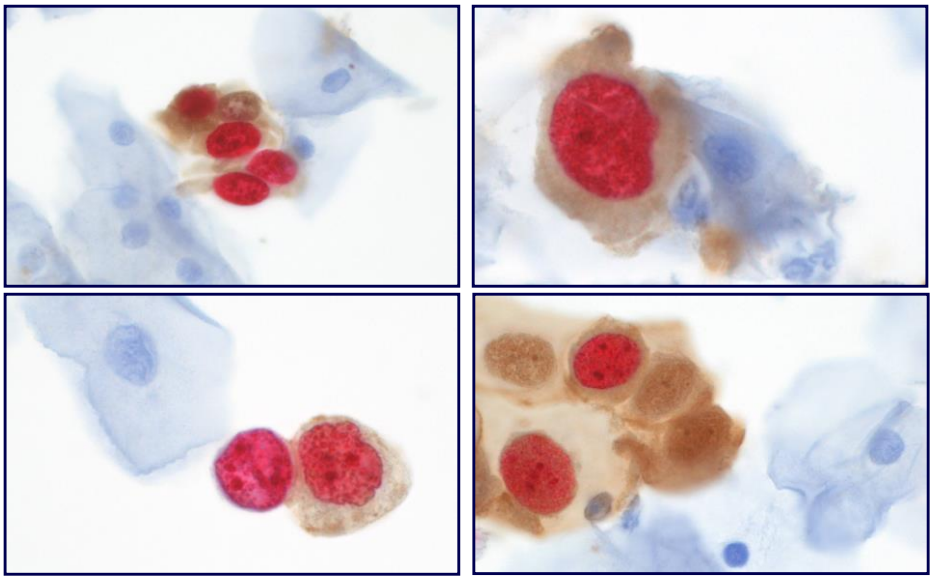
p16/Ki-67 Dual Stained Cytology



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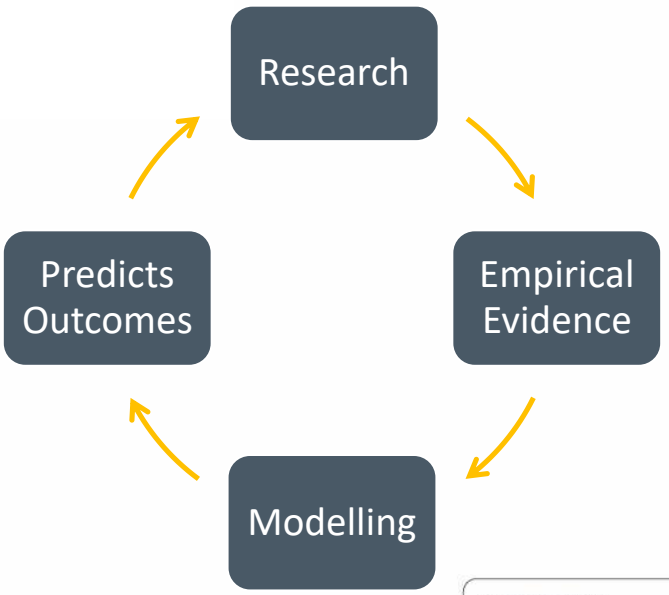

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Future directions in cervical screening

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

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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

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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

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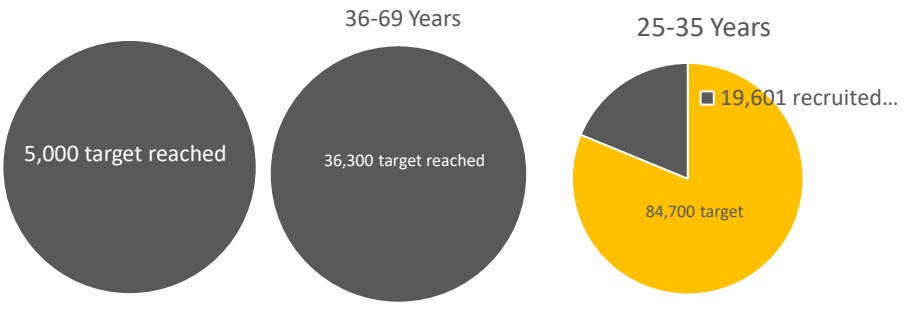

450 Practitioners actively recruiting

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

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Future directions in cervical screening

