

# Follow-up strategies after treatment (large loop excision of the transformation zone (LLETZ)) for cervical intraepithelial neoplasia (CIN): Impact of human papillomavirus (HPV) test (Review)

van der Heijden E, Lopes AD, Bryant A, Bekkers R, Galaal K



**THE COCHRANE  
COLLABORATION®**

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2015, Issue 1

<http://www.thecochranelibrary.com>

**WILEY**

## TABLE OF CONTENTS

HEADER . . . . .	1
ABSTRACT . . . . .	1
PLAIN LANGUAGE SUMMARY . . . . .	2
BACKGROUND . . . . .	2
OBJECTIVES . . . . .	4
METHODS . . . . .	4
RESULTS . . . . .	5
DISCUSSION . . . . .	5
AUTHORS' CONCLUSIONS . . . . .	6
ACKNOWLEDGEMENTS . . . . .	7
REFERENCES . . . . .	7
CHARACTERISTICS OF STUDIES . . . . .	11
DATA AND ANALYSES . . . . .	18
APPENDICES . . . . .	19
CONTRIBUTIONS OF AUTHORS . . . . .	21
DECLARATIONS OF INTEREST . . . . .	21
SOURCES OF SUPPORT . . . . .	21
DIFFERENCES BETWEEN PROTOCOL AND REVIEW . . . . .	21
NOTES . . . . .	23

[Intervention Review]

# Follow-up strategies after treatment (large loop excision of the transformation zone (LLETZ)) for cervical intraepithelial neoplasia (CIN): Impact of human papillomavirus (HPV) test

Esther van der Heijden<sup>1</sup>, Alberto D Lopes<sup>2</sup>, Andrew Bryant<sup>3</sup>, Ruud Bekkers<sup>1</sup>, Khadra Galaal<sup>2</sup>

<sup>1</sup>Department of Gynaecology and Obstetrics, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands. <sup>2</sup>Gynaecological Oncology, Princess Alexandra Wing, Royal Cornwall Hospital, Truro, UK. <sup>3</sup>Institute of Health & Society, Newcastle University, Newcastle upon Tyne, UK

Contact address: Khadra Galaal, Gynaecological Oncology, Princess Alexandra Wing, Royal Cornwall Hospital, Truro, Cornwall, TR1 3LJ, UK. [Khadra.Galaal@rcht.cornwall.nhs.uk](mailto:Khadra.Galaal@rcht.cornwall.nhs.uk). [khadragalaal@yahoo.co.uk](mailto:khadragalaal@yahoo.co.uk).

**Editorial group:** Cochrane Gynaecological Cancer Group.

**Publication status and date:** New, published in Issue 1, 2015.

**Review content assessed as up-to-date:** 6 August 2013.

**Citation:** van der Heijden E, Lopes AD, Bryant A, Bekkers R, Galaal K. Follow-up strategies after treatment (large loop excision of the transformation zone (LLETZ)) for cervical intraepithelial neoplasia (CIN): Impact of human papillomavirus (HPV) test. *Cochrane Database of Systematic Reviews* 2015, Issue 1. Art. No.: CD010757. DOI: 10.1002/14651858.CD010757.pub2.

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

## ABSTRACT

### Background

Development of cancer of the cervix is a multi-step process as before cervical cancer develops, cervical cells undergo changes and become abnormal. These abnormalities are called cervical intraepithelial neoplasia (CIN) and are associated with increased risk of subsequent invasive cancer of the cervix. Oncogenic high-risk human papillomavirus (hrHPV), the causative agent of cervical cancer and its precursor lesions, is present in up to one-third of women following large loop excision of the transformation zone (LLETZ) treatment and is associated with increased risk of residual disease and disease recurrence. HPV testing may serve as a surveillance tool for identifying women at higher risk of recurrence. High-risk human papillomavirus testing will enable us to identify women at increased risk of residual or recurrent CIN and therefore will allow us to offer closer surveillance and early treatment, when indicated.

### Objectives

- To evaluate the effectiveness and safety of hrHPV testing after large loop excision of the transformation zone (LLETZ) treatment
- To determine optimal follow-up management strategies following LLETZ treatment according to hrHPV status

### Search methods

We searched the Cochrane Gynaecological Cancer Review Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), PubMed and PsycINFO up to August 2013. We searched registers of clinical trials, abstracts of scientific meetings and reference lists of included studies, and we contacted experts in the field.

### Selection criteria

We searched for randomised control trials (RCTs) that compared follow-up management strategies following LLETZ treatment for CIN.

---

**Follow-up strategies after treatment (large loop excision of the transformation zone (LLETZ)) for cervical intraepithelial neoplasia (CIN): Impact of human papillomavirus (HPV) test (Review)**

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

## Data collection and analysis

Two review authors independently assessed whether potentially relevant studies met the inclusion criteria. No trials were found; therefore no data were analysed.

## Main results

The search identified 813 references on MEDLINE, 418 on EMBASE, 22 on CINAHL, 666 on PubMed, 291 on PsycINFO and 145 on CENTRAL. When all references were imported into EndNote and duplications were removed, 1348 references remained. Initial screening of titles and abstracts of these references revealed that 42 references were potentially eligible for this review. After reading the full-text versions, we identified no relevant trials comparing hrHPV and cytology testing versus cytology testing alone for detecting residual or recurrent disease during follow-up to LLETZ treatment of adult women with CIN.

We found no evidence on the effects of hrHPV and cytology testing on residual or recurrent CIN2 or higher lesions, anxiety and psychosexual morbidity outcomes in women undergoing colposcopy and treatment for CIN.

## Authors' conclusions

We found no evidence from RCTs to inform decisions about the best surveillance strategy for women following treatment for CIN. A prognostic systematic review is needed to investigate the risk of developing recurrent cervical intraepithelial neoplasia 2+ (CIN2+) in women with a positive hrHPV test after large loop excision of the transformation zone (LLETZ) treatment.

## PLAIN LANGUAGE SUMMARY

### Follow-up strategies for women following treatment for CIN: Impact of HPV testing

#### Background

It is widely accepted that infection with high-risk human papillomavirus (hrHPV) is associated with development of precancerous changes, namely, cervical intraepithelial neoplasia (CIN) and cervical cancer. It is also accepted that women who develop high-grade CIN and subsequently receive treatment with a procedure called large loop excision of the transformation zone (LLETZ), which uses a wire loop to remove abnormal cells, are at greater risk for developing further CIN than women who have never had CIN. Therefore, these women need regular follow-up assessment to detect additional abnormalities.

#### Main findings

We searched for randomised control trials (RCTs) that compared follow-up management strategies following LLETZ treatment for CIN. We checked 1348 titles and abstracts of potentially relevant references, but we identified no randomised controlled trials (RCTs) that met our inclusion criteria. We identified trials of interest, but they were deemed not relevant because of their focus on diagnostic outcomes and examination of how sensitive tests are, rather than on the effects of different follow-up strategies on long-term outcomes. Currently no evidence indicates whether hrHPV post-treatment testing is better or worse in terms of important long-term clinical outcomes. This review highlights the need for good quality trials in this area that do not focus solely on the diagnostic accuracy of testing.

#### Conclusion

We found no evidence from RCTs to inform decisions about the best surveillance strategy following treatment for CIN. A prognostic systematic review is needed to investigate the risks and benefits of different follow-up strategies for women after LLETZ treatment.

## Description of the condition

## BACKGROUND

Development of cancer of the cervix is a multi-step process as be-

fore cervical cancer develops, cervical cells undergo changes and become abnormal. These abnormalities are called cervical intraepithelial neoplasia (CIN) and are associated with increased risk of subsequent invasive cancer of the cervix (Pinto 2000). Cervical cancer is the second most common cancer among women up to 65 years of age and is the most frequent cause of death from gynaecological cancers worldwide. A woman's risk of developing cervical cancer by age 65 ranges from 0.69% in developed countries to 1.38% in developing countries (GLOBOCAN 2008). In Europe, about 60% of women with cervical cancer were alive five years after diagnosis (EUROCARE 2003). It is widely accepted that infection with onogenic high-risk human papillomavirus (hrHPV) is associated with development of CIN and cancer (Galaal 2011; McCredie 2008; Pinto 2000). Strong epidemiological evidence demonstrates that the major risk factor for development of preinvasive or invasive carcinoma of the cervix is HPV infection (Brisson 1994). Increased exposure to hrHPV is related to other known risk factors including high parity, increasing numbers of sexual partners, young age at first intercourse, low socioeconomic status and a history of smoking (Brisson 1994; Schiffman 1993).

## Description of the intervention

Large loop excision of the transformation zone (LLETZ), also described as the loop electrosurgical excision procedure (LEEP), is highly effective in the treatment of patients with CIN and early invasive disease (Federation of Gynecology and Obstetrics (FIGO) stage 1A1). However, following treatment, 4% to 17% of women have CIN2 or greater as the result of residual (persistent CIN confirmed on biopsy within two years of follow-up) or recurrent disease (CIN identified after two years of negative cytology) (Alvarez 1994; Bollen 1999; Jain 2001; Mitchell 1998). Previous studies have shown that risk of residual or recurrent disease is consistently associated with large lesion size before LLETZ, endocervical extension of the disease and incomplete excision of the lesion (Brockmeyer AD 2003; Costa 2003; Houfflin Debarge 2003). However, even women with clear excision margins are at risk for disease recurrence (Paraskevaidis E 2000). In addition, the risk of developing invasive cancer after treatment for high-grade CIN is five times higher than in the general population (Brown 1991; Souter 2006). This was the justification for closer surveillance of these groups of women with annual cytology and colposcopy follow-up for 10 years after treatment (Jones 2011). Therefore, women treated for CIN2 or CIN3 were recommended to have cytological follow-up six months and 12 months after treatment, and annual cytology for the next nine years, before returning to screening at the routine interval (Luesley 2010).

