Systematic review report for Questions 2a

Primary PICO question 2a

For HPV positive women who are not in treatment follow-up and who have negative or LSIL cytology and who have undergone colposcopy and the colposcopy was negative, what is the safety and effectiveness of testing with repeat HPV test at 12 months when compared with repeat cytology and HPV testing in 12 months?

Population	Study design	Intervention	Control	Outcome
HPV positive women who have undergone colposcopy and the colposcopy was **negative** and cytology was: i. negative, ii. p/d LSIL	Randomized or pseudo randomized controlled trial	Repeat HPV test at 12 months; Colposcopy (and reflex LBC test) if positive If negative HPV test in 12 months	Repeat cytology and HPV testing at 12 months: Colposcopy if HPV positive test or if cytology pHSIL or worse, and another 12 months follow-up if HPV negative p/dLSIL	Cervical cancer mortality Cervical cancer diagnosis Precancerous high grade lesion detection

dLSIL = definite LSIL; HSIL = high-grade squamous intraepithelial lesion; pHSIL = possible HSIL; pLSIL = possible LSIL; LSIL = low-grade squamous intraepithelial lesion

Randomised and pseudo-randomised controlled trials directly address the primary PICO questions 2a In the event that no relevant randomised or pseudo-randomised controlled trials were identified an indirect approach was planned with a secondary PICO question focussing on the risks of high grade lesions following a negative colposcopy for HPV positive women with negative or possible or definite LSIL referral cytology.

Secondary PICO question 2a:

For HPV positive women who are not in treatment follow-up and who have negative or LSIL cytology on referral and who had a colposcopy and the colposcopy was negative what are the predictors of subsequent detection of high-grade disease?

Population	Study design	Exposure	Comparator	Outcomes
Women who have p/dLSIL or negative cytology who have undergone colposcopy and no abnormalities were seen on colposcopy	Cohort	Negative cytology pLSIL HPV positive HPV 16 Age	pLSIL or dLSIL dLSIL HPV negative Other Ages	Cervical cancer mortality Cervical cancer diagnosis Precancerous high grade lesion detection

pLSIL = possible LSIL; dLSIL = definite LSIL; LSIL = low-grade squamous intraepithelial lesion

Definitions

A negative colposcopy is a colposcopy in which no abnormalities are seen: it does not include the subsequent reports on any biopsy taken.

Borderline nuclear abnormalities or **borderline dyskaryosis (**British Society for Clinical Cytology)
Post 2008: considered equivalent to atypical squamous cell, undetermined significance (ASC-US) in the Bethesda 2001 reporting system which is considered equivalent to possible LSIL (pLSIL) in the Australian modified Bethesda reporting system.
Pre 2009: included atypical squamous cells cannot exclude HSIL (ASC-H) which is considered equivalent to possible HSIL (pHSIL) in the Australian modified Bethesda reporting system and borderline changes in endocervical cells. (Denton KJ et al., (2008) The revised BSCC terminology for abnormal cervical cytology. Cytopathology 19: 137-157)

Mild dyskaryosis (British Society for Clinical Cytology) considered equivalent to low-grade squamous intraepithelial lesion (LSIL) in the Bethesda 2001 reporting system which is considered equivalent to definite LSIL (dLSIL) in the Australian modified Bethesda reporting system; renamed **low-grade dyskaryosis** in 2008. (Denton KJ et al., (2008) The revised BSCC terminology for abnormal cervical cytology. Cytopathology 19: 137-157)

1. Methods

1.1. Searches for existing relevant guidelines

Relevant guidelines from 2005 onwards were identified by scanning the citations identified by the literature search and searching the National Guideline Clearinghouse (http://guideline.gov/) and the Guidelines Resource Centre (www.cancerview.ca).
To be considered for adoption guidelines had to be directly relevant, based on systematic reviews of the evidence and meet the pre-specified criteria of scores of greater or equal to 70% for the domains rigour of development, clarity of presentation and editorial independence of the AGREE II instrument (http://www.agreetrust.org/resource-centre/agree-ii/).

1.2. Literature searches

To identify publications that addressed the primary PICO question Medline, PreMedline, Embase, CENTRAL, Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) databases, were searched for articles published from 2004 until 31st August 2015, using text terms and, where available, database-specific subject headings. In these databases searches for cytology testing were combined with searches for HPV and negative or normal colposcopy, and where possible, database-specific filters for identifying randomized controlled trials. To identify studies which considered Aboriginal and Torres Strait Islander (ATSI) peoples these searches were then coupled with search terms for ATSI peoples. A complete list of the terms used for search strategies

are included as Appendix A. The Cochrane systematic review database was also searched for relevant systematic reviews or meta-analyses using the terms, HPV and colposcopy, and abstracts from the 2015 EUROGIN conference were scanned for relevant studies using the term “colpos”. Reference lists of relevant articles and guidelines were checked for additional potentially relevant articles.

To identify publications that addressed the secondary PICO question Medline, PreMedline, Embase, and CENTRAL databases were searched for articles published from 2004 until 31st August 2015, specifically using text terms for negative or normal colposcopy, and more broadly, using search terms for low-grade cytological abnormalities combined with terms for HPV and for colposcopy. In addition the results of the DARE, HTA, the Cochrane systematic review database and the EUROGIN 2015 abstracts searches undertaken for the primary PICO question were reassessed against the broader inclusion criteria. A complete list of the terms used for these search strategies are included in Appendix A.

1.3. Inclusion criteria

Inclusion criteria for primary PICO question 2a

Selection criteria	Inclusion criteria	Exclusion criteria
Population	Women who have negative (NILM) or p/d LSIL (ASCUS or LSIL) cytology and who have undergone colposcopy and the colposcopy was negative	Conducted in referred population and do not specifically exclude women undergoing follow-up following treatment
Study type	Intervention	
Study design	Randomised or pseudo-randomised controlled trials or Systematic review/meta-analyses thereof	Reviews, editorials Conference proceedings other than 2015 EUROGIN conference proceedings
Intervention	Repeat HPV test at 12 months; if positive HPV test colposcopy (and reflex LBC test) if negative HPV test in 12 months	
Comparison	Repeat cytology and HPV testing at 12 months: Colposcopy if HPV positive or if cytology pHSIL or worse, and another 12 months follow-up if HPV negative p/dLSIL; repeat HPV and cytology test if tested negative on both HPV and cytology	
Outcomes	Cervical cancer mortality or Cervical cancer diagnosis or CIN3+ diagnosis or CIN2+ diagnosis or AIS diagnosis	
Search period	1st January 2004 – 31st August 2015	
Language	English	