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

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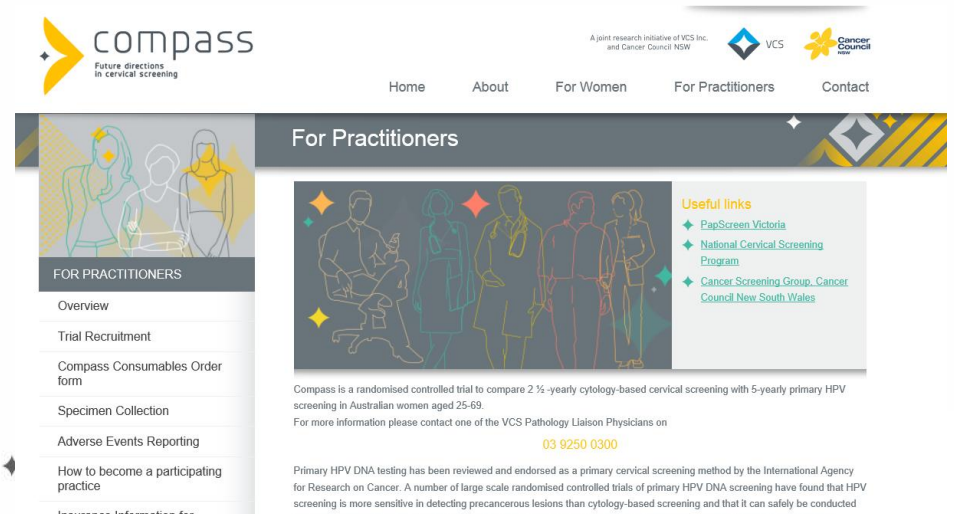
ENGAGEMENT OF GPS



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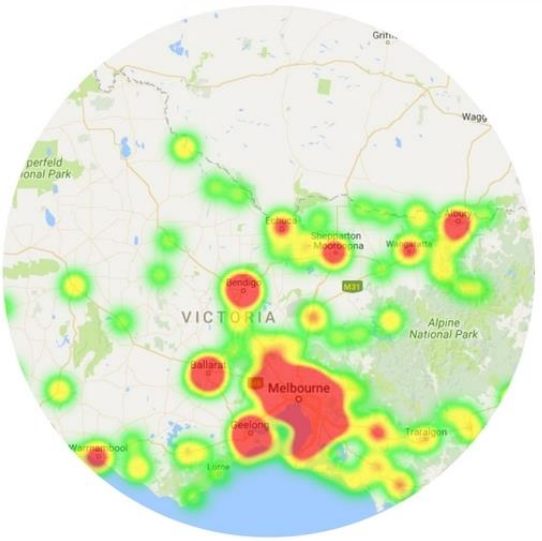
Future directions in cervical screening



450 Clinics Recruiting across Victoria

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RACGP QI & CPD*

RACGP
QI&CPD Accredited Activity
CATEGORY 1

- 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

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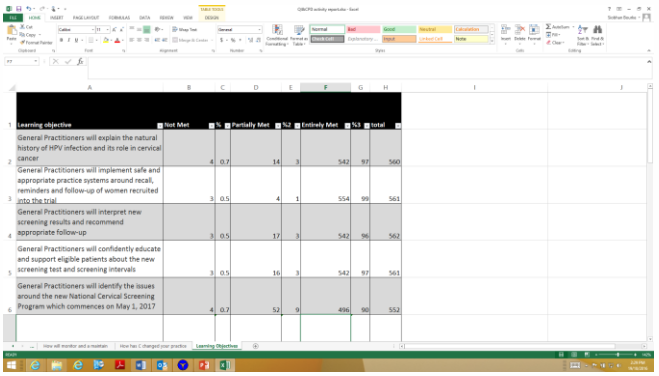
5 LEARNING OBJECTIVES FOR QI&CPD FOR RACGP AND THE COMPASS TRIAL.

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



Learning objective	Not Met	%	Partially Met	%2	Entirely Met	%3	total
General Practitioners will explain the natural history of HPV infection and its role in cervical cancer	4	0.7	14	3	542	97	560
General Practitioners will implement safe and appropriate practice systems around recall, reminders and follow-up of women recruited into the trial	3	0.5	4	1	554	99	561
General Practitioners will interpret new screening results and recommend appropriate follow-up	3	0.5	17	3	542	96	562
General Practitioners will confidently educate and support eligible patients about the new screening test and screening intervals	3	0.5	16	3	542	97	561
General Practitioners will identify the issues around the new National Cervical Screening Program which commences on May 1, 2017	4	0.7	52	9	496	90	552

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QUOTES FROM GPS

"Women Love it"

"patients are more likely to have (their) children vaccinated"

"less unsatisfactory samples since starting compass"

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More quotes from GPs

"good to translate basic science into tangible benefits for patients"