Numerous studies have suggested that hrHPV testing is more sensitive than cytology and has negative predictive value of almost 100% for detection of CIN2+ (Bias 2009; Kocken 2012; Kreimer 2006). It is suggested that "double-negative" HPV DNA and cervical cytology testing indicate higher prognostic assurance against

risk of future CIN3 than three subsequent negative conventional cervical cytology tests and may safely allow three-year or longer screening intervals for such low-risk women (Lörincz 2003). Since April 2012 the algorithm in the UK is to have 'HPV test of cure' six months after treatment for CIN. The HPV test of cure uses a woman's hrHPV status to assess her risk of having residual or recurrent disease after treatment for CIN (NHSCSP 2011). It is performed six months after treatment and includes both cytology and HPV testing. Women whose cytology samples are reported as high-grade dyskaryosis or worse are returned to colposcopy without undergoing an HPV test, then are followed up according to national guidelines (Arbyn 2007). All other women are treated according to their hrHPV test result: Those who are hrHPV-positive at test of cure are referred back to colposcopy, whereas those who are hrHPV-negative are recalled in three years and can revert to routine recall thereafter (NHSCSP 2011).

## How the intervention might work

Oncogenic high-risk human papillomavirus (hrHPV), the causative agent of cervical cancer and its precursor lesions, is present in up to one-third of women following LLETZ and is associated with increased risk of disease recurrence (Costa 2003; Paraskevaidis E 2000). Therefore, hrHPV testing may serve as a surveillance tool for identifying women at high risk of recurrence. High-risk HPV persistence after high-grade CIN removal may be associated with residual lesions or risk of disease recurrence (Sarian 2004). High-risk HPV testing will enable us to identify women at increased risk of recurrent CIN, and therefore will allow us to offer closer surveillance and early treatment when indicated. An advantage of hrHPV test of cure is improved sensitivity for the detection of residual recurrent disease; also women whose follow-up samples test negative for hrHPV need only return for two or three routine cytology tests (depending on their age) during the decade after treatment instead of requiring a minimum of 10 years of annual follow-up cytology, again reflecting the negative predictive value of a negative hrHPV test (NHSCSP 2011).

In addition, post-treatment hrHPV testing could be useful in the follow-up of patients after completion of treatment. In cases of negative post-treatment hrHPV testing, the frequency of follow-up could be reduced, particularly among patients with free margins (Houfflin Debarge 2003).

## Why it is important to do this review

Following excision of CIN using LLETZ, post-treatment CIN rates of 4% to 17% have been reported (Alvarez 1994; Bollen 1999; Jain 2001; Mitchell 1998). Therefore, follow-up after local treatment for CIN is mandatory because of the late occurrence of cervical cancer over a period of 20 years (Ghaem-Maghani 2007; Souter 1997). To prevent cervical cancer, early detection of treat-

ment failure is important. It has been suggested that persistence of hrHPV represents an independent risk factor for recurrent disease and constitutes the basis for introducing hrHPV testing in patients treated for high-grade CIN (Fallani 2008; Nam 2009). However, this policy of reducing the follow-up interval among patients with double-negative cytology and hrHPV has not been directly compared with cytological follow-up six months and 12 months after treatment and annual cytology for the next nine years before a return to screening at the routine interval. Therefore, a systematic review of current evidence is needed for a reliable evaluation of potential benefits and risks of these surveillance policies.

## OBJECTIVES

- To evaluate the effectiveness and safety of hrHPV testing after large loop excision of the transformation zone (LLETZ) treatment.
- To determine optimal follow-up strategies following LLETZ treatment according to hrHPV status.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised controlled trials (RCTs).

#### Types of participants

Adult women (18 years of age or older) undergoing LLETZ for the treatment of CIN.

#### Types of interventions

##### Intervention

Post-treatment hrHPV testing.

##### Control

Conventional cervical screening with a Papanicolaou test (Pap smear).

#### Types of outcome measures

##### Primary outcomes

- Residual or recurrent, or both, CIN2 or higher lesion.

##### Secondary outcomes

- Anxiety, measured using a validated scale.
- Psychosexual scores, measured using a validated scale.

## Search methods for identification of studies

Papers in all languages were sought and translations carried out when necessary.

### Electronic searches

See [Cochrane Gynaecological Cancer Group](#) methods used in reviews.

We searched the following electronic databases.

- The Cochrane Gynaecological Cancer Collaborative Review Group's Trial Register.
- The Cochrane Central Register of Controlled Trials (CENTRAL) to August 2013.
- MEDLINE to August 2013.
- EMBASE to August 2013.

MEDLINE, EMBASE, CENTRAL, CINAHL and PsycINFO search strategies based on terms related to the review topic are presented in [Appendix 1](#), [Appendix 2](#) and [Appendix 3](#), respectively. All relevant articles identified were found on PubMed; using the 'Related articles' feature, we performed a further search for newly published articles.

### Searching other resources

#### Unpublished and grey literature

We searched *metaRegister* (<http://www.controlled-trials.com/rct>), Physicians Data Query (<http://www.nci.nih.gov>), <http://www.clinicaltrials.gov> and <http://www.cancer.gov/clinicaltrials> for ongoing trials.

We searched conference proceedings and abstracts through ZETOC (<http://zetoc.mimas.ac.uk>) and WorldCat Dissertations.

#### Handsearching

We handsearched the citation lists of included studies, key textbooks and previous systematic reviews and contacted experts in the field to identify further reports of trials. We handsearched reports of conferences in the following sources.

- *Gynecologic Oncology* (Annual Meeting of the Society of Gynecologic Oncology).
- *International Journal of Gynecological Cancer* (Annual Meeting of the International Gynecological Cancer Society)
- *British Journal of Cancer*
- British Association for Cancer Research Meeting
- Annual Meeting of the European Society of Medical Oncology (ESMO)
- Annual Meeting of the American Society of Clinical Oncology (ASCO)

We also searched the following websites.

- British Gynaecological Cancer Society ([www.bgcs.org.uk](http://www.bgcs.org.uk)).
- European Society of Gynaecological Oncology ([www.esgo.org](http://www.esgo.org)).
- Society of Gynecologic Oncology ([www.sgo.org](http://www.sgo.org)).

### Correspondence

We planned to contact authors of relevant trials to clarify information on the quality of randomisation and other details.

### Data collection and analysis

We downloaded to the reference management database, EndNote, all titles and abstracts retrieved by electronic searching. We removed duplicates, and the remaining references were examined independently by two review authors (EH, KG). These two review authors screened the references by titles and abstracts and eliminated references that were not related to the research question. When both review authors agreed on exclusion of a reference, no further action was taken. When one or both of the review authors determined that the article may have been eligible for inclusion, we obtained the full-text article. Each review author then independently decided whether these studies were eligible. We resolved disagreements about inclusion by discussion. We contacted study authors when information required for a decision on whether a study was eligible was missing. We were not blinded to article titles or authors nor to journal titles.

All references were ultimately excluded, as they did not meet the inclusion criteria. We identified no ongoing randomised controlled trials that met our inclusion criteria through our searches of the grey literature. In future updates of this review, we will employ the methods outlined under [Differences between protocol and review](#).

## RESULTS

### Description of studies

#### Results of the search

Through our searches, we identified 813 references on MEDLINE, 418 on EMBASE, 22 on CINAHL, 666 on PubMed, 291 on PsycINFO and 145 on CENTRAL. When all references had been imported into EndNote and all duplications removed, 1348 references remained. Initial screenings of titles and abstracts of these references revealed that 42 references were potentially eligible for inclusion in this review. After reading the full-text versions, we identified no relevant studies.

### Included studies

No trials met the inclusion criteria.

### Excluded studies

A total of 42 references were excluded from the review; 37 were excluded because they were not RCTs ([Aerssens 2009](#); [Almog 2003](#); [Alonso 2006](#); [Bae 2007](#); [Bar-Am 2003](#); [Bekkers 2002](#); [Bollen 1999](#); [Brismar 2009](#); [Cecchini 2004](#); [Chao 2004](#); [Costa 2003](#); [Dogan 2011](#); [Fambrini 2008](#); [Houfflin Debarge 2003](#); [Jancar 2006](#); [Jeong 2009](#); [Jones 2011](#); [Kocken 2011](#); [Korolenkova 2011](#); [Kucera 2001](#); [Leguevaque 2010](#); [Mikolajczyk 2011](#); [Nagai 2000](#); [Nagai 2004](#); [Prato 2008](#); [Sarian 2004](#); [Sarian 2004a](#); [Smart 2010](#); [Tachezy 2006](#); [Takac 2008](#); [Trobe 2011](#); [Valasoulis 2011](#); [van Ham 2007](#); [Venturoli 2008](#); [Verguts 2006](#); [Young 2010](#); [Zielinski 2003](#)); two references ([Castle 2009](#); [Taylor 2011](#)) were relevant RCTs, but [Castle 2009](#) did not report on residual disease, and [Taylor 2011](#) merged HPV testing results with data from other intervention groups and analysed them as one; therefore no appropriate comparison was available.