AIS = adenocarcinoma in situ; ASCUS = Atypical squamous cells, undetermined significance; CIN = cervical intraepithelial neoplasia; dLSIL = definite LSIL; HSIL = high-grade squamous intraepithelial lesion; LBC = liquid-based cytology; LSIL = Low-grade squamous intraepithelial lesion; NILM = negative for intraepithelial lesion or malignancy; pHSIL = possible HSIL; pLSIL = possible LSIL

Inclusion criteria for secondary PICO question 2a

Selection criteria	Inclusion criteria	Exclusion criteria
Population	Women who have p/dLSIL or negative cytology who have undergone colposcopy and no abnormalities were seen on colposcopy	Conducted in referred population and do not specifically exclude women undergoing follow-up following treatment Symptomatic women only Women undergoing post treatment follow-up Women with "normal colposcopies" where normal colposcopy included negative biopsies Women with <CIN2 on colposcopy Adolescents only
Study type	Prognostic	
Study design	Cohort	Cross-sectional studies examining referral (baseline) HPV or cytology
Exposure	Referral or follow-up cytology or Referral or follow-up HPV status	
Comparator	Other referral or follow-up cytology, or Other referral or follow-up HPV status	
Outcomes	Cervical cancer mortality or Cervical cancer diagnosis or AIS diagnosis or CIN3+ diagnosis or CIN2+ diagnosis	
Search period	1st January 2004 – 31st August 2015	Case reports, reviews, editorials Conference proceedings other than 2015 EUROGIN conference proceedings
Language	English	

AIS = adenocarcinoma in situ; CIN = cervical intraepithelial neoplasia; CIN2+ = cervical intraepithelial neoplasia grade 2 or worse; CIN3+ = cervical intraepithelial neoplasia grade 3 or worse; dLSIL = definite LSIL; LSIL = Low-grade squamous intraepithelial lesion; pLSIL = possible LSIL

2. Results

2.1. Results of Guidelines Search

Three guidelines were identified that contained potentially relevant recommendations regarding negative colposcopies. These recommendations were not adopted as either they were not or it was unclear as to whether they were based on a systematic review. These guidelines and the reason why they were not adopted are listed in Appendix C.

2.2. Results of Literature Search

Primary PICO

The initial searches were designed to identify randomised or pseudo-randomised controlled trials directly addressing the primary PICO question. Searches of the Medline, PreMedline, Embase and CENTRAL databases identified 40 citations, DARE and HTA databases another 5 citations, the Cochrane database of systematic reviews 73 citations and EUROGIN abstracts, 16 citations; a total of 134 citations. All were excluded after examining titles and abstracts thus **no studies were found that directly addressed the primary PICO question**.

Database or Source	Number of Citations	Number of Articles Collected	Number of Articles Included	ATSI filter results
Medline, PreMedline, CENTRAL and Embase	40	0	0	N/A
Cochrane database of systematic reviews	73	0	0	N/A
HTA and DARE	5	0	0	N/A
EUROGIN	16	N/A	0	N/A
TOTAL	**134**	**0**	**0**	**N/A**

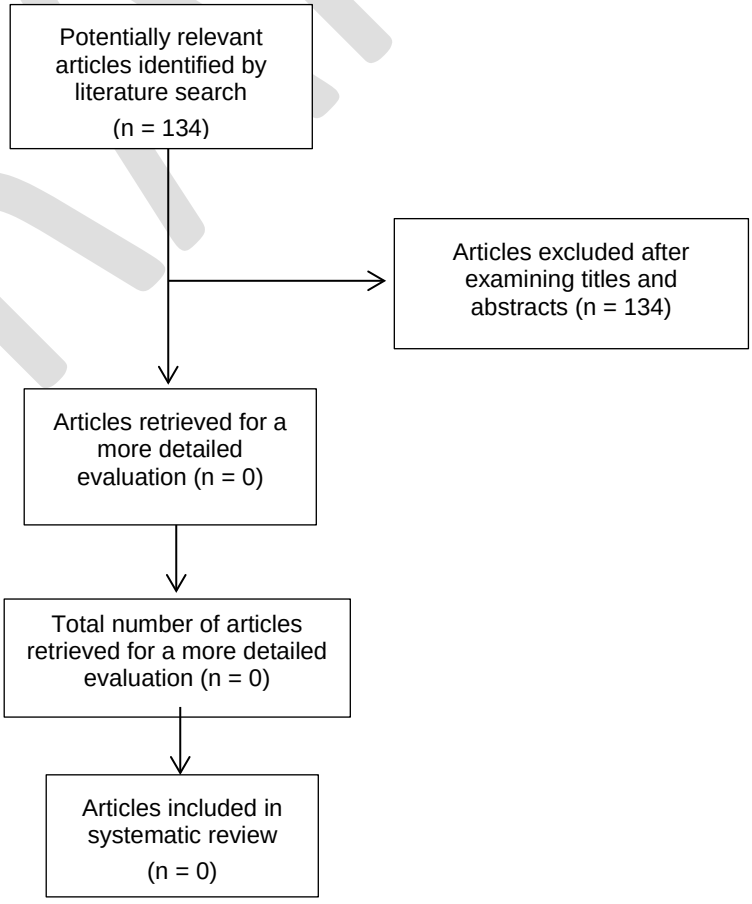

Figure 1. Process of inclusion and exclusion of studies for the primary PICO question

Secondary PICO

Searches were then broadened as pre-planned to identify studies that might address the secondary PICO question. Figure 2 outlines the steps undertaken to identify relevant articles for the systematic review. Searches of the Medline, Embase, PreMedline and CENTRAL databases using negative or normal colposcopy specific terms identified 305 citations and searches combining terms for colposcopy, HPV and low grade cytology identified 2,551 citations. When combined with those identified by HTA and DARE database and 2015 EUROGIN abstracts searches a total of 2,877 citations were identified. Titles and abstracts were examined and 31 articles were retrieved for a more detailed evaluation. An additional 5 potential citations were identified from the reference list of retrieved articles resulting in a total of 36 retrieved articles.

A total of 4 studies met the inclusion criteria for the secondary PICO question systematic review. There were no studies of Aboriginal and/or Torres Strait Islander women that met the inclusion criteria.

The retrieved articles that were not included and the reason for their exclusion are documented in Appendix C. The main reasons for exclusion were an absence of outcomes specifically for women with a negative colposcopy or for women with negative, pLSIL or dLSIL referral cytology.