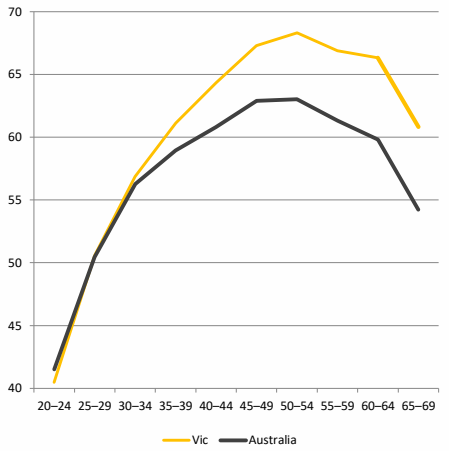
"feels good to be ahead of the game"

"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"

2 year participation 2014 - 2015



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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"

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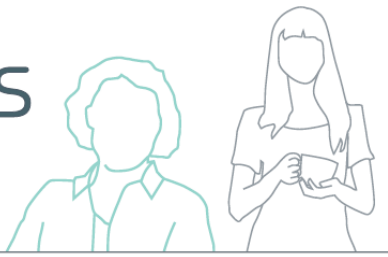

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Analysis plan
When can results be expected?

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ANALYSIS PLAN, BASELINE

Milestone	Time	Measures of Interest
Baseline	6 months after the last participant in a cohort is recruited.	Test positivity rates for primary and triage tests
		Colposcopy referral rates
		CIN2+ rates
		CIN3+ rates

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ANALYSIS PLAN, 12 MONTHS

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

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

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ANALYSIS PLAN, 2.5 YEARS LBC ARM

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

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

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ANALYSIS PLAN, SAFETY MONITORING HPV ARM

Milestone	Time	Measures of interest
2.5 year screening round in Trial Arm B	2.5 years + 9 months after the last participant in a cohort was randomized to Study Arm B at baseline *	CIN2+ rates in the safety monitoring cohort

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

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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

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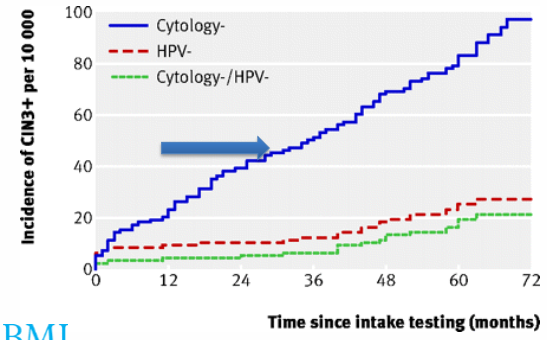
INTERNATIONAL DATA TO INFORM EXPECTED RATE:

Longitudinal results for screen-negative women



BMJ

Dillner, J. et al. Joint European Cohort Analysis. BMJ 2008

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ANALYSIS PLAN, 5 YEARS TRIAL COMPLETION

Milestone	Time	Measures of interest
5 year screening round	5 years + 9 months after the last participant in a cohort was recruited*	Cumulative CN2+ after HPV exit testing

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

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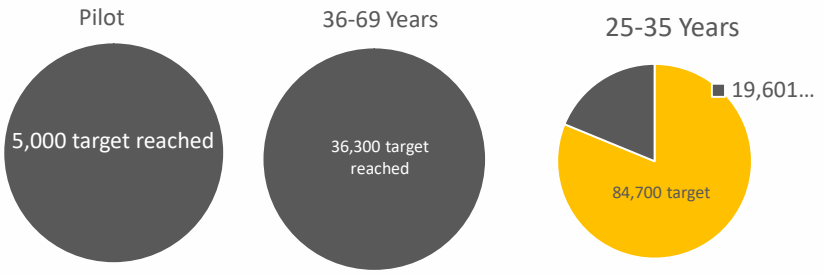

450 Practitioners actively recruiting

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

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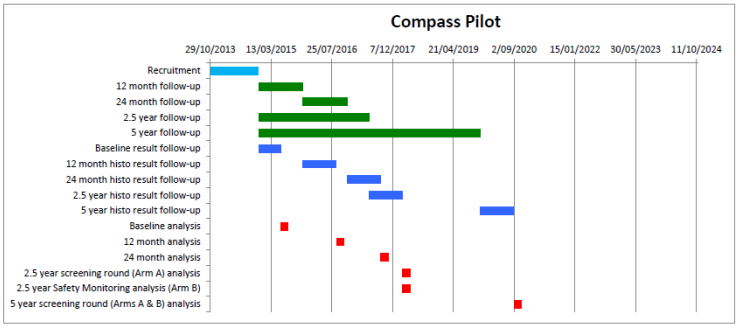
DATA ANALYSIS PLAN



	Date
Baseline analysis	1/06/2015
12 month analysis	1/09/2016
24 month analysis	1/09/2017
2.5 year screening round (Arm A) analysis	1/03/2018
2.5 year Safety Monitoring analysis (Arm B)	1/03/2018
5 year screening round (Arms A & B) analysis	1/09/2020

