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# Comparative efficacy and complication rates after local treatment for cervical intra-epithelial neoplasia and stage 1a1 cervical cancer: protocol for a systematic review and network meta-analysis from the CIRCLE Group

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## ABSTRACT

**Introduction:** Local treatments for cervical intra-epithelial neoplasia (CIN) and micro-invasive disease remove or ablate a cone-shaped part of the uterine cervix containing the abnormal cells. A trend towards less radical techniques has raised concerns that this may adversely impact the rates of precancerous and cancerous recurrence. However, there has been no strong evidence to support such claims. We hereby describe a protocol of a systematic review and network meta-analysis that will update the evidence and compare all relevant treatments in terms of efficacy and complications.

**Methods and Analysis:** Literature searches in electronic databases or trial registries will identify published and unpublished randomised controlled trials (RCTs) and cohort studies comparing the efficacy and complications amongst different excisional and ablative techniques. The excisional techniques include cold knife, laser or fischer cone, large loop or needle excision of the transformation zone and the ablative radical point diathermy, cryotherapy, cold coagulation or laser ablation. The primary outcome will be high-grade treatment failure rates, defined as recurrent/residual histologically-proven CIN2 or worse, while secondary outcomes will include treatment failure rates at CIN1+, HPV positivity rates, abnormal cytology and/or histology rates, involved margins rates, and rates of bleeding, inadequate colposcopy and cervical stenosis. We will assess the risk of bias in RCTs and observational studies using tools developed by the Cochrane Collaboration. Two authors will independently assess study eligibility, abstract the data, and assess the risk of bias. Random-effects meta-analyses and network meta-analyses will be conducted using the odds ratio for dichotomous outcomes and the mean difference for continuous outcomes. The quality of the evidence for the primary outcome will be assessed using the CINEMA tool.

**Ethics and dissemination:** Ethical approval not required. We will disseminate findings to clinicians, policy makers, patients and the public.

**PROSPERO registration number**: CRD42018115508


## ARTICLE SUMMARY

### Strengths and limitations of this study

- We plan to conduct the first network meta-analysis to assess the relative efficacy and complication rates of treatment methods for cervical pre-invasive and early micro-invasive disease.
- This study will produce comprehensive summaries of the clinical ranking of treatments and will employ methodologies that will allow the use of both randomised and observational data, aiming to utilise all published evidence.
- The results will inform clinicians, patients and clinical guidelines and will allow effective patient counselling at colposcopy clinics.
- We expect to find retrospective observational studies at high risk of recall, selection and publication bias. We will try overcoming this limitation by employing methods that aim to minimise bias.

## KEYWORDS

"Cervical Intraepithelial Neoplasia/surgery"[Mesh]
"Cervical Intraepithelial Neoplasia/therapy"[Mesh]
"Treatment Outcome"[Mesh]
"Recurrence"[Mesh]
"Conization/adverse effects"[Mesh]
"Ablation Techniques/adverse effects"[Mesh]

## INTRODUCTION

Organised screening programmes in countries such as the UK, have led to a dramatic decrease in the incidence and mortality from cervical cancer, especially when compared with the corresponding statistics for the other major cancers. Over a twenty-year period, from 1993-1995 to 2013-2015, the overall age-standardised incidence rate of cancer in females increased by 16% in the UK[1], whereas the corresponding data for cervical cancer showed a decrease of 24%[2]. Cervical cancer is largely preventable through detection and treatment of the pre-invasive precursor, cervical intra-epithelial neoplasia (CIN)[3]. The local treatment methods are divided into excisional and destructive (ablative) that aim to remove or ablate respectively a cone shaped part of the cervix that contains the 'transformation zone' with the precancerous cells. Although large loop excision of the transformation zone (LLETZ) is the most commonly used methods in the UK[4] given its ease of execution and low cost, the preference of techniques varies across Europe and internationally.

A Cochrane systematic review of RCTs concluded that all local treatment techniques are highly effective in preventing pre-invasive recurrence[5]. However, this review found no evidence of difference in treatment failure rates amongst the treatment techniques. This could be because the RCTs, and the subsequent meta-analysis might have been underpowered to detect differences between the treatments. The largest study recruited only 390 participants[6], while the majority of the rest were much smaller. A more recent, large, population-based study from Sweden[7], which included 150,883 women diagnosed and treated for CIN3 (3,148,222 woman-years), reported a doubled standardized incidence ratio for post-treatment invasive recurrence during the follow-up period of around 4 decades in comparison to the general population, and initiated debates on the impact that less radical treatments may have on the subsequent risk of invasion[8]. The trend towards techniques that remove smaller parts of the cervix can be attributed to the fact that many of these are easy to do, they are of low cost, and can be performed in an outpatient setting. Increased awareness of the impact of the more radical or deeper techniques on the risk of prematurity may have also contributed[9-20].

The impact of different techniques on the risk of pre-invasive and/or invasive recurrence remains therefore unclear. With some advocating the minimum radicality of treatment to prevent treatment-induced reproductive morbidity[10 21], and others raising concerns about the increase in the risk of future invasion[7 8], a definite answer regarding the relative merits and risks among the various treatment strategies is required.

Traditionally, treatment strategies are evaluated via large, expensive trials. Given the possibly comparable and high as well efficacy of most interventions for CIN, it is unlikely that any

adequately powered RCT assessing the relative efficacy of different treatment techniques will ever be conducted. Such a trial would require thousands of women in order to reach the statistical power needed to detect differences in the pre-invasive and invasive recurrence rates. In summary, there is currently a lack of adequately powered randomised evidence to allow us to compare the various interventions. However, there is a plethora of available observational studies in the field. These studies are a potentially valuable source of evidence, and may act as a complement to the available randomised evidence, allowing us to more accurately assess the comparative effectiveness and safety of the various treatment alternatives. In this paper, we aim to perform a systematic review of both randomised and observational studies in the field, and quantitatively synthesize their findings in meta-analyses.

Systematic reviews and pairwise meta-analyses are widely accepted as a useful tool in comparative effectiveness research, and are commonly used to summarise, critically appraise and synthesise evidence from multiple studies. Investigators aiming to address a research question identify all relevant studies, evaluate their quality, synthesise their findings (meta-analysis) and interpret the provided evidence. Systematic reviews and meta-analyses have played a key role in providing evidence on the efficacy and safety of treatment methods and management strategies in cervical cancer prevention. However, the increased number of management strategies and multiple treatment options requires the use of more advanced evidence-synthesis methods.

Network meta-analysis (NMA) is an extension of pairwise meta-analysis, for the case when multiple treatments are available for the same condition. NMA has been recognised by the National Institute of Clinical Excellence (NICE)[22] and several international Health Technology Assessment (HTA) agencies[23 24] as a methodological tool that has the potential to increase precision in treatment effect estimates but also to infer on the clinical efficacy/ safety between treatments that have never been compared in trials. NMA uses both direct evidence (i.e. coming from studies comparing head-to-head the treatments of interest) and indirect evidence (i.e. coming from studies comparing the treatments of interest via an intermediate common comparator)[25-28], allows the estimation of relative treatment effects between all available interventions, and provides a clinically useful ranking of the different competing treatments. The methodology of NMA has never been used before to assess the comparative efficacy and complications of different treatment techniques used in the management of CIN. Furthermore, novel NMA methodologies will be employed to allow the use of both randomised and observational data.

The aim of this systematic review and NMA is to compare and clinically rank the alternative treatment techniques for CIN based on their efficacy, complications and adverse effects. This NMA forms part of the CIRCLE project (**C**ervical Cancer Incidence, C**I**N Recurrence and **R**eproduction after **L**ocal **E**xcision), which aims to generate a clinically useful raking of alternative options for treatment of CIN according to their efficacy (risk of pre-invasive and invasive recurrence), morbidity and cost-effectiveness.