Database or Source	Number of Citations	Number of Articles Collected	Number of Articles Included	ATSI filter results
Negative colposcopy specific search Medline, PreMedline, CENTRAL and Embase	305	27	4	0
HTA and DARE	5	0	0	N/A
EUROGIN	16	0	0	N/A
Snowballing	N/A	5	0	N/A
Low grade cytology + HPV + colposcopy search Medline, PreMedline, CENTRAL and Embase	2551	4	0	N/A
TOTAL	**2877**	**36**	**4**	**0**

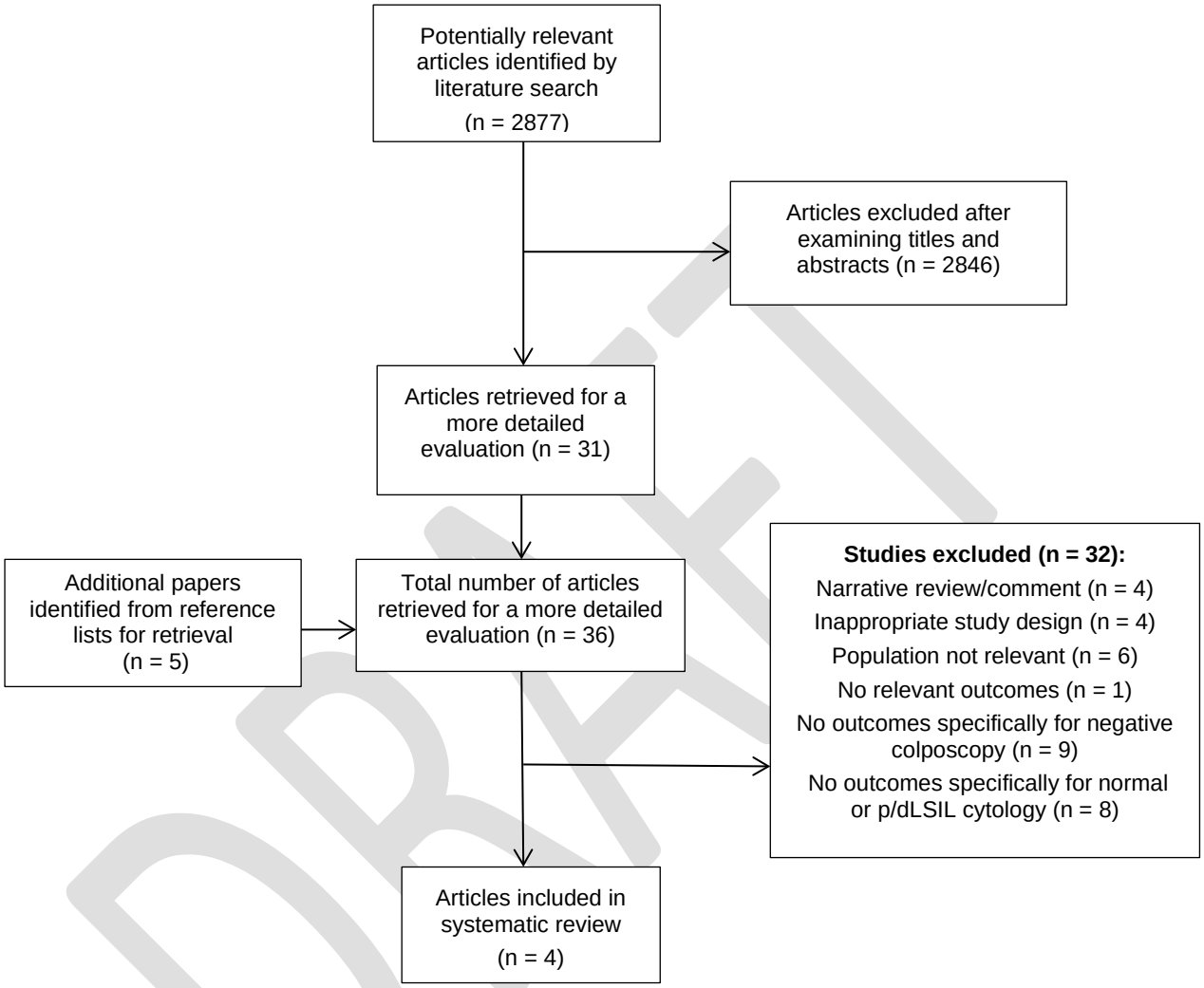

Figure 2. Process of inclusion and exclusion of studies for the secondary PICO question

2.3 Characteristics of included studies addressing secondary PICO question 2a

Table 1: Characteristics of studies examining risks of high-grade disease amongst women with initial negative or p/dLSIL cytology following a negative colposcopy

Study	Study design	Population	Prognostic factors	Outcome	Comments
TOMBOLA Cruikshank 2015 (UK)	Prospective cohort	Participants in a randomised controlled trial recruited in 1999-2003 with screen-detected BNA* (N = 672) or Mild dyskaryosis (N = 212) randomised to immediate colposcopy and colposcopy was normal Aged 20-59 years N = 884 Median age = 36 years	*Ages* 20-29 vs 30-39 vs 40-59 *Initial Hr-HPV status* Positive vs 16/18 positive vs Negative *Initial Cytology* BNA vs Mild dyskaryosis	CIN2+ Follow-up = 2.6 years (mean)	Post hoc analysis Normal colposcopy defined as one in which the transformation zone was recorded as normal and the squamocolumnar junction was visible All study colposcopists trained and accredited by British Society for Colposcopy and Cervical Pathology 30% of those with BNA or mild dyskaryosis randomised to immediate colposcopy had diagnosis of CIN2+ on immediate colposcopy Active cytological follow-up: 6-monthly cytology with colposcopy referral if moderate dyskaryosis or worse – 66 underwent follow- up colposcopy including 26 with BNA or mild dyskaryosis Exit colposcopy at 3 years with LLETZ if any persistent colposcopic abnormality 609 underwent exit colposcopy HPV status determined by GP5+/GP6+-mediated PCR immunoassay (detects 14 hr-HPV types) and genotyping undertaken using type-specific primers For analyses censored at date of exit appointment, requested to leave trial, hysterectomy, died or moved from area Loss to follow-up unclear
NHS CSP sentinel site study Kelly 2012 (UK)	Retrospective cohort	Participants in a pilot study recruited in 2001-2002 at 3 sites of HPV triage for women with screen-detected HPV positive BNA* (N = 578) or Mild dyskaryosis (N = 378) referred to colposcopy and colposcopy was normal Aged 20-64 years N = 1,063	*Ages* 20-34 vs 35-64 *Initial cytology* BNA vs Mild dyskaryosis	CIN3+ CIN2+ Follow-up = 27 months (median)	Followed with cytology testing until adequate colposcopy or a negative cytology resulting in return to routine screening Management pathways suggest multiple negative cytology results required before returned to routine screening Indications for subsequent colposcopy unclear HPV status determined by HC2 test (detects 13 hr-HPV types) with cut-off of **3 relative light units/Co**