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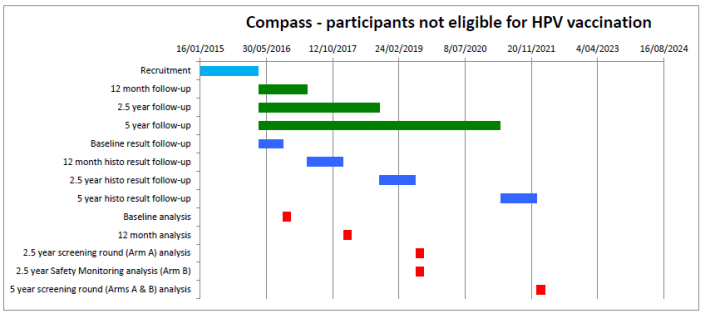
DATA ANALYSIS PLAN



	Date
Baseline analysis	1/10/2016
12 month analysis	1/01/2018
2.5 year screening round (Arm A) analysis	1/07/2019
2.5 year Safety Monitoring analysis (Arm B)	1/07/2019
5 year screening round (Arms A & B) analysis	1/01/2022

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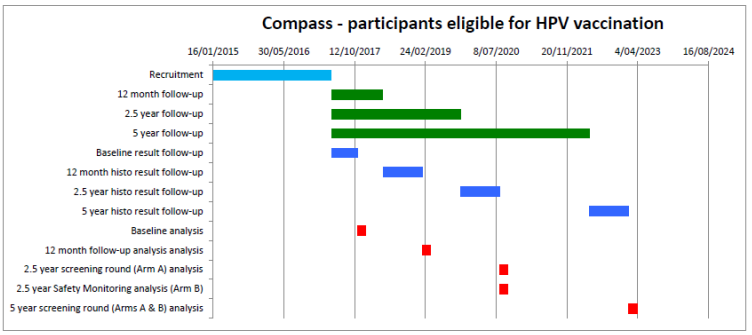
DATA ANALYSIS PLAN



*Assuming that recruitment of participants eligible for HPV Vaccination is completed by 1st May 2017.

	Date
Baseline analysis	1/11/2017
12 month follow-up analysis	1/02/2019
2.5 year screening round (Arm A) analysis	1/08/2020
2.5 year Safety Monitoring analysis (Arm B)	1/08/2020
5 year screening round (Arms A & B) analysis	1/02/2023

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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 then to prepare for renewal
- We look forward to presenting more evidence from the trial as outlined in the analysis plan.

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Acknowledgements

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- Prof Val Gebski
- Dr Michael Caruana
- Prof Dorota Gertig
- Dr Julia Brotherton
- Dr Stella Heley

ASSOCIATE INVESTIGATORS (MAIN TRIAL)
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- Dr Jeff Tan, Obstetrics and Gynaecology, The Royal Women's Hospital, Melbourne
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- Prof. Ruth Salmon

SCIENTIFIC ADVISORY COMMITTEE (SAC) MEMBERS
- Prof Bruce Armstrong (Chair)
- Prof Jonathan Carter
- A/Prof Rachel Skinner
- Prof Suzanne Garland
- Dr Deborah Bateson
- Prof Andrew Grulich
- Dr Eduardo Franco
- Ms Bridget Whelan
- A/Prof Annabelle Farnsworth *(Chair: Histopathology Review Board)*

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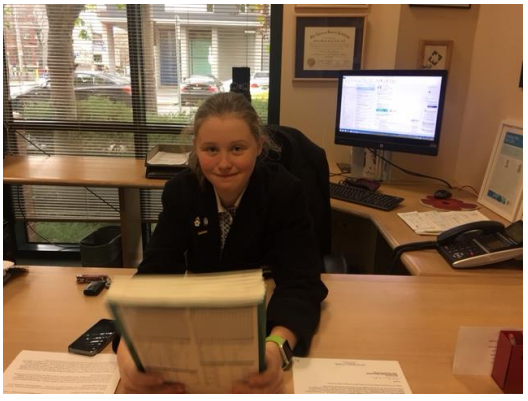
- Prof Michael Quinn, Ramsay Health (Chair)
- A/Prof Penny Blomfield, Director of Gynaecologic Oncology Services Tasmania, Royal Hobart Hospital
- Prof Gordon Wright, Director of Anatomic Pathology Gold Coast Hospital Campus
- A/Prof Katrina Sharples, Biostatistician, Preventive & Social Medicine, Dunedin School of Medicine, Health Sciences

Compass details:

Website
www.compasstrial.org.au

Pilot Study Registration
ACTRN12613001207707

Main Trial Registration:
Clinicaltrials.gov NCT02328872



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