## METHODS AND ANALYSIS

This protocol is written in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (see Supplementary File 1)[29]. PROSPERO registration will be updated if we make any amendments to this protocol.

### Eligibility criteria of studies

Types of participants

We will include women of all ages treated with local surgical treatment for CIN (or glandular intraepithelial neoplasia) or micro-invasive early cervical cancer (stage IA1). We will only include women with histological diagnosis of CIN.

Types of interventions

The treatment techniques for cervical intraepithelial neoplasia (CIN) are divided into excisional and ablative. The excisional include cold knife conisation (CKC), laser conisation (LC), needle excision of the transformation zone (NETZ), also known as straight wire excision of the transformation zone (SWETZ), large loop excision of the transformation zone (LLETZ), also known as loop electrosurgical excisional procedure (LEEP) and Fischer cone biopsy excisor (FCBE), while the ablative include radical point diathermy (RD), cryotherapy (CT), cold coagulation (CC) and laser ablation (LA). Figure 1 displays a network example of comparisons between studied treatment techniques. When the treatment is not specified, we will group these under wider categories excision (ENS) or ablation (ANS).

Outcome measures

*Primary outcome*

- High-grade treatment failure rates defined as recurrent or residual histologically-proven CIN2 or worse

*Secondary outcomes*

- Treatment failure rates defined as histologically-proven CIN1 or worse
- Abnormal cytology (defined as ASCUS or worse) and/or histology CIN1 or worse
- HPV positivity rates
- Involved margins rates (endocervical, ectocervical, or both)
- Peri-operative or post-operative bleeding
- Cervical stenosis

Primary and secondary outcomes were chosen by clinical experts of the team.

Types of studies

We will include RCTs, quasi-RCTs and observational cohort studies comparing rates of treatment failure (recurrent/residual disease) or complications amongst the abovementioned surgical techniques. Single-arm studies not presenting a comparison will be excluded. Studies will be considered regardless of time or language.

**Information sources and search strategy**

The Cochrane Gynaecological Cancer Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE will be searched for eligible studies by an experienced librarian, as presented in Supplementary File 2. Metaregister, Physicians Data Query, www.controlled-trials.com/rct, www.clinicaltrials.gov and www.cancer.gov/clinicaltrials will be searched for ongoing studies. ZETOC (http://zetoc.mimas.ac.uk) and WorldCat Dissertations will be searched for conference proceedings and theses, respectively. References of the retrieved articles and meta-analyses will be hand-searched, the "related articles" feature in MEDLINE will be employed and experts in the field will be contacted in an attempt to identify further reports of studies. Corresponding authors will be contacted for any relevant ongoing trials and unpublished data.

We will include both published and unpublished data and there will be no time, place or language restriction.

**Study selection**

Two team members will independently screen titles and abstracts of citations at level 1, using the reference management software Zotero. At level 2, the full text of all potentially eligible articles will be assessed using the same inclusion criteria. Disagreements will be resolved through discussion with a third review author.

**Data collection**

Data from the included studies will be abstracted at level 3 by two reviewers independently using an a priori developed data collection form in Excel. The following data will be abstracted from the included studies: study characteristics, including author, publication year study design, inclusion/exclusion criteria, and intervention details, participant characteristics, including age, CIN grade and smoking, and dropout rates, and outcome characteristics. In RCTs, we will prefer arm-level data (number of events and sample size per intervention arm for dichotomous data, and mean and standard deviation (SD) per intervention arm for continuous data), but if these are missing, the study-level data will be used in the analysis, e.g. reported odds ratios (ORs) for dichotomous outcomes and mean differences (MDs) for continuous outcomes, along with a measure of uncertainly (e.g., confidence interval [CI]). For continuous outcome data not reported as means and standard deviations, we will first contact the corresponding study authors for further information, but if no additional data are provided, we will perform imputation methods to derive approximate effect measures[30 31]. When an eligible study is observational, we will prefer adjusted treatment effect estimates accounting for the impact of potential confounders, but if these are missing, the unadjusted estimated treatment effects will be abstracted with a corresponding uncertainty measure (e.g. CI). Disagreements will be resolved through consensus or the involvement of a third reviewer.

**Risk of bias assessment**

RCTs will be assessed for quality and risk of bias using the Cochrane risk of bias tool[32] in the following domains: randomisation process, deviations from the intended interventions,

missing outcome data, measurement of the outcome and selection of the reported result. The risk of bias in each domain, as well as the overall risk of bias, will be rated as "low risk", "some concerns", or "high risk", after answering the signalling questions of each domain with "Yes", "Potentially Yes", "Potentially No" or "No". Non-randomised studies (NRS) will be assessed using the ROBINS-I tool[33] with potential confounding factors: grade of treated CIN, age and smoking. The following domains will be assessed for NRS: confounding, selection of participants into the study, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes and selection of the reported results. The risk of bias in each domain, as well as the overall risk of bias, will be rated as "low", "moderate", "serious", or "critical", after answering the signalling questions of each domain with "Yes", "Potentially Yes", "Potentially No" or "No". Pairs of team members will independently assess the methodological quality and risk of bias of the eligible studies. Conflicts will be resolved through discussion or with a third investigator. When inadequate information is available from the studies to rate a risk of bias item, we will contact the corresponding study authors for clarification.

**Statistical synthesis**

Characteristics of included studies and Network

For each outcome, we will produce a network plot (see for example Figure 1) of the available evidence, as well as descriptive statistics, including comparison type, publication year, study design, outcome data, and potential effect modifiers (e.g., age).

Pairwise Meta-analyses

A random-effects meta-analysis will be conducted for each pairwise comparison in each outcome using the inverse variance model and the the Hartung-Knapp-Sidik-Jonkman method to estimate each summary treatment effect and its 95% CI[34-36]. The between-study variance will be estimated with the restricted maximum likelihood estimator, whereas its 95% CI with the Q-profile approach[34 37 38]. We will also use the $I^2$ statistic along a 95% CI[39 40] to evaluate between-study heterogeneity. For continuous outcomes we will report the summary MDs, whereas for dichotomous outcomes we will use the summary ORs, along with a 95% CI. The *metafor* package[41] in R[42] will be used for all meta-analyses.

Network meta-analyses (NMA)

*Data synthesis*

A random-effects NMA will be conducted, since we anticipate methodological and clinical between-study heterogeneity. We will assume common between-study variance parameter across treatment comparisons in the network, so that comparisons informed by a single study can borrow strength from the remaining network [43 44]. This assumption is clinically reasonable because all treatments included in the network of trials are of the same nature. The between-study variance will be estimated with the DerSimonian and Laird method of moments approach[45]. We will employ the design-adjusted" and a three-level hierarchical NMA models as described in Efthimiou et al[46] by incorporating all the available information, both RCTs and NRS, in a single NMA model. We will explore the impact of assigning

different levels of credibility and subsequently down-weighting the NRS according to experts' opinion and the results of the ROBINS-I tool in several sensitivity analyses.

Similar to the pairwise meta-analysis, for continuous outcomes we will report the estimated MDs, whereas for dichotomous outcomes we will use the estimated ORs, with a 95% CI. Along the 95% CI for the summary effect size, we will report 95% prediction intervals to observe the interval within which the effect estimate is expected to lie should another trial become available[47]. To rank the efficacy for each intervention, we will calculate the ranking probabilities for all treatments, the surface under the cumulative ranking curve (SUCRA) or P-scores, and the mean ranks[48 49]. A rank-heat plot will be used to depict the SUCRA values or P-scores across all outcomes[50]. We will apply all NMA models in R[42] using the *netmeta* package[51] and *rjags*[52] package..