		With any follow-up cytology or colposcopy results N = 956 Underwent subsequent colposcopy N = 360			
Lukic 2011 (Italy)	Prospective cohort	Women enrolled in June 2008-2009 at a tertiary institution with hr-HPV positive ASC-US (N = 45) or LSIL (N = 50) referred to colposcopy and colposcopy was normal Aged 18-54 years	*Initial cytology/HPV status* HPV-positive ASC-US vs LSIL	CIN3+ CIN2+ Follow-up = 1 year	Normal colposcopy defined as one in which no lesion was evident Cytological and colposcopic follow-up – not described HPV assay not described
Smith 2006 (UK)	Retrospective cohort	Women without a history of treatment to the cervix referred to a tertiary hospital-based colposcopy clinic between 1990 and 2001 with BNA* or mild dyskaryosis and conservatively managed after initial colposcopy BNA at referral N = 805 Median age = 36.1 years Mild dyskaryosis at referral N = 1,352 Median age = 29.6 years *Subgroup with normal colposcopy and normal or BNA* smear at colposcopy* BNA* at referral N = 352 Mild dyskaryosis at referral N = 268	*Initial cytology* BNA vs Mild dyskaryosis	CIN3+ CIN2+ Follow-up for subgroup with negative coplposcopy = 159 week (median)	**HPV status not considered** Colposcopy referral if: • Mildly dyskaryotic smear • 3 borderline smears Baseline colposcopy undertaken by "experienced" colposcopists or trainee colposcopists under supervision Normal colposcopy defined as one in which no evidence of HPV infection, CIN or cancer and the transformation zone was fully visible Follow-up unclear - Assume cytological follow-up For analyses censored at date of last smear if showed no dyskaryosis , last smear prior to hysterectomy unrelated to gynaecological malignancy or worst biopsy result if CIN1 13.9% lost to follow-up

ASC-US = atypical squamous cell, undetermined significance (Bethesda 2001); BNA = borderline nuclear abnormalities; CIN = cervical intraepithelial neoplasia; CIN3+ = cervical intraepithelial neoplasia grade 3 or worse; CIN2+ = cervical intraepithelial neoplasia grade 2 or worse; HC2= Hybrid Capture II; LSIL= low-grade squamous cell lesions
** Includes possible high-grade squamous cell lesions (pHSIL) as well as possible low-grade squamous cell lesions (pLSIL)*

2.4 Assessment of risk of bias of included studies addressing secondary PICO question 2a

Methodological quality of included cohort studies is described in Tables 2-3.

Table 2: Risk of bias for the included **cohort** studies (n = 4)

Quality Category	N (%)
Selection of the exposed and non-exposed cohorts	
Low risk of bias	4 (100)
Moderate risk of bias	0 (0)
High risk of bias	0 (0)
Measurement of exposure	
Low risk of bias	4 (100)
Moderate risk of bias	0 (0)
High risk of bias	0 (0)
Measurement of outcome	
Low risk of bias	0 (0)
Moderate risk of bias	0 (0)
High risk of bias	4 (100)
Participation rate	
Low risk of bias	4 (100)
Moderate risk of bias	0 (0)
High risk of bias	0 (0)
Completeness of follow-up	
Low risk of bias	2 (50)
Moderate risk of bias	1 (25)
High risk of bias	1 (25)
Accuracy of dates of outcome or censoring	
Low risk of bias	4 (100)
Moderate risk of bias	0 (0)
Difference in follow-up between exposed and non-exposed	
Low risk of bias	3 (75)
Moderate risk of bias	1 (25)
High risk of bias	0 (0)
Difference in missing data for exposure between those with or without the outcome	
Low risk of bias	4 (100)
Moderate risk of bias	0 (0)
High risk of bias	0 (0)
Comparability of exposed and non-exposed cohorts with respect to potentially important confounding variables	
Low risk of bias	0 (0)
Moderate risk of bias	0 (0)
High risk of bias	4 (100)

Table 3: Risk of bias for the included **cohort** studies (n = 4)

	Cruickshank 2015 (TOMBOLA)	**Kelly 2012**	**Lukic 2011**	**Smith 2006**
Selection of the exposed and non-exposed cohorts	Low	Low	Low	Low
Measurement of exposure	Low	Low	Low	Low
Measurement of outcome	High	High	High	High
Participation rate	Low	Low	Low	Low
Completeness of follow-up	Moderate	High	Low	Low
Accuracy of dates of outcome or censoring	Low	Low	Low	Low
Difference in follow-up between exposed and non-exposed	Low	Moderate	Low	Low
Difference in missing data for exposure between those with or without the outcome	Low	Low	Low	Low
Comparability of exposed and non-exposed cohorts with respect to potentially important confounding variables[1]	High	High	High	High
Overall risk of bias	**High**	**High**	**High**	**High**

[1]*Age, smoking and vaccination status*

Key to overall rating
High risk of bias – high risk of bias in any domain
Moderate risk of bias – moderate or low risk of bias in all domains
Low risk of bias – all domains low risk of bias

2.5 Results from included studies addressing secondary PICO question 2a

I CIN3+ DETECTION

Table 4 Results of longitudinal studies comparing prognostic risks associated with differing referral cytology types: **CIN3 or worse**

Study	Population	Referral cytology	hr-HPV status	N	Length of follow-up	CIN3+ n	CIN3+ risk %
Referral Cytology							
NHS CSP sentinel site study (Kelly 2012)	Women with HPV positive borderline or mild dyskaryosis who underwent colposcopy and colposcopy was negative	Borderline*	positive	578	27 months (median)	20	3.5
		Mild dyskaryosis	positive	378	27 months (median)	8	2.1
Smith 2006	Women referred with borderline or mild dyskaryosis who underwent colposcopy and colposcopy was negative and **cytology was normal or borderlne* at colposcopy**	Borderline*	positive or negative	352	159 weeks (median)	1	0.3
		Mild dyskaryosis	positive or negative	268	159 weeks (median)	5	1.9
Referral cytology and HPV status combined							
Lukic 2011	Women with hr-HPV positive ASC-US or LSIL and negative colposcopy	ASC-US	positive	45	1 year	0	-
		LSIL	positive or negative	50	1 year	2	4.0