Two references were RCTs ([Bias 2009](#); [Kreimer 2006](#)) that randomly assigned women to the HPV test plus cytology combination group or the cytology test alone group, but they did not compare follow-up strategies; [Bias 2009](#) was an RCT that included 204 women diagnosed with high-grade cervical intraepithelial neoplasia lesions (CIN2-3) who were treated with large loop excision of the transformation zone (LLETZ), cold-knife conisation; or laser conisation. However, no comparison was performed of the two modalities of follow-up management strategies used following treatment for CIN. Similarly, [Kreimer 2006](#) was an RCT that included 610 women who underwent the loop electrosurgical excision procedure (LEEP) with a primary endpoint of post-LEEP detection of CIN2+, but the two modalities of follow-up management strategies after treatment for CIN were not compared.

### Risk of bias in included studies

No trials were found; therefore the risk of bias tool was not applied.

### Effects of interventions

No data were available.

## DISCUSSION

### Summary of main results

No consensus has been reached regarding the duration of post-treatment surveillance, but patients treated for cervical intraepithelial neoplasia (CIN) are at increased risk for cervical cancer as compared with the general population for at least 10 years after treatment (Leguevaque 2010). A test that predicts successful outcomes after treatment for CIN allowing reduction in the follow-up period would be particularly helpful. Several studies suggest that follow-up after treatment should combine the high-risk human papillomavirus (hrHPV) test with conventional cytology, as it identifies patients with a high risk of recurrence. Women are managed according to their hrHPV test result: Those who are hrHPV-positive at test of cure are referred back to colposcopy, whereas those who are hrHPV-negative are recalled in three years and can revert to routine recall thereafter (Leguevaque 2010).

This review identified no studies that compared post-treatment hrHPV testing with cytology 'test of cure' versus post-treatment cytological follow-up at six months and 12 months after treatment, and annual cytology for the next nine years before a return to screening at the routine interval. No randomised trials have directly compared the long-term outcomes of two follow-up management strategies. However, several studies have evaluated the risk of persistent recurrence of CIN after treatment. No studies have compared long-term outcomes (high-grade CIN (CIN2+) and cervical cancer rates) of these two treatment strategies. Studies have found similar short-term high-grade CIN rates in women who underwent hrHPV testing as part of their follow-up strategy. However, this would be expected, as in a randomised study, post-treatment groups should be well balanced and the actual treatment (large loop excision of the transformation zone (LLETZ)) the same in both groups, hence similar high-grade residual disease. A prognostic review, looking at the risk of developing recurrent high-grade CIN and cervical cancer among women with a positive hrHPV test after LLETZ treatment, would be valuable.

### Quality of the evidence

No studies met the inclusion criteria for this review, so no evidence is available for assessment.

### Potential biases in the review process

A comprehensive search including a thorough search of the grey literature was performed; all studies were sifted and data extracted independently by at least two review authors. The review was restricted to randomised controlled trials (RCTs), which provide the strongest level of available evidence. Hence we made every attempt to minimise bias in the review process. The greatest threat to the validity of this review is likely to be the possibility of publication bias (i.e. studies that did not find the treatment to have been effective may not have been published). We were unable to assess this possibility, as we found no eligible trials.

### Agreements and disagreements with other studies or reviews

We found no studies directly comparing the two modalities of follow-up management strategies after treatment for CIN. Clinical factors for recurrence, including the presence of positive endocervical margins, remain an important factor.

We identified no studies that reported on anxiety or psychosexual outcomes. However, we identified one relevant prospective study (Kocken 2011) that reported on disease recurrence in terms of positive versus negative hrHPV results in women who underwent hrHPV testing with cytology. Women with negative results for co-testing (cytology and hrHPV) had five-year risk of CIN grade 2+ of 1.0% (95% confidence interval (CI) 0.2 to 4.6) and 10-year risk of 3.6% (95% CI 1.1 to 10.7). The five-year risk of CIN grade 3 or higher was 0.0% (95% CI 0.0 to 3.0), and the 10-year risk was 0.0% (95% CI 0.0 to 5.3). We did identify two RCTs (Bias 2009; Kreimer 2006) (including 552 women in total), but they did not meet our inclusion criteria because of their focus on diagnostic outcomes and examination of the sensitivity/specificity of hrHPV testing for residual disease. These trials found no differences in risk of residual disease at two years between women who received hrHPV testing with cytology and those who received cytology alone. This would be expected, as the intervention to prevent CIN2+ was the same (LLETZ), thus demonstrating that the comparison groups were well balanced. These studies also suggest that an added hrHPV test may confer an advantage over the cervical smear test alone, as data suggest that women with negative hrHPV testing during follow-up after treatment for high-grade CIN are at low risk for CIN2+ and could return to a routine three-yearly screening programme. Data on anxiety and psychosexual outcomes were not reported in either trial.

## AUTHORS' CONCLUSIONS

### Implications for practice

We found no current evidence from RCTs to guide optimal follow-up strategies in the treatment of women with CIN2+.

A prognostic review investigating the risk of developing recurrent cervical intraepithelial neoplasia 2+ (CIN2+) in women with a positive hrHPV test after LLETZ treatment is required.

### Implications for research

- With the move to primary hrHPV screening in several countries, further studies comparing primary hrHPV testing post treatment for CIN versus hrHPV and cytology are needed to determine the optimal follow-up strategy. Primary hrHPV screening has greater sensitivity compared with cytology (average 27%) but has lower specificity (average 8%) (Franco 2003). Follow-up strategies incorporating hrHPV testing alone would



allow the detection of higher percentages of women with recurrent abnormalities, as hrHPV testing has higher sensitivity compared with cytology alone. In many countries hrHPV testing is used in both screening and follow-up strategies. Therefore we would recommend that future studies should be designed to compare hrHPV testing alone versus hrHPV and cytology testing in the follow-up treatment for high-grade CIN. This would allow us to evaluate the effects of hrHPV testing added to the current follow-up strategy.

- Ideally, well-designed large multi-centre (ideally multi-national) RCTs addressing hrHPV testing in the follow-up of treatment for CIN2+ are needed. Trial authors should follow the CONSORT statement checklist in providing complete and clear documentation (Hopewell 2008).
- Data on disease recurrence ideally should include time-to-event outcomes when results can be presented in six-month

intervals.

- Trials are needed to evaluate interventions introducing anxiety and psychosexual outcomes in relation to hrHPV testing.

## ACKNOWLEDGEMENTS

We thank Jo Morrison for clinical and editorial advice, Jane Hayes for the search strategy design and Gail Quinn and Clare Jess for their contributions to the editorial process. We also thank the referees for many helpful comments and suggestions.

The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane Gynaecological Cancer Group.

The views and opinions expressed herein are those of the review authors and do not necessarily reflect those of the NIHR, the National Health Service (NHS) or the Department of Health.

## REFERENCES

### References to studies excluded from this review

#### Aerssens 2009 {published data only}

Aerssens A, Claeys P, Beerens E, Garcia A, Weyers S, Van Renterghem L, et al. Prediction of recurrent disease by cytology and HPV testing after treatment of cervical intraepithelial neoplasia. *Cytopathology* 2009;20(1):27–35.

#### Almog 2003 {published data only}

Almog B, Gamzu R, Kuperminc MJ, Levin I, Fainaru O, Niv J, et al. Human papilloma virus testing in patient follow-up post cone biopsy due to high-grade cervical intraepithelial neoplasia. *Gynecologic Oncology* 2003;88(3):345–50.

#### Alonso 2006 {published data only}

Alonso I, Torne A, Puig-Tintore LM, Esteve R, Quinto L, Campo E, et al. Pre- and post-conization high-risk HPV testing predicts residual/recurrent disease in patients treated for CIN 2-3. *Gynecologic Oncology* 2006;103(2):631–6.

#### Bae 2007 {published data only}

Bae JH, Kim CJ, Park TC, Namkoong SE, Park JS. Persistence of human papillomavirus as a predictor for treatment failure after loop electrosurgical excision procedure. *Internal Journal of Gynecological Cancer* 2007;17(6):1271–7.

#### Bar-Am 2003 {published data only}

Bar-Am A, Gamzu R, Levin I, Fainaru O, Niv J, Almog B. Follow-up by combined cytology and human papillomavirus testing for patients post-cone biopsy: results of a long-term follow-up. *Gynecologic Oncology* 2003;91(1):149–53.

#### Bekkers 2002 {published data only}

Bekkers RL, Melchers WJ, Bakkers JM, Hanselaar AG, Quint WG, Boonstra H, et al. The role of genotype-specific

human papillomavirus detection in diagnosing residual cervical intraepithelial neoplasia. *International Journal of Cancer* 2002;102(2):148–51.

#### Bias 2009 {published data only}

Bais AG, Eijkemans MJ, Rebolj M, Snijders PJ, Verheijen RH, van M, et al. Post-treatment CIN: randomised clinical trial using hrHPV testing for prediction of residual/recurrent disease. *International Journal of Cancer* 2009;124(4):889–95.

#### Bollen 1999 {published data only}

Bollen LJM, Tjong-A-Hung SP, Van Velden J, Mol BW, Ten FWJ, Ter J, et al. Prediction of recurrent and residual cervical dysplasia by human papillomavirus detection among patients with abnormal cytology. *Gynecologic Oncology* 1999;72(2):199–201.

#### Brismar 2009 {published data only}

Brismar S, Johansson B, Borjesson M, Arbyn M, Andersson S. Follow-up after treatment of cervical intraepithelial neoplasia by human papillomavirus genotyping. *American Journal of Obstetrics and Gynecology* 2009;201(1):17.e1–8.

#### Castle 2009 {published data only}

Castle PE, Kreimer AR, Wacholder S, Wheeler CM, Koutsky LA, Rydzak G, et al. Influence of loop electrosurgical excision procedure on subsequent acquisition of new human papillomavirus infections. *Journal of Infectious Disease* 2009;199(11):1612–20.