*Assessment of the transitivity assumption*

One of the prerequisite assumptions in NMA is the transitivity assumption, under which the effect modifiers have a similar distribution across treatment comparisons in a network[27 53 54]. Potential effect modifiers expected to influence the estimated treatment effects include year of study, method of ascertainment of exposure/outcome (hospital records, registries or interviews/questionnaires), age, smoking and grade of CIN. For each pairwise comparison with available direct evidence we will summarize these characteristics and will visually inspect the similarity of the identified studies. We will also investigate the inclusion and exclusion criteria of all studies, to make sure that patients, treatments and outcomes in the studies are sufficiently similar in all aspects that might modify relative treatment effects.

*Assessment of statistical inconsistency*

Consistency in a network of trials will be evaluated both locally and globally. We will first assess the consistency assumption locally by separating the direct from the indirect evidence for every comparison in a network to make judgements about their statistical differences, using the back-calculation method[55]. Then we will assess consistency in each network globally using the design-by-treatment interaction model[56]. We will conceptually explore for potential intransitivity in every network even in the absence of evidence for inconsistency, since the inconsistency tests have low power to detect true inconsistency[57 58]. If no substantial inconsistency is identified in the network of RCTs, we will then evaluate the agreement between RCTs and NRS using the same local and global approaches. Both local (back-calculation method) and global (design-by-treatment interaction model) assessments will be performed under the random-effects model in R[42] using the *netmeta* package[51].

In the NMA including both RCTs and NRS, we will assess for differences between the different study designs[46]. For each treatment comparison we will summarize evidence by up to four different types: direct randomised, indirect randomised, direct non-randomised and indirect non-randomised. If important discrepancies between these types are found, these will be investigated to confirm that the transitivity assumption holds (e.g. when randomised and non-randomised evidence are very different in terms of populations, interventions, etc., the

transitivity assumption may be violated). If disagreement occurs for a certain characteristic, this will be explored through a network meta-regression model[26].

*Exploring heterogeneity and inconsistency: subgroup analyses and meta-regression*
The between-study heterogeneity will be explored by comparing the estimated between-study variance with the empirical distribution derived by Rhodes et al for continuous data[59] and the one derived by Turner et al for dichotomous data[60]. We will also compare 95% CIs with the 95% prediction intervals to infer on the magnitude of the between-study variance.

If at least 10 studies are available, the following potential sources of heterogeneity and/or inconsistency will be explored for the primary outcome using subgroup or meta-regression analyses: year of study, method of ascertainment of exposure/outcome (hospital records, registries or interviews/questionnaires), age, smoking and grade of CIN.

*Reporting bias and small study effects*
We will assess small-study effects by visually exploring the funnel-plot for each treatment, and the comparison adjusted funnel plot[61] when at least 10 studies are available. We will also conduct a network meta-regression using the study variance as a covariate[62 63].

**Assessment of the credibility of the evidence**
For the primary outcome, two team members will determine the degree of confidence in the estimated NMA results using CINEMA[64] and the relevant online tool (http://cinema.ispm.ch/). The six CINEMA domains, within-study bias (i.e., risk of bias in the included studies), across-study bias (i.e., publication and reporting bias), indirectness, imprecision, heterogeneity and incoherence (i.e., differences between direct and indirect evidence)[64], will first be rated as high quality, and then they will be downgraded if judged appropriate to moderate, low, or very low quality.

## ETHICS AND DISSEMINATION

We do not require ethical approval for this review. We aim to disseminate the results to clinicians, academic researchers, health agencies and decision makers, to patients and the public. We will publish the results in high impact open access journals and disseminate findings though presentations at medical conferences. The data will become available in public repositories. We will develop information sheets and briefings, highlighting the key findings and circulate newsletters. We will work closed with the Jo's Trust, charity in cervical cancer that frequently organises events to educate the public and also engage the media with interviews. We circulate findings in the Imperial College webpage and will circulate newsletters.

**Figure 1.** Network of possible pairwise comparisons between eligible treatment methods
Abbreviations: **FCBE**=Fischer cone biopsy excision; **LLETZ**= large loop excision of the transformation zone, also known as **LEEP**=loop electrosurgical excisional procedure; **NETZ**=needle excision of the transformation, also known as **SWETZ**=straight wire excision

of the transformation zone; **LC**=laser conisation; **CKC**=cold knife conisation; **LA**=laser ablation; **CC**=cold coagulation; **CT**=cryotherapy; **RD**=radical point diathermy

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## STATEMENTS

### Declaration

The corresponding author had full access to all the data in the study and the final responsibility for the decision to submit for publication.

The senior author MK (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted.

**Author statement**

The study was conceived and designed by MK, GS and EP. The protocol was drafted by AA, MK, AAV, OE, IK, GS and was revised critically for important intellectual content by all authors (AA, AAV, OE, IK, HN, SL, MP, PMH, PB, EP, GS, MK).

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All contributors are listed as authors.

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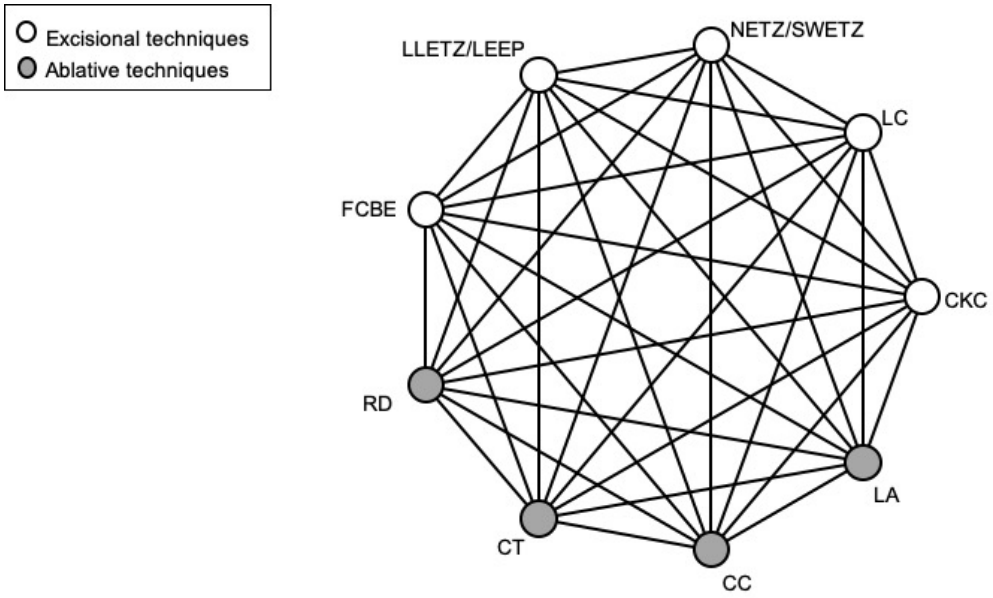
**Competing interests statement**

We have read and understood BMJ policy on declaration of interests and declare that we have no conflict of interests. All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work**.**

Dr Kyrgiou has received travel and conference expenses, honoraria and consultancy fees for commercial companies (Inovio, MSD etc); these activities are not related to the project.

**Data sharing**

No additional data available.