ASC-US = atypical squamous cell, undetermined significance (Bethesda 2001); CIN3+ = cervical intraepithelial neoplasia grade 3 or worse; CI = confidence interval; hr-HPV = high risk HPV type; LSIL = low-grade squamous cell lesions
** includes possible high-grade squamous cell lesions (pHSIL) as well as possible low-grade squamous cell lesions (pLSIL)*

II CIN2+ DETECTION

Table 5 Results of longitudinal studies comparing prognostic risks associated with differing ages, HPV statuses and cytology types: **CIN2 or worse**

Study	Population	Referral cytology	hr-HPV status	Age	N	Length of follow-up	CIN2+ n	CIN2+ risk (95% CI)	Risk ratio (95% CI)
Referral Cytology									
TOMBOLA (Cruickshank 2015)	Women with borderline or mild dyskaryosis and negative colposcopy	Borderline*	positive or negative	20-59	672	2.6 years (mean)	22	3.3% 1.24 per 100 women years	0.32 (0.18-0.58)[2]
		Mild dyskaryosis	positive or negative	20-59	212	2.6 years (mean)	21	9.9% 3.88 per 100 women years	reference
NHS CSP sentinel site study (Kelly 2012)	Women with HPV positive borderline or mild dyskaryosis and negative colposcopy	Borderline *	positive	20-64 years	578	27 months (median)	33	5.7%^^	
		Mild dyskaryosis	positive	20-64 years	378	27 months (median)	18	4.8%^^	
Smith 2006	Women referred with borderline or mild dyskaryosis who underwent colposcopy and colposcopy was negative and **cytology was normal or borderline* at colposcopy**	Borderline*	NR	NR	352	5-year cumulative rate	5	1.3%**	
		Mild dyskaryosis	NR	NR	268	5-year cumulative rate	15	8.5%**	
Referral HPV status									
TOMBOLA (Cruickshank 2015)	Women with borderline or mild dyskaryosis and negative colposcopy	Borderline* or mild dyskaryosis	negative	20-59	529	2.6 years (mean)	15	2.8% 1.07 per 100 women years	reference
		Borderline* or mild dyskaryosis	positive	20-59	268	2.6 years (mean)	23	8.6% 3.33 per 100 women years	3.1 (1.62-5.95)[2]
		Borderline* or mild dyskaryosis	16/18 positive	20-59	125	2.6 years (mean)	8	6.4% 2.49 per 100 women years	NR
Referral cytology and HPV status combined									
TOMBOLA	Women with borderline or mild dyskaryosis and	Borderline*	negative	20-59	433	2.6 years (mean)	10	2.3%	reference

(Cruickshank 2015)	negative colposcopy							0.87 per 100 women years	
		Borderline*	positive	20-59	175	2.6 years (mean)	11	6.2% 2.42 per 100 women years	2.78 (1.18-6.54) [2]
		Mild dyskaryosis	negative	20-59	96	2.5 years (mean)	5	5.2% 2.01 per 100 women years	2.31 (0.79-6.75) [2]
		Mild dyskaryosis	positive	20-59	93	2.5 years (mean)	12	12.9% 5.10 per 100 women years	5.86 (2.53-13.56) [2]
Lukic 2011	Women with hr-HPV positive ASC-US or LSIL and negative colposcopy	ASC-US	positive	NR	45	1 year	0	-	
		LSIL	positive or negative	NR	50	1 year	9	18.0%	
Age									
TOMBOLA (Cruickshank 2015)	Women with borderline or mild dyskaryosis and negative colposcopy	Borderline* or mild (dyskaryosis	positive or negative	20-59	884	2.6 years (mean)	43	4.9% 1.86 per 100 women years	
				20-29	293	2.5 years (mean)	22	7.5% 2.98 per 100 women years	reference
				30-39	258	2.6 years (mean)	14	5.4% 2.06 per 100 women years	0.78 (0.37-1.66) [1]
				40-59	333	2.7 years (mean)	7	2.1% 0.78 per 100 women years	0.45 (0.18-1.11) [1]
NHS CSP sentinel site study (Kelly 2012)	Women with HPV-positive borderline or mild dyskaryosis and negative colposcopy	Borderline* or mild dyskaryosis	positive	20-64	956	27 months (median)	51	5.3% (4.0 – 7.0)	
				20-34	585	NR	29	5.0%^	
				35-64	371	NR	22	5.9%^	

ASC-US = atypical squamous cell, undetermined significance (Bethesda 2001); CIN2+ = cervical intraepithelial neoplasia grade 2 or worse; CI = confidence interval; hr-HPV = high risk HPV type; LSIL = low -grade squamous intraepithelial lesion; NR = not reported

** includes possible high-grade squamous cell lesions (pHSIL) as well as possible low-grade squamous cell lesions (pLSIL)*

*** 5-year cumulative rate calculations based on Kaplan-Maier curves*

^ p = 0.51

^^ p = 0.52

[1] adjusted for combination of recruitment cytology and HPV status

1 univariate analysis

3. Body of Evidence for Secondary PICO question 2a

I CIN3+ RISK

Name of study	Study type	Population (N)	Level of evidence*	Risk of bias**	Length of follow-up	Risk of CIN3+ (%)	Relevance of evidence*
Referral cytology							
Kelly 2012	Retrospective cohort	Women with borderline# (60%) or mild dyskaryosis (40%) and negative colposcopy with follow-up cytology or subsequent colposcopy results N = 956	III-2	High	27 months (median)	HPV+ve borderline# **3.5** HPV+ve mild dyskaryosis **2.1**	1
Smith 2006	Retrospective cohort	Women with borderline# (57%) or mild dyskaryosis (43%) and negative colposcopy *with normal or borderline cytology at colposcopy* N = 620	III-2	High	159 weeks (median)	Borderline# **0.3** Mild dyskaryosis **1.9**	1
Referral cytology and HPV status combined							
Lukic 2011	Prospective cohort	Women with HPV positive ASC-US (47%) or LSIL (53%) and negative colposcopy N = 95	II	High	1 year	HPV+ve ASC-US **-** LSIL **4.0**	1

ASC-US = atypical squamous cell, undetermined significance (Bethesda 2001); CIN3+ = cervical intraepithelial neoplasia grade 3 or worse; LSIL = low-grade squamous cell lesions
 # includes possible high-grade squamous cell lesions (pHSIL) as well as possible low-grade squamous cell lesions (pLSIL)

**Refer to appendix B for detailed explanations of rating scores; ** See Tables 2-3 for appraisals of risk of bias*

Clinical significance of size of effect is addressed in the assessment of clinical impact in the NHMRC evidence statement form.