#### Cecchini 2004 {published data only}

Cecchini S, Carozzi F, Confortini M, Zappa M, Ciatto S. Persistent human papilloma virus infection as an indicator of risk of recurrence of high-grade cervical intraepithelial neoplasia treated by the loop electrosurgical excision procedure. *Tumori* 2004;90(2):225–8.

- Chao 2004** *{published data only}*  
Chao A, Lin CT, Hsueh S, Chou HH, Chang TC, Chen MY, et al. Usefulness of human papillomavirus testing in the follow-up of patients with high-grade cervical intraepithelial neoplasia after conization. *American Journal of Obstetrics and Gynecology* 2004;**190**(4):1046–51.
- Costa 2003** *{published data only}*  
Costa S, De Simone P, Venturoli S, Cricca M, Zerbini ML, Musiani M, et al. Factors predicting human papillomavirus clearance in cervical intraepithelial neoplasia lesions treated by conization. *Gynecologic Oncology* 2003;**90**(2):358–65.
- Dogan 2011** *{published data only}*  
Dogan NU, Salman MC, Yuce K. The role of HPV DNA testing in the follow-up of cervical intraepithelial neoplasia after loop electrosurgical excision procedure. *Archives of Gynecology and Obstetrics* 2011;**283**(4):871–7.
- Fambrini 2008** *{published data only}*  
Fambrini M, Penna C, Pieralli A, Bussani C, Fallani MG, Andersson KL, et al. PCR detection rates of high risk human papillomavirus DNA in paired self-collected urine and cervical scrapes after laser CO2 conization for high-grade cervical intraepithelial neoplasia. *Gynecologic Oncology* 2008;**109**(1):59–64.
- Houfflin Debarge 2003** *{published data only}*  
Houfflin Debarge V, Collinet P, Vinatier D, Ego A, Dewilde A, Borman F, et al. Value of human papillomavirus testing after conization by loop electrosurgical excision for high-grade squamous intraepithelial lesions. *Gynecologic Oncology* 2003;**90**(3):587–92.
- Jancar 2006** *{published data only}*  
Jancar N, Rakar S, Poljak M, Fujs K, Kocjan BJ, Vrtacnik-Bokal E. Efficiency of three surgical procedures in eliminating high-risk human papillomavirus infection in women with precancerous cervical lesions. *European Journal of Gynaecological Oncology* 2006;**27**(3):239–42.
- Jeong 2009** *{published data only}*  
Jeong NH, Lee NW, Kim HJ, Kim T, Lee KW. High-risk human papillomavirus testing for monitoring patients treated for high-grade cervical intraepithelial neoplasia. *The Journal of Obstetrics and Gynaecology Research* 2009;**35**(4):706–11.
- Jones 2011** *{published data only}*  
Jones J, Saleem A, Rai N, Shylasree TS, Ashman S, Gregory K, et al. Human papillomavirus genotype testing combined with cytology as a 'test of cure' post treatment: the importance of a persistent viral infection. *Journal of Clinical Virology* 2011;**52**(2):88–92.
- Kocken 2011** *{published data only}*  
Kocken M, Helmerhorst TJ, Berkhof J, Louwers JA, Nobbenuis MA, Bais AG, et al. Risk of recurrent high-grade cervical intraepithelial neoplasia after successful treatment: a long-term multi-cohort study. *The Lancet Oncology* 2011;**12**(5):441–50.
- Korolenkova 2011** *{published data only}*  
Korolenkova LI. [Value of HPV (hybrid capture 2) testing for assessing the effectiveness of conservative surgical treatment in CIN2-3/carcinoma in situ and microinvasive cervical cancer]. *Voprosy Onkologii* 2011;**57**(3):322–6.
- Kreimer 2006** *{published data only}*  
Kreimer AR, Guido RS, Solomon D, Schiffman M, Wacholder S, Jeronimo J, et al. Human papillomavirus testing following loop electrosurgical excision procedure identifies women at risk for posttreatment cervical intraepithelial neoplasia grade 2 or 3 disease. *Cancer Epidemiology Biomarker and Prevention* 2006;**15**(5):908–14.
- Kucera 2001** *{published data only}*  
Kucera E, Sliutz G, Czerwenka K, Breitenecker G, Leodolter S, Reinthaller A. Is high-risk human papillomavirus infection associated with cervical intraepithelial neoplasia eliminated after conization by large-loop excision of the transformation zone?. *European Journal of Obstetrics Gynecology and Reproductive Biology* 2001;**100**(1):72–6.
- Leguevaque 2010** *{published data only}*  
Leguevaque P, Motton S, Decharme A, Soule-Tholy M, Escourrou G, Hoff J. Predictors of recurrence in high-grade cervical lesions and a plan of management. *European Journal of Surgical Oncology* 2010;**36**(11):1073–9.
- Mikolajczyk 2011** *{published data only}*  
Mikolajczyk K, Kedzia W, Zaba R, Silny W. Evaluation of HPV DNA HR assay in females as a marker of recurrent disease following treatment of cervical intraepithelial neoplasia. *Ginekologia Polska* 2011;**82**(9):670–4.
- Nagai 2000** *{published data only}*  
Nagai Y, Maehama T, Asato T, Kanazawa K. Persistence of human papillomavirus infection after therapeutic conization for CIN 3: is it an alarm for disease recurrence?. *Gynecologic Oncology* 2000;**79**(2):294–9.
- Nagai 2004** *{published data only}*  
Nagai N, Mukai K, Oshita T, Shiroyama Y, Ohama K. Human papillomavirus DNA status after loop excision for cervical intraepithelial neoplasia grade III: a prospective study. *International Journal of Molecular Medicine* 2004;**13**(4):589–93.
- Prato 2008** *{published data only}*  
Prato B, Ghelardi A, Gadducci A, Marchetti I, Di Cristofano C, Di Coscio G, et al. Correlation of recurrence rates and times with posttreatment human papillomavirus status in patients treated with loop electrosurgical excision procedure conization for cervical squamous intraepithelial lesions. *International Journal of Gynecological Cancer* 2008;**18**(1):90–4.
- Sarian 2004** *{published data only}*  
Sarian LO, Derchain SF, Pitta Dda R, Morais SS, Rabelo-Santos SH. Factors associated with HPV persistence after treatment for high-grade cervical intra-epithelial neoplasia with large loop excision of the transformation zone (LLETZ). *Journal of Clinical Virology* 2004;**31**(4):270–4.
- Sarian 2004a** *{published data only}*  
Sarian LO, Derchain SFM, Andrade LAA, Tambascia J, Morais SS, Syrjanen KJ. HPV DNA test and Pap smear in detection of residual and recurrent disease following loop

- electrosurgical excision procedure of high-grade cervical intraepithelial neoplasia. *Gynecologic Oncology* 2004;**94**(1): 181–6.
- Smart 2010** *{published data only}*  
Smart OC, Sykes P, Macnab H, Jennings L. Testing for high risk human papilloma virus in the initial follow-up of women treated for high-grade squamous intraepithelial lesions. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 2010;**50**(2):164–7.
- Tachezy 2006** *{published data only}*  
Tachezy R, Mikyskova I, Ludvikova V, Rob L, Kucera T, Slavik V, et al. Longitudinal study of patients after surgical treatment for cervical lesions: detection of HPV DNA and prevalence of HPV-specific antibodies. *European Journal of Clinical Microbiology and Infectious Diseases* 2006;**25**(8): 492–500.
- Takac 2008** *{published data only}*  
Takac I. Human papillomavirus infection in patients with residual or recurrent cervical intraepithelial neoplasia. *Tumori* 2008;**94**(1):83–6.
- Taylor 2011** *{published data only}*  
Taylor S, Wang C, Wright TC, Denny L, Kuhn L. A comparison of human papillomavirus testing of clinician-collected and self-collected samples during follow-up after screen-and-treat. *International Journal of Cancer* 2011;**129**(4):879–86.
- Trope 2011** *{published data only}*  
Trope A, Jonassen CM, Sjoborg KD, Nygard M, Dahl FA, Alfsen GC, et al. Role of high-risk human papillomavirus (HPV) mRNA testing in the prediction of residual disease after conisation for high-grade cervical intraepithelial neoplasia. *Gynecologic Oncology* 2011;**123**(2):257–62.
- Valasoulis 2011** *{published data only}*  
Valasoulis G, Koliopoulos G, Founta C, Kyrgiou M, Tsoumpou I, Valari O, et al. Alterations in human papillomavirus-related biomarkers after treatment of cervical intraepithelial neoplasia. *Gynecologic Oncology* 2011;**121**(1):43–8.
- van Ham 2007** *{published data only}*  
Van Ham MAPC, Van D, Bekkers RLM, Bulten J, Melchers WJG, Massuger LFAG. High-risk HPV presence in cervical specimens after a large loop excision of the cervical transformation zone: significance of newly detected hr-HPV genotypes. *Journal of Medical Virology* 2007;**79**(3): 314–9.
- Venturoli 2008** *{published data only}*  
Venturoli S, Ambretti S, Cricca M, Leo E, Costa S, Musiani M, et al. Correlation of high-risk human papillomavirus genotypes: persistence and risk of residual or recurrent cervical disease after surgical treatment. *Journal of Medical Virology* 2008;**80**(8):1434–40.
- Verguts 2006** *{published data only}*  
Verguts J, Bronselaer B, Donders G, Arbyn M, Van Eldere J, Drijkoningen M, et al. Prediction of recurrence after treatment for high-grade cervical intraepithelial neoplasia: the role of human papillomavirus testing and age at conisation. *BJOG* 2006;**113**(11):1303–7.
- Young 2010** *{published data only}*  
Young TK, Lee JM, Hur SY, Cho CH, Kim YT, Seung CK, et al. Clearance of human papillomavirus infection after successful conization in patients with cervical intraepithelial neoplasia. *International Journal of Cancer* 2010;**126**(8): 1903–9.
- Zielinski 2003** *{published data only}*  
Zielinski GD, Rozendaal L, Voorhorst FJ, Berkhof J, Snijders PJ, Risse EJ, et al. HPV testing can reduce the number of follow-up visits in women treated for cervical intraepithelial neoplasia grade 3. *Gynecologic Oncology* 2003;**91**(1):67–73.