Network of possible pairwise comparisons between eligible treatment methods

235x142mm (72 x 72 DPI)

**Supplementary File 1: Reporting checklist for protocol of a systematic review**

Based on the PRISMA-P guidelines.

| | | Reporting Item | Page Number |
|---|---|---|---|
| Identification | #1a | Identify the report as a protocol of a systematic review | 1 |
| Update | #1b | If the protocol is for an update of a previous systematic review, identify as such | N/A (no previous NMA) |
| | #2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | 2 |
| Contact | #3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | 1 |
| Contribution | #3b | Describe contributions of protocol authors and identify the guarantor of the review | 14 |
| | #4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | 4 |
| Sources | #5a | Indicate sources of financial or other support for the review | 15 |
| Sponsor | #5b | Provide name for the review funder and / or sponsor | 15 |
| Role of sponsor or funder | #5c | Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol | 15 |
| Rationale | #6 | Describe the rationale for the review in the context of what is already known | 3-4 |
| Objectives | #7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | 4 |
| Eligibility criteria | #8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | 5 |

| | | | |
|---|---|---|---|
| Information sources | #9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | 5-6 |
| Search strategy | #10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | 5; Supplementary File 2 |
| Study records - data management | #11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | 6 |
| Study records - selection process | #11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) | 6 |
| Study records - data collection process | #11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | 6 |
| Data items | #12 | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications | 6 |
| Outcomes and prioritization | #13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | 5 |
| Risk of bias in individual studies | #14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | 6-7 |
| Data synthesis | #15a | Describe criteria under which study data will be quantitatively synthesised | 7 |
| | #15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ) | 7-8 |
| | #15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | 8-9 |
| | #15d | If quantitative synthesis is not appropriate, describe the type of | N/A |

| | | | |
|---|---|---|---|
| | | summary planned | |
| Meta-bias(es) | #16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | 9 |
| Confidence in cumulative evidence | #17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | 9 |

**Supplementary File 2: Search algorithms**

**Medline Ovid RCT only**

1 exp Cervical Intraepithelial Neoplasia/
2 CIN.mp.
3 (cervi* and (intraepithel* or epithel*)).mp.
4 (cervi* and dysplasia).mp.
5 (cervi* and carcinoma in situ).mp.
6 (cervi* and cancer in situ).mp.
7 (cervi* and (precancer* or pre-cancer*)).mp.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 surgery.fs.
10 exp Gynecologic Surgical Procedures/
11 (surg* or ablat* or excis* or cryotherapy or laser* or cone or conisation or biopsy or transformation zone or LLETZ or LEEP).mp.
12 9 or 10 or 11
13 8 and 12
14 randomized controlled trial.pt.
15 controlled clinical trial.pt.
16 randomized.ab.
17 placebo.ab.
18 clinical trials as topic.sh.
19 randomly.ab.
20 trial.ti.
21 14 or 15 or 16 or 17 or 18 or 19 or 20
22 13 and 21

**Medline Ovid NON RCT only**

1. exp Cervical Intraepithelial Neoplasia/
2. CIN.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3. (cervi* and (intraepithel* or epithel*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4. (cervi* and dysplasia).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

5. (cervi* and carcinoma in situ).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
6. (cervi* and cancer in situ).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7. (cervi* and (precancer* or pre-cancer*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. surgery.fs.
10. exp Gynecologic Surgical Procedures/
11. (surg* or ablat* or excis* or cryotherapy or laser* or cone or conisation or biopsy or transformation zone or LLETZ or LEEP).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
12. 9 or 10 or 11
13. 8 and 12
14. randomized controlled trial.pt.
15. controlled clinical trial.pt.
16. randomized.ab.
17. placebo.ab.
18. clinical trials as topic.sh.
19. randomly.ab.
20. trial.ti.
21. groups.ab.
22. exp cohort studies/
23. exp case-control studies/
24. (cohort* or prospective* or retrospective* or (case* and (control* or series))).mp.
25. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. (animals not (humans and animals)).sh.
27. 25 not 26
28. 13 and 27

**Embase Ovid RCT only**

1 exp Uterine Cervix Carcinoma in Situ/

2 CIN.mp.
3 (cervi* and (intraepithel* or epithel*)).mp.
4 (cervi* and dysplasia).mp.
5 (cervi* and carcinoma in situ).mp.
6 (cervi* and cancer in situ).mp.
7 (cervi* and (precancer* or pre-cancer*)).mp.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 su.fs.
10 exp gynecologic surgery/
11 (surg* or ablat* or excis* or cryotherapy or laser* or cone or conisation or biopsy or transformation zone or LLETZ or LEEP).mp.
12 9 or 10 or 11
13 8 and 12
14 crossover procedure/
15 double-blind procedure/
16 randomized controlled trial/
17 single-blind procedure/
18 random*.mp.
19 factorial*.mp.
20 (crossover* or cross over* or cross-over*).mp.
21 placebo*.mp.
22 (double* adj blind*).mp.
23 (singl* adj blind*).mp.
24 assign*.mp.
25 allocat*.mp.
26 volunteer*.mp.
27 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28 13 and 27

**Embase Ovid All Studies**

1. exp Uterine Cervix Carcinoma in Situ/
2. CIN.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
3. (cervi* and (intraepithel* or epithel*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]

4. (cervi* and dysplasia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
5. (cervi* and carcinoma in situ).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
6. (cervi* and cancer in situ).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
7. (cervi* and (precancer* or pre-cancer*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. su.fs.
10. exp gynecologic surgery/
11. (surg* or ablat* or excis* or cryotherapy or laser* or cone or conisation or biopsy or transformation zone or LLETZ or LEEP).mp.
12. 9 or 10 or 11
13. 8 and 12
14. exp controlled clinical trial/
15. randomized.ab.
16. randomly.ab.
17. trial.ab.
18. groups.ab.
19. exp cohort analysis/
20. cohort*.mp.
21. exp retrospective study/
22. exp prospective study/
23. (case* and series).mp.
24. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. 13 and 24

**CENTRAL**

#1 MeSH descriptor Cervical Intraepithelial Neoplasia explode all trees
#2 CIN
#3 cervi* and (intraepithel* or epithel*)
#4 cervi* and dysplasia
#5 cervi* and carcinoma in situ
#6 cervi* and cancer in situ
#7 cervi* and (precancer* or pre-cancer*)
#8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)

#9 Any MeSH descriptor with qualifier(s): [Surgery - SU]
#10 MeSH descriptor: [Gynecologic Surgical Procedures] explode all trees
#11 surg* or ablat* or excis* or cryotherapy or laser* or cone or conisation or biopsy or transformation zone or LLETZ or LEEP
#12 #9 or #10 or #11
#13 #8 and #12

BMJ Open

# Comparative efficacy and complication rates after local treatment for cervical intra-epithelial neoplasia and stage 1a1 cervical cancer: protocol for a systematic review and network meta-analysis from the CIRCLE Group

| | |
|---|---|
| Journal: | *BMJ Open* |
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| Primary Subject Heading: | Obstetrics and gynaecology |
| Secondary Subject Heading: | Evidence based practice |

| | |
|---|---|
| Keywords: | "Cervical Intraepithelial Neoplasia/surgery"[Mesh], "Cervical Intraepithelial Neoplasia/therapy"[Mesh], "Treatment Outcome"[Mesh], "Recurrence"[Mesh], "Conization/adverse effects"[Mesh], "Ablation Techniques/adverse effects"[Mesh] |
| | |

# Comparative efficacy and complication rates after local treatment for cervical intra-epithelial neoplasia and stage 1a1 cervical cancer: protocol for a systematic review and network meta-analysis from the CIRCLE Group

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**Word Count:** 3345

## ABSTRACT

**Introduction:** Local treatments for cervical intra-epithelial neoplasia (CIN) and micro-invasive disease remove or ablate a cone-shaped part of the uterine cervix containing the abnormal cells. A trend towards less radical techniques has raised concerns that this may adversely impact the rates of precancerous and cancerous recurrence. However, there has been no strong evidence to support such claims. We hereby describe a protocol of a systematic review and network meta-analysis that will update the evidence and compare all relevant treatments in terms of efficacy and complications.