II CIN2+ DETECTION

Name of study	Study type	Population (N)	Level of evidence*	Risk of bias**	Length of follow-up	Risk of CIN2+	Relevance of evidence*
Referral cytology							
Cruickshank 2015	Prospective cohort	Women with borderline[#] (76%) or mild dyskaryosis (24%) and negative colposcopy N = 884	II	High	2.6 years (mean)	Borderline[#] **1.24** /100 women years RR (95%) = **0.32** (0.18-0.58)[2] Mild dyskaryosis **3.88** /100 women years (reference)	1
Kelly 2012	Retrospective cohort	Women with borderline[#] (60%) or mild dyskaryosis (40%) and negative colposcopy with follow-up cytology or subsequent colposcopy results N = 956	III-2	High	27 months (median)	HPV+ve borderline[#] **5.7%** HPV+ve mild dyskaryosis **4.8%** *p = 0.52*	1
Smith 2006	Retrospective cohort	Women with borderline[#] (57%) or mild dyskaryosis (43%) and negative colposcopy *with normal or borderline cytology at colposcopy* N = 620	III-2	High	5-year cumulative rate	Borderline[#] **1.3%^** Mild dyskaryosis **8.5%^**	1
Referral HPV status							
Cruickshank 2015	Prospective cohort	Women with borderline[#] or mild dyskaryosis and negative colposcopy N = 797	II	High	2.6 years (mean)	HPV negative **1.07** per 100 women years (reference) HPV positive **3.33** per 100 women years RR (95%) = **3.1** (1.62-5.95)[2] HPV16/18 positive 2.49 per 100 women years NR	1

Referral cytology and HPV status combined							
Cruickshank 2015	Prospective cohort	Women with borderline[#] or mild dyskaryosis and negative colposcopy N = 797	II	High	2.6 years (mean)	HPV-ve Borderline[#] HPV+ve Borderline[#] HPV-ve mild dyskaryosis HPV+ve mild dyskaryosis	**0.87** per 100 women years (reference) **2.42** per 100 women years RR (95%) = **2.78** (1.18-6.54) [2] **2.01** per 100 women years RR (95%) = **2.31** (0.79-6.75) [2] **5.10** per 100 women years RR (95%) = **5.86** (2.53-13.6)[2]	1
Lukic 2011	Prospective cohort	Negative colposcopy N = 95	II	High	1 year	HPV+ve ASC-US LSIL	- **18.0%**	1
Age							
Cruickshank 2015	Prospective cohort	Women with borderline[#] (76%) or mild dyskaryosis (24%) and negative colposcopy N = 884	II	High	2.6 years (mean)	Aged 20-29 years Aged 30-39 years Aged 40-49 years	**2.98** per 100 women years (Reference) **2.06** per 100 women years RR (95%) = **0.78** (0.37 -1.66)[1] **0.78** per 100 women years RR (95%) = **0.45** (0.18 -1.11)[1]	1
Kelly 2012	Retrospective cohort	Women with borderline[#] (60%) or mild dyskaryosis (40%) and negative colposcopy with follow-up cytology or subsequent colposcopy results N = 956	III-2	High	27 months (median)	Aged 20-34 years Aged 35-64 years	**5.0%** **5.9%** *p = 0.51*	1

ASC-US = atypical squamous cell, undetermined significance (Bethesda 2001); CIN2+ = cervical intraepithelial neoplasia grade 2 or worse; CI = confidence interval; hr-HPV = high risk HPV type; LSIL = low -grade squamous intraepithelial lesion; NR = not reported; RR = risk ratio

[#] *includes possible high-grade squamous cell lesions (pHSIL) as well as possible low-grade squamous cell lesions (pLSIL)*

^ *5-year cumulative rate calculations based on Kaplan-Maier curves*

[1] *adjusted for combination of recruitment cytology and HPV status*

[2] *univariate analysis*

**Refer to appendix B for detailed explanations of rating scores; ** See Tables 2-3 for appraisals of risk of bias*

Clinical significance of size of effect is addressed in the assessment of clinical impact in the NHMRC evidence statement form.

References: Included Studies

1. Cruickshank ME, Cotton SC, Sharp L et al. Management of women with low grade cytology: how reassuring is a normal colposcopy examination? *BJOG: An International Journal of Obstetrics & Gynaecology*. 2015;122:380-386.

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3. Lukic A, Sbenaglia G, Carico E et al. Prediction of clinical outcome using p16INK4a immunocytochemical expression in low-grade squamous intraepithelial lesions and high-risk HPV-positive atypical squamous cells of undetermined significance in patients with and without colposcopic evident cervical disease. *Experimental and Therapeutic Medicine*. 2011;2:853-858.

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4 Appendices

Appendix A: Search strategies

1. Primary PICO search strategies

For Medline, Premedline, Embase and CENTRAL databases (via Ovid):

#	Searches
1	HPV.mp.
2	hr$HPV.mp.
3	papillomavirus.mp.
4	exp Papillomavirus Infections/
5	exp Papillomaviridae/
6	exp DNA Probes, HPV/
7	1 or 2 or 3 or 4 or 5 or 6
8	exp Vaginal Smears/
9	((cervi* or vagina* or pap) and (smear* or screen* or test*)).tw.
10	papanicolaou.tw.
11	LBC.mp.
12	cytolog$.mp.
13	8 or 9 or 10 or 11 or 12
14	exp Colposcopy/
15	colposcop$.mp.
16	14 or 15
17	randomized controlled trial.pt.
18	controlled clinical trial.pt.
19	placebo.ab.
20	randomi?ed.ab.
21	randomly.ab.
22	trial.ab.
23	groups.ab.
24	17 or 18 or 19 or 20 or 21 or 22 or 23
25	7 and 13 and 16 and 24
26	(negative adj5 colposcop*).mp.
27	(normal adj5 colposcop*).mp.
28	26 or 27
29	25 and 28
30	limit 29 to english language
31	limit 30 to humans

32	limit 31 to yr="2004 - 2015"
33	limit 32 to (conference abstract or conference paper or conference proceeding or "conference review" or editorial)
34	32 not 33
35	remove duplicates from 34

Used the Cochrane sensitivity maximizing filter for identifying randomized controlled trials (http://handbook.cochrane.org, accessed 12/09/2015)

ATSI search terms used

#	Searches
1	((exp Australia/ OR Australia$.ti,ab) AND (Oceanic ancestry group/ OR aborigin$.ti,ab. OR indigenous.mp.)) OR torres strait$ islander$.ti,ab