## Additional references

- Alvarez 1994**  
Alvarez RD, Helm CW, Edwards RP, Naumann RW, Partridge EE, Shingleton HM, et al. Prospective randomized trial of LLETZ versus laser ablation in patients with cervical intraepithelial neoplasia. *Gynecologic Oncology* 1994;**52**(2): 175–9.
- Arbyn 2007**  
Arbyn M, Herbert A, Schenck U, Nieminen P, Jordan J, Mcgoogan E, et al. European guidelines for quality assurance in cervical cancer screening: recommendations for collecting samples for conventional and liquid-based cytology. *Cytopathology* 2007;**18**:133–9.
- Brisson 1994**  
Brisson J, Morin C, Fortier M, Roy M, Bouchard C, Leclerc J, et al. Risk factors for cervical intraepithelial neoplasia: differences between low- and high-grade lesions. *American Journal of Epidemiology* 1994;**140**(8):700–10.
- Brockmeyer AD 2003**  
Brockmeyer AD, Wright JD, Gao F, Powell MA. Persistent and recurrent cervical dysplasia after loop electrosurgical excision procedure. *American Journal of Obstetrics and Gynecology* 2005;**192**(5):1379–81.
- Brown 1991**  
Brown JV, Peters WA, Corwin DJ. Invasive carcinoma after cone biopsy for cervical intraepithelial neoplasia. *Gynecologic Oncology* 1991;**40**(1):25–8.
- Deeks 2001**  
Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Davey Smith G, Altman DG editor(s). *Systematic Reviews in Health Care: Meta-Analysis in Context*. 2nd Edition. London: BMJ Publication Group, 2001.
- DerSimonian 1986**  
DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**:177–88.
- EUROCARE 2003**  
Sant M, Aareleid T, Berrino F, Bielska Lasota M, Carli PM, Favre J, et al. and the EUROCARE Working Group.

- EUROCARE-3: survival of cancer patients diagnosed 1990-94: results and commentary. *Annals of Oncology* 2003;**14** (Suppl 5):v61-v118.
- Fallani 2008**  
Fallani MG, Penna C, Marchionni M, Bussani C, Pieralli A, Andersson KL, et al. Prognostic significance of high-risk HPV persistence after laser CO2 conization for high-grade CIN: a prospective clinical study. *European Journal of Gynaecological Oncology* 2008;**29**(4):378-82.
- Franco 2003**  
Franco EL. Chapter 13: Primary screening of cervical cancer with human papillomavirus tests. *Journal of the National Cancer Institute. Monographs* 2003;**31**:89-96.
- Galaal 2011**  
Galaal K, Bryant A, Deane KH, Al-Khaduri M, Lopes AD. Interventions for reducing anxiety in women undergoing colposcopy. *Cochrane Database of Systematic Reviews* 2011, Issue CD006013. [DOI: 10.1002/14651858.CD006013.pub3]
- Ghaem-Maghani 2007**  
Ghaem-Maghani S, Sagi S, Majeed G, Soutter WP. Incomplete excision of cervical intraepithelial neoplasia and risk of treatment failure: a meta-analysis. *Lancet Oncology* 2007;**8**(11):985-93.
- GLOBOCAN 2008**  
Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008, Cancer incidence and mortality worldwide. IARC CancerBase No. 10 [Internet]. Lyon, France, 2010; Vol. International Agency for Research on Cancer: <http://globocan.iarc.fr>.
- Higgins 2003**  
Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**: 557-60.
- Higgins 2011**  
Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1 [updated March 2011]. [www.cochrane-handbook.org](http://www.cochrane-handbook.org). The Cochrane Collaboration, 2011.
- Hogewoning 2003**  
Hogewoning CJ, Bleeker MC, van den Brule AJ, Voorhorst FJ, Snijders PJ, Berkhof J, et al. Condom use promotes regression of cervical intraepithelial neoplasia and clearance of human papillomavirus: a randomized clinical trial. *International Journal of Cancer* 2003;**107**(5):811-6.
- Hopewell 2008**  
Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. *PLoS Medicine* 2008;**5**(1):e20. doi:10.1371/journal.pmed.0050020.
- Jain 2001**  
Jain S, Tseng CJ, Horng SG, Soongy K, Pao CC. Negative predictive value of human papillomavirus test following conization of the cervix uteri. *Gynecologic Oncology* 2001;**82**(1):177-80.
- Kocken 2012**  
Kocken M, Uijterwaal MH, de Vries AL, Berkhof J, Ket JC, Helmerhorst TJ, et al. High-risk human papillomavirus testing versus cytology in predicting post-treatment disease in women treated for high-grade cervical disease: a systematic review and meta-analysis. *Gynecologic Oncology* 2012;**125**(2):500-7.
- Luesley 2010**  
Luesley D, Leeson S. *Colposcopy and Programme Management: Guidelines for the NHS Cervical Screening Programme. NHSCSP Publication No. 20*. 2nd Edition. Sheffield: NHSCSP, 2010.
- Lörincz 2003**  
Lörincz AT. Screening for cervical cancer: new alternatives and research. *Salud Publica Mex* 2003;**45**(Suppl 3): S376-87.
- McCredie 2008**  
McCredie MR, Sharples KJ, Paul C, Baranyai J, Medley G, Jones RW, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. *Lancet Oncology* 2008;**9**(5):425-34.
- Mitchell 1998**  
Mitchell MF, Tortolero-Luna G, Cook E, Whittaker L, Rhodes-Morris H, Silva E. A randomized clinical trial of cryotherapy, laser vaporization, and loop electrosurgical excision for treatment of squamous intraepithelial lesions of the cervix. *Obstetrics and Gynecology* 1998;**92**(5):737-44.
- Nam 2009**  
Nam K, Chung S, Kim J, Jeon S, Bae D. Factors associated with HPV persistence after conization in patients with negative margins. *Journal of Gynecological Oncology* 2009;**20**(2):91-5.
- NHSCSP 2011**  
NHSCSP. Evaluation of sentinel sites for HPV triage and test of Cure, 2011. <http://www.cancerscreening.nhs.uk/cervical/sentinelfinalreport.pdf> (accessed 24 September 2012).
- Nobbenhuis 2001**  
Nobbenhuis MA, Meijer CJ, van den Brule AJ, Rozendaal L, Voorhorst FJ, Risse EK, et al. Addition of high-risk HPV testing improves the current guidelines on follow-up after treatment for cervical intraepithelial neoplasia. *British Journal of Cancer* 2001;**84**(6):796-801.
- Paraskevaidis E 2000**  
Paraskevaidis E, Lolis ED, Koliopoulos G, Alamanos Y, Fotiou S, Kitchener HC. Cervical intraepithelial neoplasia outcomes after large loop excision with clear margins. *Obstetrics and Gynecology* 2000;**95**:828-31.
- Parmar 1998**  
Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature

for survival endpoints. *Statistics in Medicine* 1998;**17**(24): 2815–34.

**Pinto 2000**

Pinto AP, Crum CP. Natural history of cervical neoplasia: defining progression and its consequence. *Clinical Obstetrics and Gynecology* 2000;**43**(2):352–62.

**Schiffman 1993**

Schiffman MH, Bauer HM, Hoover RN, Glass AG, Cadell DM, Rush BB, et al. Epidemiologic evidence showing that human papillomavirus infection causes most cervical intraepithelial neoplasia. *Journal of the National Cancer Institute* 1993;**85**(12):958–64.

**Souter 2006**

Soutter WP, Sasieni P, Panoskaltis T. Long-term risk of invasive cervical cancer after treatment of squamous cervical intraepithelial neoplasia. *International Journal of Cancer* 2006;**118**(8):2048–55.

**Soutter 1997**

Soutter WP, de Barros Lopes A, Fletcher A, Monaghan JM, Duncan ID, Paraskevaidis E, et al. Invasive cervical cancer after conservative therapy for cervical intraepithelial neoplasia. *Lancet* 1997;**349**(9057):978–80.