**Methods and Analysis:** Literature searches in electronic databases (CENTRAL, MEDLINE, EMBASE) or trial registries will identify published and unpublished randomised controlled trials (RCTs) and cohort studies comparing the efficacy and complications amongst different excisional and ablative techniques. The excisional techniques include cold knife, laser or fischer cone, large loop or needle excision of the transformation zone and the ablative radical point diathermy, cryotherapy, cold coagulation or laser ablation. The primary outcome will be residual/recurrent disease defined as abnormal histology or cytology of any grade, while secondary outcomes will include treatment failure rates defined as high-grade histology or cytology, histologically-confirmed CIN1+ or histologically-confirmed CIN2+, HPV positivity rates, involved margins rates, bleeding and cervical stenosis rates. We will assess the risk of bias in RCTs and observational studies using tools developed by the Cochrane Collaboration. Two authors will independently assess study eligibility, abstract the data, and assess the risk of bias. Random-effects meta-analyses and network meta-analyses will be conducted using the odds ratio for dichotomous outcomes and the mean difference for continuous outcomes. The quality of the evidence for the primary outcome will be assessed using the CINEMA tool.

**Ethics and dissemination:** Ethical approval not required. We will disseminate findings to clinicians, policy makers, patients and the public.

**PROSPERO registration number**: CRD42018115508


## ARTICLE SUMMARY

### Strengths and limitations of this study

- We plan to conduct the first network meta-analysis to assess the relative efficacy and complication rates of treatment methods for cervical pre-invasive and early micro-invasive disease.
- This study will produce comprehensive summaries of the clinical ranking of treatments and will employ methodologies that will allow the use of both randomised and observational data, aiming to utilise all published evidence.
- The results will inform clinicians, patients and clinical guidelines and will allow effective patient counselling at colposcopy clinics.
- We expect to find retrospective observational studies at high risk of recall, selection and publication bias. We will try to overcome this limitation by employing methods that aim to minimise bias.

**KEYWORDS**
"Cervical Intraepithelial Neoplasia/surgery"[Mesh]
"Cervical Intraepithelial Neoplasia/therapy"[Mesh]
"Treatment Outcome"[Mesh]
"Recurrence"[Mesh]
"Conization/adverse effects"[Mesh]
"Ablation Techniques/adverse effects"[Mesh]

## INTRODUCTION

Organised screening programmes in countries such as the UK, have led to a dramatic decrease in the incidence and mortality from cervical cancer, especially when compared with the corresponding statistics for the other major cancers. Over a twenty-year period, from 1993-1995 to 2013-2015, the overall age-standardised incidence rate of cancer in females increased by 16% in the UK[1], whereas the corresponding data for cervical cancer showed a decrease of 24%[2]. Cervical cancer is largely preventable through detection and treatment of the pre-invasive precursor, cervical intra-epithelial neoplasia (CIN)[3]. The local treatment methods are divided into excisional and destructive (ablative) that aim to remove or ablate respectively a cone shaped part of the cervix that contains the 'transformation zone' with the precancerous cells. Although large loop excision of the transformation zone (LLETZ) is the most commonly used methods in the UK[4] given its ease of execution and low cost, the preference of techniques varies across Europe and internationally.

A Cochrane systematic review of RCTs concluded that all local treatment techniques are highly effective in preventing pre-invasive recurrence[5]. However, this review found no evidence of difference in treatment failure rates amongst the treatment techniques. This could be because the RCTs, and the subsequent meta-analysis might have been underpowered to detect differences between the treatments. The largest study recruited only 390 participants[6], while the majority of the rest were much smaller. A larger population-based study from Sweden[7], which included 150,883 women diagnosed and treated for CIN3 (3,148,222 woman-years), reported a doubled standardized incidence ratio for post-treatment invasive recurrence during the follow-up period of around 4 decades in comparison to the general population, and initiated debates on the impact that less radical treatments may have on the subsequent risk of invasion[8]. The trend towards techniques that remove smaller parts of the cervix can be attributed to the fact that many of these are easy to do, they are of low cost, and can be performed in an outpatient setting. Increased awareness of the impact of the more radical or deeper techniques on the risk of prematurity may have also contributed[9-20].

The impact of different techniques on the risk of pre-invasive and/or invasive recurrence remains therefore unclear. With some advocating the minimum radicality of treatment to prevent treatment-induced reproductive morbidity[10 21], and others raising concerns about the increase in the risk of future invasion[7 8], a definite answer regarding the relative merits and risks among the various treatment strategies is required.

Traditionally, treatment strategies are evaluated via large, expensive trials. Given the possibly comparable (and high) efficacy of most interventions for CIN, it is unlikely that any adequately powered RCT assessing the relative efficacy of different treatment techniques will ever be conducted. Such a trial would require thousands of women in order to reach the statistical power needed to detect differences in the pre-invasive and invasive recurrence rates. In summary, there is currently a lack of adequately powered randomised evidence to allow us to compare the various interventions. However, there is a plethora of available observational studies in the field. These studies are a potentially valuable source of evidence, and may act as a complement to the available randomised evidence, allowing us to more accurately assess the comparative effectiveness and safety of the various treatment alternatives. In this paper, we aim to perform a systematic review of both randomised and observational studies in the field, and quantitatively synthesize their findings in meta-analyses.

Systematic reviews and pairwise meta-analyses are widely accepted as a useful tool in comparative effectiveness research, and are commonly used to summarise, critically appraise and synthesise evidence from multiple studies. Investigators aiming to address a research question identify all relevant studies, evaluate their quality, synthesise their findings (meta-analysis) and interpret the provided evidence. Systematic reviews and meta-analyses have played a key role in providing evidence on the efficacy and safety of treatment methods and management strategies in cervical cancer prevention. However, the increased number of management strategies and multiple treatment options requires the use of more advanced evidence-synthesis methods.

Network meta-analysis (NMA) is an extension of pairwise meta-analysis, for the case when multiple treatments are available for the same condition. NMA has been recognised by the National Institute of Clinical Excellence (NICE)[22] and several international Health Technology Assessment (HTA) agencies[23 24] as a methodological tool that has the potential to increase precision in treatment effect estimates but also to infer on the clinical efficacy/ safety between treatments that have never been compared in trials. NMA uses both direct evidence (i.e. coming from studies comparing head-to-head the treatments of interest) and indirect evidence (i.e. coming from studies comparing the treatments of interest via an intermediate common comparator)[25-28], allows the estimation of relative treatment effects between all available interventions, and provides a clinically useful ranking of the different competing treatments. The methodology of NMA has never been used before to assess the comparative efficacy and complications of different treatment techniques used in the management of CIN. Furthermore, novel NMA methodologies will be employed to allow the use of both randomised and observational data.

The aim of this systematic review and NMA is to compare and clinically rank the alternative treatment techniques for CIN based on their efficacy, complications and adverse effects. This NMA forms part of the CIRCLE project (**C**ervical Cancer Incidence, C**I**N Recurrence and **R**eproduction after **L**ocal **E**xcision), which aims to generate a clinically useful raking of

alternative options for treatment of CIN according to their efficacy (risk of pre-invasive and invasive recurrence), morbidity and cost-effectiveness.

## METHODS AND ANALYSIS

This protocol is written in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (see Supplementary File 1)[29]. PROSPERO registration will be updated if we make any amendments to this protocol. The start date was 1st of October 2018 with expected end date 1st of October 2020.