From the Lowitja Institute at http://www.lowitja.org.au/litsearch-background-information accessed 30/09/2013)

For Health Technology Assessments (HTA) and Database of Abstracts of Reviews of Effects (DARE) databases (via Ovid):

#	Searches
1	HPV.mp.
2	hr$HPV.mp.
3	papillomavirus.mp.
4	exp Papillomavirus Infections/
5	exp Papillomaviridae/
6	exp DNA Probes, HPV/
7	1 or 2 or 3 or 4 or 5 or 6
8	exp Vaginal Smears/
9	((cervi* or vagina* or pap) and (smear* or screen* or test*)).tw.
10	papanicolaou.tw.
11	LBC.mp.
12	cytolog$.mp.
13	8 or 9 or 10 or 11 or 12
14	exp Colposcopy/
15	colposcop$.mp.
16	14 or 15
17	(negative adj5 colposcop*).mp.
18	(normal adj5 colposcop*).mp.
19	17 or 18
20	7 and 13 and 16
21	19 and 20

For Cochrane Database of Systematic Reviews:

#	Searches
1	colposcop$.mp.
2	HPV.mp.
3	1 or 2

2. Secondary PICO search strategies

a. Specific for negative or normal colposcopy

For Medline, Premedline, Cochrane Central Register of Controlled trials and EMBASE databases (via Ovid):

#	Searches
1	(negative adj5 colposcop*).mp.
2	(normal adj5 colposcop*).mp.
3	1 or 2
4	remove duplicates from 3
5	limit 4 to english language
6	limit 5 to human
7	limit 6 to yr = "2004 -Current"

b. Broadened to identify studies dealing with low-grade cytology, HPV and colposcopy

For Medline, Premedline and CENTRAL databases (via Ovid):

#	Searches
1	HPV.mp.
2	hr$HPV.mp.
3	papillomavirus.mp.
4	exp Papillomavirus Infections/
5	exp Papillomaviridae/
6	exp DNA Probes, HPV/
7	1 or 2 or 3 or 4 or 5 or 6
8	hybrid capture.mp.
9	HC2.mp.
10	HCII.mp.
11	(hybrid adj5 capture).mp.
12	realtime.mp.

13	cervista.mp.
14	amplicor.mp.
15	cobas 4800.mp.
16	linear array.mp.
17	(linear adj3 array).mp.
18	papillocheck.mp.
19	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20	exp Polymerase Chain Reaction/
21	pcr.mp.
22	20 or 21
23	7 or 19 or 22
24	exp Vaginal Smears/
25	((cervi* or vagina*) and (smear* or screening* or test*)).tw.
26	(pap adj5 smear).tw.
27	papanicolaou.tw.
28	LBC.mp.
29	cytolog$.mp.
30	exp Uterine Cervical Dysplasia/
31	cervical dysplasia.mp.
32	(cervi* adj5 dysplasia).mp.
33	(dyskaryosis or dyskariosis).mp.
34	ASCUS.mp.
35	ASC US.mp.
36	ASC$US.mp.
37	ASC R.mp.
38	(atypical squamous adj4 cervi$).mp.
39	atypical endocervical.mp.
40	atypical gland$.mp.
41	AGUS.mp.
42	((borderline or low-grade) adj3 abnormal$).mp.
43	((borderline or low-grade) adj3 cytology).mp.
44	SIL.mp.
45	LSIL.mp.
46	L-SIL.mp.
47	LGSIL$.mp.
48	pLSIL$.mp.
49	dLSIL$.mp.

50	low-grade squamous intraepithelial.mp.
51	possible low-grade squamous intraepithelial.mp.
52	definite low-grade squamous intraepithelial.mp.
53	24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52
54	exp Colposcopy/
55	colposcop$.mp.
56	54 or 55
57	Surveillance.mp.
58	56 or 57
59	23 and 53 and 58

For Embase database (via Embase):

#	Searches
1.	'hpv 16'/exp OR 'hpv 16'
2.	'hpv18'/exp OR 'hpv18'
3.	'hpv31'/exp OR 'hpv31'
4.	'hpv33'/exp OR 'hpv33'
5.	'hpv35'/exp OR 'hpv35'
6.	'hpv45'/exp OR 'hpv45'
7.	'hpv 52'/exp OR 'hpv 52'
8.	'hpv 58'/exp OR 'hpv 58'
9.	'hpv'/exp OR 'hpv'
10.	'human papillomavirus'/exp OR 'human papillomavirus'
11.	'human papillomavirus test'
12.	hr*hpv
13.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
15.	'vagina smear'/exp OR 'vagina smear'
16.	'uterine cervix cytology'/exp OR 'uterine cervix cytology'
17.	'uterine cervix dysplasia'/exp OR 'uterine cervix dysplasia'
18.	cervi* OR vagina* AND (smear* OR screen* OR test*)
19.	pap* NEAR/5 smear*
20.	papanicolaou

21.	'papanicolaou test'/exp OR 'papanicolaou test'
22.	lbc
23.	cytolog*
24.	cervi* NEAR/5 dysplasia
25.	dyskaryosis OR dyskariosis
26.	ascus OR 'asc us' OR 'asc r'
27.	'asc-us' OR 'asc-r'
28.	atypical AND squamous NEAR/4 cervi*
29.	'atypical endocervical'
30.	atypical NEXT/1 gland*
31.	agus
32.	(borderline OR 'low-grade') NEAR/3 abnormal*
33.	(borderline OR 'low-grade') NEAR/3 cytology
35.	sil* OR lsil* OR 'l-sil' OR lgsil* OR plsil* OR dlsil* OR 'p/dlsil'
36.	'low-grade squamous intraepithelial'
37.	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32OR #33 OR #35 OR #36
38.	'colposcopy'/exp
39.	colposcop*
40.	surveillance
41.	#38 OR #39 OR #40
42.	#13 AND #37 AND #41
43.	#13 AND #37 AND #41 AND [2004-2015]/py
44.	#13 AND #37 AND #41 AND [2004-2015]/py AND [english]/lim
45.	#13 AND #37 AND #41 AND [2004-2015]/py AND [english]/lim AND [embase]/lim
46.	#13 AND #37 AND #41 AND [2004-2015]/py AND [english]/lim AND [embase]/lim AND [medline]/lim
47.	#44 NOT #46

For Health Technology Assessments (HTA) and Database of Abstracts of Reviews of Effects (DARE) databases (via OvidSP):

