Systematic review report for questions 5b

PICO Question 5b: For women who are HPV positive with atypical glandular cells of undetermined significance (AGUS) or possible high grade glandular lesion (confirmed on review) and negative colposcopy what is the safety and effectiveness of repeating HPV and cytology testing when compared with treatment with excisional cone biopsy?

Population	Study design	Intervention	Control	Outcomes
Women who are HPV positive with AGUS or possible HGGA (confirmed on review) and colposcopy negative	Randomized or pseudo-randomized controlled trial	Repeat HPV and liquid based cytology testing at 6 months	Excisional cone biopsy	Cervical cancer mortality Other gynaecologic cancer diagnosis (endometrial, ovarian) Cervical cancer diagnosis Precancerous high grade lesion (including AIS) detection

AGUS = atypical glandular cells of undetermined significance; AIS = adenocarcinoma in situ; HGGA = high grade glandular lesion

Definitions

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

Possible high-grade glandular lesion corresponds to the category of atypical glandular cells, possibly neoplastic (AGC-FN) in the 2001 Bethesda System which corresponds to possible high grade glandular lesion.

1. METHODS

1.1 Searches for existing relevant guidelines

Relevant recent (2005 onwards) guidelines 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 PICO questions 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.

1.3 Inclusion Criteria for PICOs 5b

Selection criteria	Inclusion criteria
Study type	Intervention
Study design	Randomised controlled trial (RCT) or pseudo-randomised controlled trial or Systematic reviews or meta-analyses of RCTs or pseudo-randomised controlled trials
Population	Women who are HPV positive with atypical endocervical cells of undetermined significance, atypical glandular cells of undetermined significance or possible high grade glandular lesion, and colposcopy negative
Intervention	Repeat HPV and liquid based cytology testing at 6 months
Comparator	Excisional cone biopsy
Outcomes	Cervical cancer mortality or Cervical cancer diagnosis or Other gynaecologic cancer diagnosis (endometrial, ovarian) or Precancerous high grade lesion (including AIS) detection
Language	English
Publication period	After 31st December 2003 and before1st September 2015

Conference proceedings other than those from the EUROGIN 2015 were excluded.

2 RESULTS

2.1 Results of Guidelines Searches

Three sets of guidelines (listed in Appendix C) were identified that contained potentially relevant recommendations. These recommendations either were not based systematic reviews of the evidence or it was unclear as to whether they were based on systematic reviews of the evidence and thus were not adopted as they did not meet the pre-specified AGREE II criteria for adoption.

2.2 Results of Literature Searches

Figure 1 outlines the process of identifying relevant articles for the systematic reviews. 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 PICO question**. As such, there were no studies of Aboriginal and/or Torres Strait Islander women that met the inclusion criteria.

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**

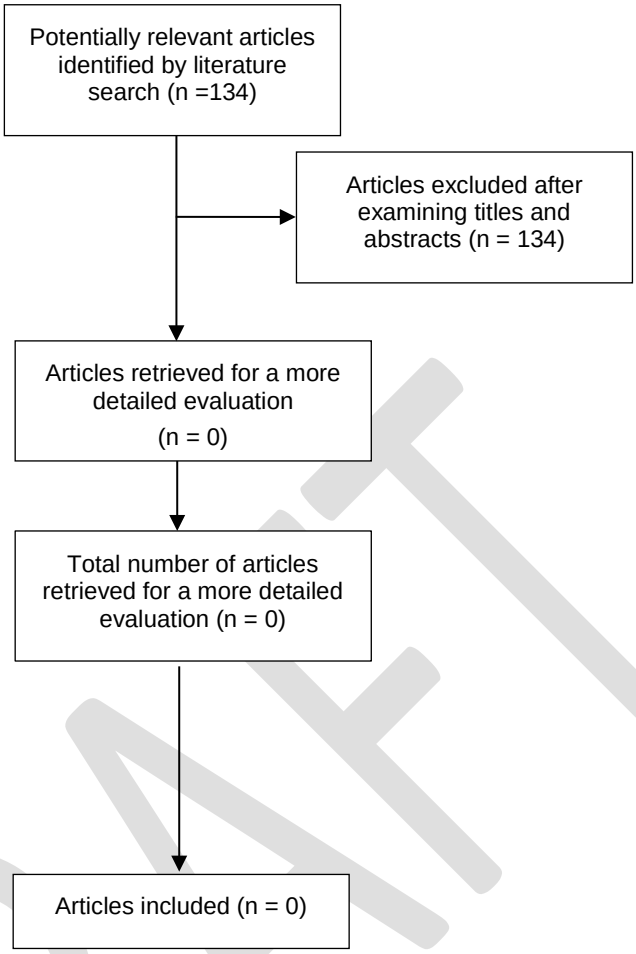

Figure 1. Process of inclusion and exclusion of studies

APPENDICES

Appendix A: Search strategies used

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

Appendix B:

NHMRC Evidence Hierarchy for Intervention studies

Level	Study design
I	Meta-analysis or a systematic review of level II studies
II	Randomised controlled trial or a phase III/IV clinical trial
III-1	Pseudo-randomised controlled trial or a meta-analysis/systematic review of level III-1 studies
III-2	Comparative study with concurrent controls: - Phase II clinical trial - Non-randomised, experimental trial9 - Controlled pre-test/post-test study - Adjusted indirect comparisons - Interrupted time series with a control group - Cohort study - Case-control study or a meta-analysis/systematic review of level III-2 studies
III-3	A comparative study without concurrent controls: - Phase I clinical trial - Historical control study - Two or more single arm study10 - Unadjusted indirect comparisons - Interrupted time series without a parallel control group or a meta-analysis/systematic review of level III-3 studies
IV	Case series with either post-test or pre-test/post-test outcomes or a meta-analysis/systematic review of level IV studies

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

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