### Eligibility criteria of studies

Types of participants

We will include women of all ages treated with local surgical treatment for CIN (or glandular intraepithelial neoplasia) or micro-invasive early cervical cancer (stage IA1). We will only include women with histological diagnosis of CIN on punch biopsy or cone.

Types of interventions

The treatment techniques for cervical intraepithelial neoplasia (CIN) are divided into excisional and ablative. The excisional include cold knife conisation (CKC), laser conisation (LC), needle excision of the transformation zone (NETZ), also known as straight wire excision of the transformation zone (SWETZ), large loop excision of the transformation zone (LLETZ), also known as loop electrosurgical excisional procedure (LEEP) and Fischer cone biopsy excisor (FCBE), while the ablative include radical point diathermy (RD), cryotherapy (CT), cold coagulation (CC) and laser ablation (LA). Figure 1 displays a network example of comparisons between studied treatment techniques. When the treatment is not specified, we will group these under wider categories excision (ENS) or ablation (ANS).

Outcome measures

*Primary outcome*

- Treatment failure rates defined as any abnormal cytology [ASCUS (atypical squamous cells of undetermined significance) or worse] or histology (CIN1 or worse)

*Secondary outcomes*

- Treatment failure rates defined as high-grade abnormal cytology [HSIL (high-grade squamous intraepithelial lesion) or worse] or histology (CIN2 or worse)
- Treatment failure rates defined as residual or recurrent histologically-proven CIN1 or worse
- Treatment failure rates defined as residual or recurrent histologically-proven CIN2 or worse
- HPV positivity rates
- Involved margins rates (incomplete excision of the lesion): both, endocervical, ectocervical involvement
- Peri-operative or post-operative bleeding
- Cervical stenosis

Primary and secondary outcomes were chosen by clinical experts of the team. Treatment failure rates and HPV positivity rates will be reported at 6 to 12 months intervals based on the available data and reported intervals in the included studies.

Types of studies

We will include RCTs, quasi-RCTs and observational cohort studies comparing rates of treatment failure (recurrent/residual disease) or complications amongst the abovementioned surgical techniques. Single-arm studies not presenting a comparison will be excluded. Studies will be considered regardless of time or language.

**Information sources and search strategy**

The Cochrane Gynaecological Cancer Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE will be searched for eligible studies by an experienced librarian, as presented in Supplementary File 2. Metaregister, Physicians Data Query, www.controlled-trials.com/rct, www.clinicaltrials.gov, www.cancer.gov/clinicaltrials and WHO Registry Network (https://www.who.int/ictrp/network/en/) will be searched for ongoing studies. ZETOC (http://zetoc.mimas.ac.uk) and WorldCat Dissertations will be searched for conference proceedings and theses, respectively. References of the retrieved articles and meta-analyses will be hand-searched, the "related articles" feature in MEDLINE will be employed and experts in the field will be contacted in an attempt to identify further reports of studies. Corresponding authors will be contacted for any relevant ongoing trials and unpublished data.

We will include both published and unpublished data and there will be no time, place or language restriction; articles in language other than English will be translated using online translation services.

**Study selection**

Two team members will independently screen titles and abstracts of citations at level 1, using the reference management software Zotero. At level 2, the full text of all potentially eligible articles will be assessed using the same inclusion criteria. Disagreements will be resolved through discussion with a third review author.

**Data collection**

Data from the included studies will be abstracted at level 3 by two reviewers independently using an a priori developed data collection form in Excel. The following data will be abstracted from the included studies: study characteristics, including author, publication year, country, study design, inclusion/exclusion criteria, and intervention details, participant characteristics, including age, CIN grade and smoking, and dropout rates, and outcome characteristics. In RCTs, we will prefer arm-level data (number of events and sample size per intervention arm for dichotomous data, and mean and standard deviation (SD) per intervention arm for continuous data), but if these are missing, the study-level data will be used in the analysis, e.g. reported odds ratios (ORs) for dichotomous outcomes and mean

differences (MDs) for continuous outcomes, along with a measure of uncertainly (e.g., confidence interval [CI]). For continuous outcome data not reported as means and standard deviations, we will first contact the corresponding study authors for further information, but if no additional data are provided, we will perform imputation methods to derive approximate effect measures[30 31]. When an eligible study is observational, we will prefer adjusted treatment effect estimates accounting for the impact of potential confounders, but if these are missing, the unadjusted estimated treatment effects will be abstracted with a corresponding uncertainty measure (e.g. CI). Disagreements will be resolved through consensus or the involvement of a third reviewer.

**Risk of bias assessment**

RCTs will be assessed for quality and risk of bias using the Cochrane risk of bias tool[32] in the following domains: randomisation process, deviations from the intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. The risk of bias in each domain, as well as the overall risk of bias, will be rated as "low risk", "some concerns", or "high risk", after answering the signalling questions of each domain with "Yes", "Potentially Yes", "Potentially No" or "No". Non-randomised studies (NRS) will be assessed using the ROBINS-I tool[33] with potential confounding factors: grade of treated CIN, age and smoking. The following domains will be assessed for NRS: confounding, selection of participants into the study, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes and selection of the reported results. The risk of bias in each domain, as well as the overall risk of bias, will be rated as "low", "moderate", "serious", or "critical", after answering the signalling questions of each domain with "Yes", "Potentially Yes", "Potentially No" or "No". Pairs of team members will independently assess the methodological quality and risk of bias of the eligible studies. Conflicts will be resolved through discussion or with a third investigator. When inadequate information is available from the studies to rate a risk of bias item, we will contact the corresponding study authors for clarification.

**Statistical synthesis**

Characteristics of included studies and Network

For each outcome, we will produce a network plot (see for example Figure 1) of the available evidence, as well as descriptive statistics, including comparison type, publication year, study design, outcome data, and potential effect modifiers (e.g., age).

Pairwise Meta-analyses

A random-effects meta-analysis will be conducted for each pairwise comparison in each outcome using the inverse variance model and the the Hartung-Knapp-Sidik-Jonkman method to estimate each summary treatment effect and its 95% CI[34-36]. The between-study variance will be estimated with the restricted maximum likelihood estimator, whereas its 95% CI with the Q-profile approach[34 37 38]. We will also use the $I^2$ statistic along a 95% CI[39 40] to evaluate between-study heterogeneity. For continuous outcomes we will report the summary MDs, whereas for dichotomous outcomes we will use the summary ORs, along with a 95% CI. The *metafor* package[41] in R[42] will be used for all meta-analyses.

Network meta-analyses (NMA)

*Data synthesis*

A random-effects NMA will be conducted, since we anticipate methodological and clinical between-study heterogeneity. We will assume common between-study variance parameter across treatment comparisons in the network, so that comparisons informed by a single study can borrow strength from the remaining network [43 44]. This assumption is clinically reasonable because all treatments included in the network of trials are of the same nature. The between-study variance will be estimated with the DerSimonian and Laird method of moments approach[45]. We will employ NMA models that account for different propensity of bias across different study designs as described in Efthimiou et al[46]. We will explore the impact of assigning different levels of credibility and subsequently down-weight the NRS according to experts' opinion and the results of the ROBINS-I tool in several sensitivity analyses.

Similar to the pairwise meta-analysis, for continuous outcomes we will report the estimated MDs, whereas for dichotomous outcomes we will use the estimated ORs, with a 95% CI. Along the 95% CI for the summary effect size, we will report 95% prediction intervals, i.e. the intervals within which the true underlying treatment effect is expected to lie in a new trial[47]. To rank the efficacy for each intervention, we will calculate the ranking probabilities for all treatments, the surface under the cumulative ranking curve (SUCRA) or P-scores, and the mean ranks[48 49]. A rank-heat plot will be used to depict the SUCRA values or P-scores across all outcomes[50]. We will apply all NMA models in R[42] using the *netmeta* package[51] and *rjags*[52] package.