\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aerssens 2009	<p>A prospective study, which included 138 women treated for CIN2+ by LEEP. Follow-up visits were scheduled at 6 weeks, 6 months, 1 year and 2 years. Each visit, women were given a cytology and high-risk HPV (hrHPV) test, and colposcopy was performed. Cytology, hrHPV presence, persistent hrHPV infection and combinations of these tests at different time points during follow-up were correlated with histologically confirmed residual/recurrent disease</p> <p><b>Reason for exclusion:</b> not an RCT</p>
Almog 2003	<p>A prospective cohort study, which included 96 women who had undergone cone biopsy because of the diagnosis of CIN2-3. Follow-up visits took place every 6 months within the first 2 years. Each visit, cytology was performed; 2 consecutive abnormal smears dictated to referral for colposcopy-directed biopsy with HPV testing performed only before colposcopy. HPV load was compared with cytology for detection of residual disease</p> <p><b>Reason for exclusion:</b> not an RCT; HPV testing took place only in women with an abnormal cytology</p>
Alonso 2006	<p>A prospective study, which included 203 women with a diagnosis of CIN2+ and treated by LEEP conisation. Follow-up was scheduled after 6, 12, 18 and 24 months, and yearly after this period. Every visit, cytology and colposcopy were performed. hrHPV testing was performed after 6 months in 133 cases and after 12 months in 70 cases. Correlation between residual/recurrent disease and cytology and hrHPV test results was calculated</p> <p><b>Reason for exclusion:</b> not an RCT</p>
Bae 2007	<p>A retrospective study, which included 120 women treated for CIN2+. Follow-up visits were scheduled every 3 to 6 months the first year, then annually. During follow-up, specimens were tested for persistence of hrHPV. The correlation between persistence of hrHPV and residual/recurrent disease was calculated</p> <p><b>Reason for exclusion:</b> not an RCT; no comparison with cytology</p>
Bar-Am 2003	<p>A prospective study, which included 67 women with CIN2+ who underwent cone biopsy. All women had follow-up for 3 years with a 6-month interval visit and another for 2 years annually. Every follow-up visit, an hrHPV test and a cytology test were performed. Correlation between cytology and hrHPV results was calculated, and the hrHPV clearance rate during the follow-up period is shown</p> <p><b>Reason for exclusion:</b> not an RCT</p>
Bekkers 2002	<p>A prospective study, which included 90 women treated for CIN2+ with LLETZ. Two liquid-based cervical scrapes were taken after 3 months and 6 months, and cytology was taken at every follow-up visit (median cytological follow-up of 32 months (24 to 47 months)). hrHPV testing was performed at liquid-based cervical scrapes. Performance of hrHPV testing at 3 months and 6 months after LLETZ and performance of conventional cytology at 3 months and 6 months after LLETZ were calculated using the gold standard (cytology follow-up and colposcopy after 6 months)</p> <p><b>Reason for exclusion:</b> not an RCT</p>
Bias 2009	<p>RCT, which included 204 women diagnosed with high-grade cervical intraepithelial neoplasia lesions (CIN2-3) who were treated with large loop excision of the transformation zone (LLETZ), cold-knife conisation or laser conisation. However, the 2 modalities of follow-up management strategies after treatment</p>

(Continued)

	for CIN were not compared
Bollen 1999	<p>A prospective study, which included 43 women with abnormal cytology after treatment for cervical dysplasia. All women were referred for colposcopy, and before colposcopy HPV tests were done and biopsies were taken for histological examination. hrHPV test results were compared with histological results, and test parameters were calculated</p> <p><b>Reason for exclusion:</b> not an RCT; participants did not meet our inclusion criteria</p>
Brismar 2009	<p>A prospective observational study, which included 90 women who underwent cytological testing and hrHPV genotyping at the follow-up visit after conisation. One arm (33) had follow-up within 12 months, and the other arm (57) had follow-up after 12 months. Cone specimens were genotyped retrospectively. HPV types before and after conisation were compared and correlated with residual/recurrent disease</p> <p><b>Reason for exclusion:</b> not an RCT; test results after 6 months of follow-up not specified</p>
Castle 2009	<p>A randomised clinical trial, which included 195 women who were HPV positive at enrolment and were treated with LEEP and compared them with 1625 HPV-positive women who underwent colposcopy (women CIN grade &lt; 2) to determine the acquisition of new HPV infection among women treated with LEEP</p> <p><b>Reason for exclusion:</b> did not report on residual/recurrent disease</p>
Cecchini 2004	<p>A prospective study, which included 84 women treated for CIN2+ with LEEP. HPV testing was performed before LEEP and 6 months after treatment and cytology-colposcopy follow-up was performed every 6 months. Correlation between recurrent disease and baseline characteristics was calculated, and hrHPV and cytological test results in relation to recurrence were reported</p> <p><b>Reason for exclusion:</b> not an RCT</p>
Chao 2004	<p>A prospective study, which included 765 women treated for CIN2+ with conisation. Follow-up at 3-, 6- and 12-month intervals included cytology and colposcopy. "HPV DNA testing was determined at the discretion of the responsible physicians." Correlation between major events (repeat conisation or hysterectomy for cytological/histological HSIL+) and minor events (CIN1) with hrHPV and cytology test results is calculated</p> <p><b>Reason for exclusion:</b> not an RCT; hrHPV testing was performed only when consultant decided to do so</p>
Costa 2003	<p>A prospective study, which included 252 women with CIN lesions treated with conisation and followed up with hrHPV detection, cytology, colposcopy and punch biopsy (mean follow-up 10.26 ± 7.25 months). Factors predicting viral clearance were elaborated</p> <p><b>Reason for exclusion:</b> not an RCT; did not report on residual/recurrent disease; follow-up mean 10 months</p>
Dogan 2011	<p>A prospective cohort study, which included 37 HPV-positive women (CIN1, 2, 3) treated with LEEP and followed up with cytology and HPV testing after 3 months and 6 months. To assess HPV testing for detection of recurrent/residual CIN after LEEP and to evaluate the effects of LEEP on clearance of HPV in CIN1 lesions</p> <p><b>Reason for exclusion:</b> not an RCT; CIN1 lesions included</p>
Fambrini 2008	<p>A prospective follow-up study, which included 52 women treated for high-grade CIN with laser conisation. Follow-up was scheduled at 3, 6 and 12 months after treatment with cytology and hrHPV testing on self-collected urine and cervical scrapes. Diagnostic accuracy and predictive values for treatment failure were evaluated for both urinary and cervical HPV testing and for follow-up cytology</p>

(Continued)

	<b>Reason for exclusion:</b> not an RCT
Houfflin Debarge 2003	<p>A prospective follow-up study, which included 205 women with CIN2+ diagnosed by a conisation specimen. All women were followed up at 3- and 6-month intervals, with mean follow-up of 18.1 months (<math>\pm</math> 12). Each visit consisted of hrHPV testing, cytology, colposcopic assessment and colposcopically directed punch biopsy of the cervix (if indicated). Correlation between pretreatment and post-treatment hrHPV test results and residual/recurrent disease and correlation between hrHPV status and margins were calculated</p> <p><b>Reason for exclusion:</b> not an RCT</p>
Jancar 2006	<p>A prospective study, which included 214 women with low- and high-grade CIN who were tested for hrHPV infection before undergoing surgery. hrHPV-positive women had follow-up with hrHPV and cytology testing after surgery. hrHPV-negative women had follow-up with cytology testing alone. The efficiency of different surgical techniques (laser vaporisation, LLETZ and cold-knife conisation) in eliminating hrHPV infection was evaluated, and hrHPV persistence was reported</p> <p><b>Reason for exclusion:</b> not an RCT; did not report on recurrent/residual disease; low-grade CIN lesions were not excluded and cytology test results were not reported</p>
Jeong 2009	<p>A prospective study, which included 95 women treated for high-grade CIN with LEEP and conisation. Follow-up visits were scheduled at 3, 6, 12, 18 and 24 months after treatment and included hrHPV DNA and cytology testing. Diagnostic test accuracy outcomes for detecting recurrent disease using colposcopy-directed biopsy within 24 months after treatment were reported</p> <p><b>Reason for exclusion:</b> not an RCT</p>
Jones 2011	<p>A prospective study, which included 98 women treated for CIN2+ with LLETZ. hrHPV testing was performed 6 months before and after treatment. Cytology and histology results were available. Diagnostic test accuracy outcomes for predicting recurrent disease for different follow-up strategies were estimated</p> <p><b>Reason for exclusion:</b> not an RCT</p>
Kocken 2011	<p>A prospective study, which included 435 women from three previous studies (<a href="#">Bias 2009</a>; <a href="#">Hogewoning 2003</a>; <a href="#">Nobbenhuis 2001</a>). All women (median age 33, range 21 to 70 years) were treated for CIN grade 2 or 3 (358 by LLETZ and 77 with cold-knife conisation). At every follow-up visit after 6, 12 and 24 months, all women were hrHPV- and cytology-tested. The cumulative risk of post-treatment CIN2+ (recurrent disease) was calculated. For women who had not developed CIN at 24 months after treatment, the risk of post-24-month CIN was estimated</p> <p><b>Reason for exclusion:</b> not an RCT</p>
Korolenkova 2011	<p>A prospective study, which included 525 women given treatment for CIN2-3/CIS and microinvasive cervical cancer to evaluate the value of hrHPV testing for detection of residual/recurrent disease compared with cytology and colposcopy. Further details not specified, only abstract available</p> <p><b>Reason for exclusion:</b> not an RCT; women with microinvasive cervical cancer not excluded</p>
Kreimer 2006	<p>RCT, which included 610 women who underwent loop electrosurgical excision procedure (LEEP) with primary endpoint of post-LEEP detection of CIN2+. However, the 2 modalities of follow-up management strategies after treatment for CIN were not compared</p>
Kucera 2001	<p>A prospective study, which included 142 women treated for CIN1-3 with conisation and followed up before and 3, 6 and 12 months after treatment with cervical sampling and hrHPV testing. Differences in the rate of hrHPV DNA positivity after LLETZ between specific risk groups (primary hrHPV infection, CIN grades, positive margins) were determined</p> <p><b>Reason for exclusion:</b> not an RCT; CIN1 lesions included</p>



(Continued)