#	**Searches**
1	HPV.mp.

2	hr$HPV.mp.
3	papillomavirus.mp.
4	exp Papillomavirus Infections/
5	exp Papillomaviridae/
6	exp DNA Probes, HPV/
7	1 or 2 or 3 or 4 or 5 or 6
8	hybrid capture.mp.
9	HC2.mp.
10	HCII.mp.
11	(hybrid adj5 capture).mp.
12	realtime.mp.
13	cervista.mp.
14	amplicor.mp.
15	cobas 4800.mp.
16	linear array.mp.
17	(linear adj3 array).mp.
18	papillocheck.mp.
19	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20	exp Polymerase Chain Reaction/
21	pcr.mp.
22	20 or 21
23	7 or 19 or 22
24	exp Vaginal Smears/
25	((cervi* or vagina*) and (smear* or screening* or test*)).tw.
26	(pap adj5 smear).tw.
27	papanicolaou.tw.
28	LBC.mp.
29	cytolog$.mp.
30	exp Uterine Cervical Dysplasia/
31	cervical dysplasia.mp.
32	(cervi* adj5 dysplasia).mp.
33	(dyskaryosis or dyskariosis).mp.
34	ASCUS.mp.
35	ASC US.mp.
36	ASC$US.mp.
37	ASC R.mp.
38	(atypical squamous adj4 cervi$).mp.

39	atypical endocervical.mp.
40	atypical gland$.mp.
41	AGUS.mp.
42	((borderline or low-grade) adj3 abnormal$).mp.
43	((borderline or low-grade) adj3 cytology).mp.
44	SIL.mp.
45	LSIL.mp.
46	L-SIL.mp.
47	LGSIL$.mp.
48	pLSIL$.mp.
49	dLSIL$.mp.
50	low-grade squamous intraepithelial.mp.
51	possible low-grade squamous intraepithelial.mp.
52	definite low-grade squamous intraepithelial.mp.
53	24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52
54	exp Colposcopy/
55	colposcop$.mp.
56	54 or 55
57	Surveillance.mp.
58	56 or 57
59	23 and 53 and 58

Appendix B:

Level of evidence rating criteria – Risk assessment studies

Level	Study design
I	Meta-analysis or a systematic review of level II studies
II	Prospective cohort studies
III-1	All or none
III-2	Retrospective cohort studies
III-3	Case control studies
IV	Cross-sectional studies or case series

According to the standards of the National Health and Medical Research Council

Relevance of the Evidence

Rating	Relevance
1	Evidence of an effect on patient-relevant clinical outcomes including benefits and harms, quality of life and survival.
2	Evidence of an effect on a surrogate outcome* that has been shown to be predictive of patient-relevant outcomes for the same intervention.
3	Evidence of an effect on proven surrogate outcomes but for a different intervention.
4	Evidence of an effect on proven surrogate outcomes but for a different intervention and population.
5	Evidence confined to unproven surrogate outcomes.

**'surrogate outcome' refers to reasonable indicators of whether there has been some effect (e.g. blood pressure measurements or levels of serum cholesterol)*

Points for considering patient-relevant outcomes:
i) The goal of decision making in health care is to choose the intervention(s) (which may include doing nothing) that is (are) most likely to deliver the outcomes that patients find desirable.
ii) Surrogate outcomes (such as blood pressure measurements or levels of serum cholesterol) may be reasonable indicators of whether there has been some effect. However, they should not be the basis for clinical decisions unless they reliably predict an effect on the way the patient feels, otherwise they will not be of interest to the patient or their carers.
iii) All possible outcomes that are of most interest to patients (particularly harms) should be identified and evaluated.

Adapted from table 1.10 of: National Health and Medical Research Council. How to use the evidence: assessment and application of scientific evidence. Canberra: NHMRC; 2000.
http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/cp69.pdf

Appendix C:

Potentially relevant guidelines identified and reason why not adopted

Year	Organization	Title	Reason why not adopted
2012	American Society for Colposcopy and Cervical Pathology.	Updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors	Consensus based on literature searches and KPNC data
2012	Society of Obstetricians and Gynaecologists of Canada	Colposcopic management of abnormal cervical cytology and histology	Consensus based
2008	European Cancer Screening Network and European Cancer Network	European guidelines for quality assurance in cervical cancer screening: recommendations for clinical management of abnormal cervical cytology, Part 1	Unclear as to whether based on systematic reviews – full document no longer available at published website

Excluded Studies

Study	Reason for Exclusion
Adams 2006	Participants women with negative biopsy not negative colposcopy
Alouini 2015	Letter to editor
Bjerre 2008	No follow-up results for women with a normal colposcopy
Cantor 2008	No separate analysis for referral cytology of p/dLSIL
Carcopino 2012	No outcomes specifically for women with initial normal colposcopy
Carozzi 2013a	No outcomes specifically for women with initial normal colposcopy
Carozzi 2013b	No outcomes specifically for women with initial normal colposcopy
Castle 2009	Reports initial cytology and colposcopy results for cases only on follow-up
Castle 2011	No outcomes specifically for women with initial normal colposcopy
Davies 2015	No separate analysis for referral cytology of p/dLSIL
Del Pinto 201	No outcomes specifically for women with initial normal colposcopy and referral cytology of p/dLSIL
Elfgren 2005	No follow-up of women with negative colposcopy; cross-sectional results only
Gage 2010	No outcomes specifically for women with initial normal colposcopy
Giorgi Rossi 2013	No separate analysis for referral cytology of p/dLSIL
Huh 2014	No follow-up of women with negative colposcopy; cross-sectional results only
Jeronimo 2006	Review
Kourounis 2004	No outcomes of interest – histology not reported
Lanneau 2007	Did not include women with referral cytology of p/dLSIL
Luesley 2009	No separate analysis for referral cytology of p/dLSIL
Massad 2009	No outcomes specifically for women with normal colposcopy
Massad 2015	Commentary
Mesher 2011	No outcomes specifically for women with initial normal colposcopy
Porras 2012	No separate analysis for referral cytology of p/dLSIL
Pretorius 2004	Participants women with CIN2+ diagnosis
Pretorius 2006a	No separate analysis for referral cytology of p/dLSIL
Pretorius 2006b	Case series – no comparison of prognostic factors
Pretorius 2011	No separate analysis for referral cytology of p/dLSIL
Puertas 2011	Did not include women with referral cytology of p/dLSIL
Walker 2006	Outcomes for subsequent not initial normal colposcopy – no follow-up for negative colposcopy
Wiesenfeld 2015	Commentary
Winsley 2014	Participants women with negative biopsy not negative colposcopy
Yang 2008	No separate analysis for referral cytology of p/dLSIL

References: Excluded Studies

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