*Assessment of the transitivity assumption*

One of the prerequisite assumptions in NMA is the transitivity assumption, under which the effect modifiers have a similar distribution across treatment comparisons in a network[27 53 54]. For the participants characteristics that are described in the inclusion criteria of our systematic review (section type of participants), it is reasonable to assume that all treatments we plan to compare (section type of interventions) are "jointly randomisable". That means that any patient that fulfils that inclusion criteria, could potentially be assigned to any of the interventions. Potential effect modifiers expected to influence the estimated treatment effects include year of study, level of income of study country (as defined by World Bank[55]), method of ascertainment of exposure/outcome (hospital records, registries or interviews/questionnaires), age, smoking and grade of CIN. For each pairwise comparison with available direct evidence we will summarize these characteristics and will visually inspect the similarity of the identified studies. We will also investigate the inclusion and exclusion criteria of all studies, to make sure that patients, treatments and outcomes in the studies are sufficiently similar in all aspects that might modify relative treatment effects. More specifically, we will compare the patient characteristics (such as severity, age, parity etc) across the different treatments. If these characteristics are found to have a similar distribution across treatments then transitivity is supported. If differences are found, then these will be addressed in subgroup and sensitivity analyses.

*Assessment of statistical inconsistency*

Consistency in a network of trials will be evaluated both locally and globally. We will first assess the consistency assumption locally by separating the direct from the indirect evidence for every comparison in a network to make judgements about their statistical differences, using the back-calculation method[56]. Then we will assess consistency in each network globally using the design-by-treatment interaction model[57]. We will conceptually explore for potential intransitivity in every network even in the absence of evidence for inconsistency, since the inconsistency tests have low power to detect true inconsistency[58 59]. If no substantial inconsistency is identified in the network of RCTs, we will then evaluate the agreement between RCTs and NRS using the same local and global approaches. Both local (back-calculation method) and global (design-by-treatment interaction model) assessments will be performed under the random-effects model in R[42] using the *netmeta* package[51].

In the NMA including both RCTs and NRS, we will assess for differences between the different study designs[46]. For each treatment comparison we will summarize evidence by up to four different types: direct randomised, indirect randomised, direct non-randomised and indirect non-randomised. If important discrepancies between these types are found, these will be investigated to confirm that the transitivity assumption holds (e.g. when randomised and non-randomised evidence are very different in terms of populations, interventions, etc., the transitivity assumption may be violated). If disagreement occurs for a certain characteristic, this will be explored through a network meta-regression model[26].

*Exploring heterogeneity and inconsistency: subgroup analyses and meta-regression*

The between-study heterogeneity will be explored by comparing the estimated between-study variance with the empirical distribution derived by Rhodes et al for continuous data[60] and the one derived by Turner et al for dichotomous data[61]. We will also compare 95% CIs with the 95% prediction intervals to infer on the magnitude of the between-study variance.

If at least 10 studies are available, the following potential sources of heterogeneity and/or inconsistency will be explored for the primary outcome using subgroup or meta-regression analyses: year of study, level of income of study country (as defined by World Bank[55]), method of ascertainment of exposure/outcome (hospital records, registries or interviews/questionnaires), age, smoking, grade of CIN, and disease severity (e.g., women treated for high-grade CIN, exclusion of cases of microinvasion). In order to minimise potential bias due to confounding from NRS (e.g. type of treatment or outcome affected by severity), we will also perform a sensitivity analysis excluding NRS without adjusted effect estimates.

*Reporting bias and small study effects*

We will assess small-study effects by visually exploring the funnel-plot for each treatment, and the comparison adjusted funnel plot[62] when at least 10 studies are available. We will also conduct a network meta-regression using the study variance as a covariate[63 64].

**Assessment of the credibility of the evidence**

For the primary outcome, two team members will determine the degree of confidence in the estimated NMA results using CINEMA[65] and the relevant online tool (http://cinema.ispm.ch/). The six CINEMA domains, within-study bias (i.e., risk of bias in the included studies), across-study bias (i.e., publication and reporting bias), indirectness, imprecision, heterogeneity and incoherence (i.e., differences between direct and indirect evidence)[65], will first be rated as high quality, and then they will be downgraded if judged appropriate to moderate, low, or very low quality.

**Patient and Public involvement**

Patients and the wider public have been involved from the design of this proposal through clinics and the Jo's Cervical Cancer Trust. They have assisted study design and to formulate the research questions. Their involvement will continue throughout the study on regular 6 monthly meetings and will guide the priority questions to be addressed, the development of research reports in lay language and the dissemination of the results.

**ETHICS AND DISSEMINATION**

We do not require ethical approval for this review. We aim to disseminate the results to clinicians, academic researchers, health agencies and decision makers, to patients and the public. We will publish the results in high impact open access journals and disseminate findings though presentations at medical conferences. The data will become available in public repositories. We will develop information sheets and briefings, highlighting the key findings and circulate newsletters. We will work closed with the Jo's Trust, charity in cervical cancer that frequently organises events to educate the public and also engage the media with interviews. We circulate findings in the Imperial College webpage and will circulate newsletters.

**Figure 1.** Network of possible pairwise comparisons between eligible treatment methods Abbreviations: **FCBE**=Fischer cone biopsy excision; **LLETZ**= large loop excision of the transformation zone, also known as **LEEP**=loop electrosurgical excisional procedure; **NETZ**=needle excision of the transformation, also known as **SWETZ**=straight wire excision of the transformation zone; **LC**=laser conisation; **CKC**=cold knife conisation; **LA**=laser ablation; **CC**=cold coagulation; **CT**=cryotherapy; **RD**=radical point diathermy

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## STATEMENTS

### Declaration

The corresponding author had full access to all the data in the study and the final responsibility for the decision to submit for publication.
The senior author MK (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted.

### Author statement

The study was conceived and designed by MK, GS and EP. The protocol was drafted by AA, MK, AAV, OE, IK, GS and was revised critically for important intellectual content by all authors (AA, AAV, OE, IK, HN, SL, MP, PMH, PB, EP, GS, MK).

### Acknowledgements

We thank patients and patient representatives for their contribution to designing this study and developing the research questions.

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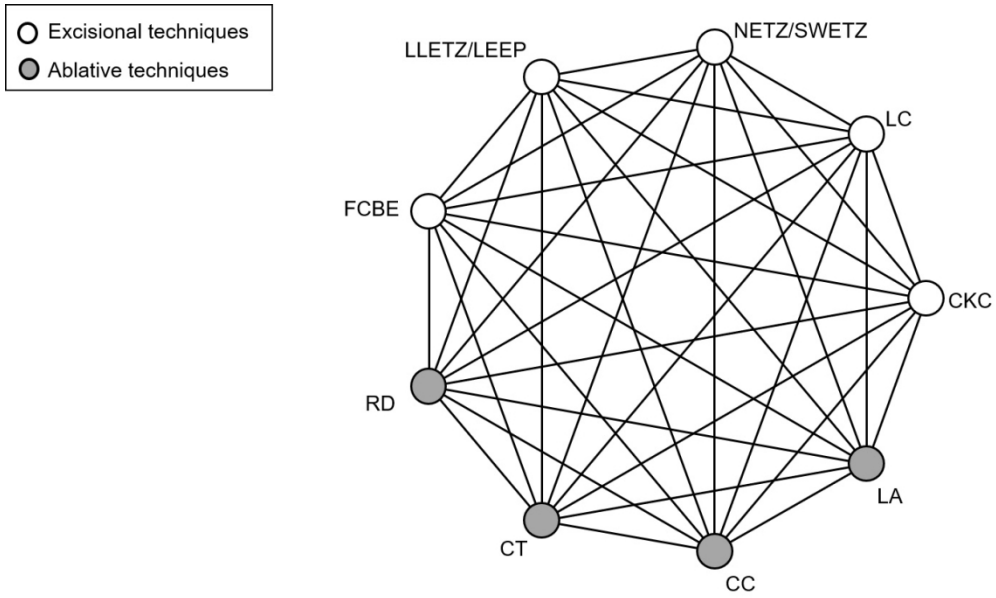
### Competing interests statement

We have read and understood BMJ policy on declaration of interests and declare that we have no conflict of interests. All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work**.**
Dr Kyrgiou has received travel and conference expenses, honoraria and consultancy fees for commercial companies (Inovio, MSD etc); these activities are not related to the project.