Leguevaque 2010	<p>A retrospective study, which included 352 women treated for high-grade lesions with standard surgical treatment. Treatment was followed up with colposcopy, cytology and HPV before and 4 to 6 months after treatment</p> <p><b>Outcome:</b> recurrence/residual disease and predictive factors (positive margins, pretreatment HPV, positive HPV test 6 months post treatment)</p> <p><b>Reason for exclusion:</b> not an RCT</p>
Mikolajczyk 2011	<p>This study included 107 women who were treated for CIN and underwent 14-month follow-up with regular cytological and molecular evaluations. Recurrence disease rates and corresponding hrHPV test results were reported. No further details; only abstract available</p> <p><b>Reason for exclusion:</b> not an RCT</p>
Nagai 2000	<p>A prospective study, which included 58 women who were hrHPV-tested before treatment for severe dysplasia or carcinoma in situ. After conisation, women were followed up for a mean follow-up period of 31.8 months (range 12 to 72 months) with a cytology test, an hrHPV examination and colposcopic assessment at every visit. Women with no recurrence or with recurrence of CIN1 or CIN2 were given no intervention, and women with recurrence of CIN3 underwent reconisation. The correlation between DNA persistence, hrHPV types and CIN recurrence was assessed</p> <p><b>Reason for exclusion:</b> not an RCT</p>
Nagai 2004	<p>A prospective study, which included 161 women who underwent LLETZ for CIN3. Cervical smear cytology and hrHPV testing were performed at 3, 6 and 12 months, and then at 6- to 12-month intervals over the following 3 years. The relation between hrHPV DNA status and recurrence of CIN was reported</p> <p><b>Reason for exclusion:</b> not an RCT</p>
Prato 2008	<p>A prospective study, which included 119 women who underwent LEEP for CIN. All women had follow-up including cytology and colposcopy after 3, 6 and 12 months in the first year post treatment, and every 6 to 12 months after the first year. hrHPV testing was performed at the time of LEEP and 3 to 6 months later. The correlation between recurrence rates, margin status and post-treatment hrHPV status was assessed</p> <p><b>Reason for exclusion:</b> not an RCT</p>
Sarian 2004	<p>A prospective cohort study, which included 94 women submitted to LLETZ with confirmed CIN2-3 in the cone specimen. Follow-up was scheduled 6 and 12 months after treatment. Every visit included a participant interview, conventional cytology, hrHPV testing and colposcopic examination. The association between characteristics of participants (age, smoking, age at first intercourse, glandular involvement, oral hormonal contraception, margin status) and their cervical lesions with hrHPV-type persistence was determined</p> <p><b>Reason for exclusion:</b> not an RCT; did not report on residual/recurrent disease</p>
Sarian 2004a	<p>A prospective study, which included 107 women who were treated for CIN2+ with LEEP. Follow-up was scheduled 6 and 12 months after treatment. Every visit included a participant interview, conventional cytology, hrHPV testing and colposcopic examination. Performance indicators were calculated for cytology and HCII assay for detecting residual or recurrent disease</p> <p><b>Reason for exclusion:</b> not an RCT</p>
Smart 2010	<p>A prospective study, which included 100 women treated for high-grade CIN. All women underwent cytology, hrHPV testing and colposcopic examination at the first follow-up visit (mean time interval of first follow-up 9 months). The aim of this study was to determine the prevalence of hrHPV and cytological abnormalities at first follow-up visit post treatment. The feasibility, safety and cost benefit of omitting routine colposcopy as a first-line investigation were evaluated</p>

(Continued)

	<b>Reason for exclusion:</b> not an RCT
Tachezy 2006	<p>A prospective study, which included 198 women surgically treated for low- and high-grade CIN together with 35 age-matched controls. Follow-up was scheduled for 18 months at 6-month intervals. Every visit included cytological and colposcopic examination, and a sample for hrHPV detection and a blood sample for specific HPV antibodies were taken. The principal aims of this study were to test whether persistence of high-risk human papillomavirus (HPV) DNA was predictive of recurrent disease in women after surgical treatment for cervical lesions, to distinguish between persistent and newly acquired hrHPV infection and to observe the effects of surgical treatment on levels of HPV-specific antibodies</p> <p><b>Reason for exclusion:</b> not an RCT; low-grade lesions included; no report on residual/recurrent disease</p>
Takac 2008	<p>A prospective study, which included 797 women treated for CIN with conisation. In 38 women with residual or recurrent CIN in whom reconisation was performed, infection with hrHPV types was analysed</p> <p><b>Reason for exclusion:</b> not an RCT; aim of study did not meet our research question: hrHPV status determined only in women with reconisation, no cytology results and no follow-up strategy</p>
Taylor 2011	<p>An RCT, which randomly assigned 6553 women to 3 groups: (1) visual inspection with acetic acid-and-treat group, (2) HPV-and-treat group or (3) control group. The first 2 groups received cryotherapy, and the control group was given no cryotherapy. At 6 months after randomisation/cryotherapy, all women received hrHPV testing using both clinician-collected and self-collected specimens, cytology testing and colposcopy. A subset of women (n = 1455) had extended follow-up with colposcopy at 12 months. Tests performed included hrHPV testing using self-collected and clinician-collected samples as well as cytology for identifying CIN2+ among women who did and did not undergo cryotherapy</p> <p><b>Reason for exclusion:</b> hrHPV testing and other intervention groups merged and analysed as 1 group; therefore no appropriate comparison</p>
Trope 2011	<p>A prospective study, which included 344 women treated for CIN2+ by conisation. All women were cytology-, hrHPV AMPLICOR- and PreTect hrHPV-Proofer mRNA-tested after 6 months and 12 months. After 18 months, a biopsy specimen was taken for histological analysis. Residual CIN2+ outcomes after 18 months were reported, as were the correlation between resection margins and residual CIN2+ and the correlation between hrHPV and cytology test results and residual CIN2+</p> <p><b>Reason for exclusion:</b> not an RCT</p>
Valasoulis 2011	<p>A prospective study, which included 190 women who were scheduled to undergo treatment for CIN1-3. A cytology sample was taken preoperatively and 6 months postoperatively for hrHPV genotyping. Alterations in various HPV-related biomarkers 6 months post treatment and correlation with risk factors and individual characteristics and their role in the prediction of recurrent/residual disease were assessed</p> <p><b>Reason for exclusion:</b> not an RCT; did not exclude CIN1 lesions</p>
van Ham 2007	<p>A prospective study, which included 90 women treated for CIN2+ with LLETZ. Within 6 months post treatment, cervical smears were collected and histopathological and cytological examination was performed. HPV and cytology tests were done, and in cases of positive results, hrHPV genotypes were specified. The aim of the study was to obtain greater insight into the appearance of new hrHPV types after surgical treatment</p> <p><b>Reason for exclusion:</b> not an RCT; did not report on residual/recurrent disease; no cytology result reported</p>
Venturoli 2008	<p>A prospective study, which included 72 women who underwent LEEP for high-grade CIN with at least 2 follow-up visits within 24 months and were hrHPV-tested within 30 days before treatment. For 2 years all women were followed up at 6-month intervals with cytology and colposcopy. hrHPV tests were performed</p>

(Continued)

	<p>only 6 months post treatment. 6-Month postoperative hrHPV status was correlated with preoperative hrHPV genotype and residual/recurrent disease</p> <p><b>Reason for exclusion:</b> not an RCT</p>
Verguts 2006	<p>A prospective study, which included 72 women treated with conisation for CIN2/3. Every 3 to 6 months, an hrHPV test was performed, and every 6 months for 2 years, participants underwent cytological and colposcopic examination. hrHPV status was correlated with recurrent/residual disease</p> <p><b>Reason for exclusion:</b> not an RCT</p>
Young 2010	<p>A prospective study, which included 287 women from 7 medical centres in Korea who underwent LEEP for the treatment of CIN. Only women with tumour-free endocervical and exocervical resection margins of LEEP specimens and hrHPV test documentation before treatment were included. All women had follow-up visits every 3 months the first year and every 6 months the second year. At every visit, women underwent pelvic examination, cervical inspection, hrHPV testing with HC2 and a cervical smear. Aims of the study were to evaluate the rate and pattern of hrHPV infection clearance after successful conisation for CIN and to identify factors associated with effective clearance. The numbers of women with persistent hrHPV infection after LEEP and residual/recurrent disease after follow-up are reported</p> <p><b>Reason for exclusion:</b> not an RCT; cytology result outcomes not presented</p>
Zielinski 2003	<p>A prospective study, which included 108 women treated for histologically confirmed CIN3 lesions. Follow-up with cytology was scheduled at 3, 6, 12 and 24 months post treatment. At the 3-month post-treatment visit, all women were also hrHPV-tested. Only hrHPV-positive women were given hrHPV tests during further follow-up visits. Diagnostic test accuracy outcomes for predicting recurrent disease for additional hrHPV testing and conservative management are reported</p> <p><b>Reason for exclusion:</b> not an RCT; only women with CIN3 lesions included</p>

## DATA AND ANALYSES

### Comparison 1. Cytology and HPV vs cytology alone

---

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Residual/recurrent CIN2+ at 2 years	0	0	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]

---

## APPENDICES

### Appendix 1. MEDLINE search strategy

1. Uterine Cervical Neoplasms/
2. Cervical Intraepithelial Neoplasia/
3. CIN\*.mp.
4. (cervi\* adj5 (cancer\* or tumor\* or tumour\* or malignan\* or neoplas\* or carcinoma\* or adenocarcinoma\* or precancer\* or precancer\* or dysplasia)).mp.
5. 1 or 2 or 3 or 4
6. surgery.fs.
7. (LLETZ or LEEP).mp.
8. transformation zone.mp.
9. (conisation or conization).mp.
10. laser.mp.
11. excis\*.mp.
12. cryotherapy.mp.
13. 6 or 7 or 8 or 9 or 10 or 11 or 12
14. HPV.mp.
15. exp Papillomavirus Infections/
16. exp papillomaviridae/
17. papillomavir\*.mp.
18. 14 or 15 or 16 or 17
19. 5 and 13 and 18
20. randomized controlled trial.pt.
21. controlled clinical trial.pt.
22. randomized.ab.
23. placebo.ab.
24. clinical trials as topic.sh.
25. randomly.ab.
26. trial.ti.
27. 20 or 21 or 22 or 23 or 24 or 25 or 26
28. 19 and 27

key:

mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier, pt=publication type

ab=abstract, sh=subject heading, ti=title

### Appendix 2. EMBASE search strategy

EMBASE Ovid

1. exp uterine cervix tumor/
2. uterine cervix carcinoma in situ/
3. CIN\*.mp.
4. (cervi\* adj5 (cancer\* or tumnor\* or tumour\* or malignan\* or neoplas\* or carcinoma\* or adenocarcinoma\* or precancer\* or precancer\* or dysplasia)).mp.
5. 1 or 2 or 3 or 4
6. su.fs.
7. (LLETZ or LEEP).mp.
8. transformation zone.mp.