### Data sharing

No additional data available.

**Copyright statement**




Network of possible pairwise comparisons between eligible treatment methods

117x71mm (300 x 300 DPI)

**Supplementary File 1: Reporting checklist for protocol of a systematic review**

Based on the PRISMA-P guidelines.

| | | Reporting Item | Page Number |
|---|---|---|---|
| Identification | #1a | Identify the report as a protocol of a systematic review | 1 |
| Update | #1b | If the protocol is for an update of a previous systematic review, identify as such | N/A (no previous NMA) |
| | #2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | 2 |
| Contact | #3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | 1 |
| Contribution | #3b | Describe contributions of protocol authors and identify the guarantor of the review | 14 |
| | #4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | 4 |
| Sources | #5a | Indicate sources of financial or other support for the review | 15 |
| Sponsor | #5b | Provide name for the review funder and / or sponsor | 15 |
| Role of sponsor or funder | #5c | Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol | 15 |
| Rationale | #6 | Describe the rationale for the review in the context of what is already known | 3-4 |
| Objectives | #7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | 4 |
| Eligibility criteria | #8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | 5 |

| | | | |
|---|---|---|---|
| Information sources | #9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | 5-6 |
| Search strategy | #10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | 5; Supplementary File 2 |
| Study records - data management | #11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | 6 |
| Study records - selection process | #11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) | 6 |
| Study records - data collection process | #11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | 6 |
| Data items | #12 | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications | 6 |
| Outcomes and prioritization | #13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | 5 |
| Risk of bias in individual studies | #14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | 6-7 |
| Data synthesis | #15a | Describe criteria under which study data will be quantitatively synthesised | 7 |
| | #15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ) | 7-8 |
| | #15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | 8-9 |
| | #15d | If quantitative synthesis is not appropriate, describe the type of | N/A |

| | | | |
|---|---|---|---|
| | | summary planned | |
| Meta-bias(es) | #16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | 9 |
| Confidence in cumulative evidence | #17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | 9 |

**Supplementary File 2: Search algorithms**

**Medline Ovid RCT only**

1 exp Cervical Intraepithelial Neoplasia/
2 CIN.mp.
3 (cervi* and (intraepithel* or epithel*)).mp.
4 (cervi* and dysplasia).mp.
5 (cervi* and carcinoma in situ).mp.
6 (cervi* and cancer in situ).mp.
7 (cervi* and (precancer* or pre-cancer*)).mp.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 surgery.fs.
10 exp Gynecologic Surgical Procedures/
11 (surg* or ablat* or excis* or cryotherapy or laser* or cone or conisation or biopsy or transformation zone or LLETZ or LEEP).mp.
12 9 or 10 or 11
13 8 and 12
14 randomized controlled trial.pt.
15 controlled clinical trial.pt.
16 randomized.ab.
17 placebo.ab.
18 clinical trials as topic.sh.
19 randomly.ab.
20 trial.ti.
21 14 or 15 or 16 or 17 or 18 or 19 or 20
22 13 and 21

**Medline Ovid NON RCT only**

1. exp Cervical Intraepithelial Neoplasia/
2. CIN.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3. (cervi* and (intraepithel* or epithel*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4. (cervi* and dysplasia).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

5. (cervi* and carcinoma in situ).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
6. (cervi* and cancer in situ).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7. (cervi* and (precancer* or pre-cancer*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. surgery.fs.
10. exp Gynecologic Surgical Procedures/
11. (surg* or ablat* or excis* or cryotherapy or laser* or cone or conisation or biopsy or transformation zone or LLETZ or LEEP).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
12. 9 or 10 or 11
13. 8 and 12
14. randomized controlled trial.pt.
15. controlled clinical trial.pt.
16. randomized.ab.
17. placebo.ab.
18. clinical trials as topic.sh.
19. randomly.ab.
20. trial.ti.
21. groups.ab.
22. exp cohort studies/
23. exp case-control studies/
24. (cohort* or prospective* or retrospective* or (case* and (control* or series))).mp.
25. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. (animals not (humans and animals)).sh.
27. 25 not 26
28. 13 and 27

**Embase Ovid RCT only**

1 exp Uterine Cervix Carcinoma in Situ/

2 CIN.mp.
3 (cervi* and (intraepithel* or epithel*)).mp.
4 (cervi* and dysplasia).mp.
5 (cervi* and carcinoma in situ).mp.
6 (cervi* and cancer in situ).mp.
7 (cervi* and (precancer* or pre-cancer*)).mp.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 su.fs.
10 exp gynecologic surgery/
11 (surg* or ablat* or excis* or cryotherapy or laser* or cone or conisation or biopsy or transformation zone or LLETZ or LEEP).mp.
12 9 or 10 or 11
13 8 and 12
14 crossover procedure/
15 double-blind procedure/
16 randomized controlled trial/
17 single-blind procedure/
18 random*.mp.
19 factorial*.mp.
20 (crossover* or cross over* or cross-over*).mp.
21 placebo*.mp.
22 (double* adj blind*).mp.
23 (singl* adj blind*).mp.
24 assign*.mp.
25 allocat*.mp.
26 volunteer*.mp.
27 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28 13 and 27

**Embase Ovid All Studies**

1. exp Uterine Cervix Carcinoma in Situ/
2. CIN.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
3. (cervi* and (intraepithel* or epithel*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]

4. (cervi* and dysplasia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
5. (cervi* and carcinoma in situ).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
6. (cervi* and cancer in situ).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
7. (cervi* and (precancer* or pre-cancer*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. su.fs.
10. exp gynecologic surgery/
11. (surg* or ablat* or excis* or cryotherapy or laser* or cone or conisation or biopsy or transformation zone or LLETZ or LEEP).mp.
12. 9 or 10 or 11
13. 8 and 12
14. exp controlled clinical trial/
15. randomized.ab.
16. randomly.ab.
17. trial.ab.
18. groups.ab.
19. exp cohort analysis/
20. cohort*.mp.
21. exp retrospective study/
22. exp prospective study/
23. (case* and series).mp.
24. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. 13 and 24

**CENTRAL**

#1 MeSH descriptor Cervical Intraepithelial Neoplasia explode all trees
#2 CIN
#3 cervi* and (intraepithel* or epithel*)
#4 cervi* and dysplasia
#5 cervi* and carcinoma in situ
#6 cervi* and cancer in situ
#7 cervi* and (precancer* or pre-cancer*)
#8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)

#9 Any MeSH descriptor with qualifier(s): [Surgery - SU]
#10 MeSH descriptor: [Gynecologic Surgical Procedures] explode all trees
#11 surg* or ablat* or excis* or cryotherapy or laser* or cone or conisation or biopsy or transformation zone or LLETZ or LEEP
#12 #9 or #10 or #11
#13 #8 and #12