9. (conisation or conization).mp.
10. laser.mp.
11. excis\*.mp.
12. cryotherapy.mp.
13. 6 or 7 or 8 or 9 or 10 or 11 or 12
14. HPV.mp.
15. exp papovavirus/
16. papillomavir\*.mp.
17. 14 or 15 or 16
18. 5 and 13 and 17
19. crossover procedure/
20. double-blind procedure/
21. randomized controlled trial/
22. single-blind procedure/
23. random\*.mp.
24. factorial\*.mp.
25. (crossover\* or cross over\* or cross-over\*).mp.
26. placebo\*.mp.
27. (double\* adj blind\*).mp.
28. (singl\* adj blind\*).mp.
29. assign\*.mp.
30. allocat\*.mp.
31. volunteer\*.mp.
32. 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
33. 18 and 32
34. (exp animal/ or nonhuman/ or exp animal experiment/) not human/
35. 33 not 34

key

[mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

### Appendix 3. CENTRAL search strategy

CENTRAL

1. MeSH descriptor: [Uterine Cervical Neoplasms] this term only
2. MeSH descriptor: [Cervical Intraepithelial Neoplasia] this term only
3. CIN\*
4. (cervi\* adj5 (cancer\* or tumor\* or tumour\* or malignan\* or neoplas\* or carcinoma\* or adenocarcinoma\* or precancer\* or pre-cancer\* or dysplasia))
5. #1 or #2 or #3 or #4
6. Any MeSH descriptor with qualifier(s): [Surgery - SU]
7. (LLETZ or LEEP)
8. transformation zone
9. (conisation or conization)
10. laser
11. excis\*
12. cryotherapy
13. #6 or #7 or #8 or #9 or #10 or #11 or #12
14. HPV
15. MeSH descriptor: [Papillomavirus Infections] explode all trees
16. MeSH descriptor: [Papillomaviridae] explode all trees
17. papillomavir\*

18. #14 or #15 or #16 or #17

19. #5 and #13 and #18

## CONTRIBUTIONS OF AUTHORS

Esther van der Heijden (EH) is the main author of the review. EH, Andrew Bryant (AB) and Khadra Galaal (KG) performed the sift, extracted data and co-wrote the manuscript. AB entered data into RevMan. AB and KG developed and drafted the review. Alberto Lopes and Ruud Bekkers provided clinical expertise and critically appraised drafts of the review. All review authors approved the final version.

## DECLARATIONS OF INTEREST

None known.

## SOURCES OF SUPPORT

### Internal sources

- No sources of support supplied

### External sources

- Department of Health, UK.
- NHS Cochrane Collaboration Programme Grant Scheme CPG-506

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

All references were ultimately excluded, as they clearly did not meet the inclusion criteria. We identified no ongoing randomised controlled trials that met our inclusion criteria from our searches of the grey literature. In future updates of the review, we will employ the following methods.

Copies of the full text of relevant references will be obtained, as outlined in the [Methods](#) section. Eligibility of retrieved papers will be assessed independently by two review authors. Disagreements will be resolved by discussion between the two review authors. Reasons for exclusion will be documented.

### Data extraction and management

We will abstract data for the included studies as recommended in Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* version 5.1 ([Higgins 2011](#)). Two review authors will extract data independently and will include the following.

- Study author, year of publication and journal citation (including language).
- Country.
- Setting.
- Inclusion and exclusion criteria.
- Study design, methodology.
- Study population.
  - Total number enrolled.
  - Participant characteristics.
    - ◊ Age.

- ◇ Race.
- ◇ Co-morbidities.
- ◇ Previous treatment.
- CIN details at diagnosis.
  - CIN2, CIN3 details.
- Intervention details.
  - Post-treatment HPV testing in combination with cytology testing ± HPV typing.
  - Criteria for referral to colposcopy.
- Comparison details.
  - Conventional cervical screening with Pap smear.
  - Criteria for referral to colposcopy.
- Risk of bias in study (see below).
- Duration of follow-up and follow-up intervals.
- Outcomes: See above.
  - For each outcome: outcome definition (with diagnostic criteria if relevant).
  - Unit of measurement (if relevant).
  - For scales: upper and lower limits, and whether high or low score is good.
  - Results: number of participants allocated to each intervention group.
  - For each outcome of interest: sample size; missing participants; reasons for loss to follow-up.

We will extract data on outcomes as below.

- For time-to-event (developing recurrent CIN2 or higher lesion) data, we will extract the log of the hazard ratio [ $\log(\text{HR})$ ] and its standard error from trial reports (if these are not reported, we will attempt to estimate them from other reported statistics using the methods of [Parmar 1998](#)).
- For dichotomous outcomes (e.g. developing recurrent CIN2 or higher lesion if not expressed as time-to-event data), we will extract the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed at endpoint (e.g. residual/recurrent disease) to estimate a risk ratio (RR).
- For continuous outcomes (e.g. anxiety, psychosexual scores), we will extract the final value and the standard deviation of the outcome of interest and the number of participants assessed at endpoint in each treatment arm at the end of follow-up to estimate the mean difference (if trials measured outcomes on the same scale) or the standardised mean difference (if trials measured outcomes on different scales) between treatment arms and its standard error.

When possible, all extracted data will be those relevant to an intention-to-treat analysis in which participants are analysed in the groups to which they were assigned.

We will note the time points at which outcomes were collected and reported.

Data will be abstracted independently by two review authors (EH, KG) onto a data abstraction form specially designed for the review. We will resolve differences between review authors by discussion or by appeal to a third review author (AB).

### Assessment of risk of bias in included studies

We will assess the risk of bias of included RCTs in accordance with guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* using the tool of The Cochrane Collaboration and the criteria specified in Chapter 8 ([Higgins 2011](#)). This will include assessment of the following.

- Sequence generation.
- Allocation concealment.
- Blinding (will be restricted to blinding of outcome assessors, as not possible to blind participants and healthcare providers to interventions).
- Incomplete outcome data.
  - We will record the proportion of participants whose outcomes are not reported at the end of the study. We will code the satisfactory level of loss to follow-up for each outcome as follows.
    - ◇ Yes, if fewer than 20% of participants are lost to follow-up and reasons for loss to follow-up are similar in both treatment arms.



◇ No, if more than 20% of participants are lost to follow-up or reasons for loss to follow-up are different between treatment arms.

◇ Unclear, if loss to follow-up is not reported.

- Selective reporting of outcomes.
- Other possible sources of bias.

The risk of bias tool will be applied independently by two review authors (EH, KG) and differences will be resolved by discussion or by appeal to a third review author (AB). Results will be summarised in both a risk of bias graph and a risk of bias summary. Results of meta-analyses will be interpreted in the light of findings with respect to risk of bias.

### Measures of treatment effect

We will use the following measures of the effects of treatment.

- For time-to-event data, we will use the hazard ratio (HR), if possible.
- For dichotomous outcomes, we will use the risk ratio (RR).
- For continuous outcomes, we will use the mean difference between treatment arms.

### Dealing with missing data

We will not impute missing outcome data for any of the outcomes.

### Assessment of heterogeneity

We will assess heterogeneity between studies by visual inspection of forest plots, by estimation of the percentage of heterogeneity between trials that cannot be ascribed to sampling variation (Higgins 2003), by a formal statistical test of the significance of heterogeneity (Deeks 2001) and, if possible, by subgroup analyses (Subgroup analysis and investigation of heterogeneity). If evidence suggests substantial heterogeneity, possible reasons for this will be investigated and reported.

### Assessment of reporting biases

We will examine funnel plots corresponding to meta-analyses of the primary outcome to assess the potential for small-study effects such as publication bias.

### Data synthesis

If sufficient clinically similar trials are available, their results will be pooled in meta-analyses.

- For time-to-event data, we will pool HRs using the generic inverse variance facility of RevMan 5.
- For dichotomous outcomes, we will calculate the RR for each trial and will pool the RRs.
- For continuous outcomes, we will pool mean differences between treatment arms at the end of follow-up if all trials measured the outcome on the same scale; otherwise we will pool standardised mean differences.

We will use random-effects models with inverse variance weighting for all meta-analyses (DerSimonian 1986).

### Sensitivity analysis

We will perform sensitivity analyses excluding studies at high risk of bias.

## NOTES

Parts of the Methods section of this review are based on a standard template established by the Cochrane Gynaecological Cancer Group.