Cochrane Library

Cochrane Database of Systematic Reviews

Health education interventions to promote early presentation and referral for women with symptoms of endometrial cancer (Protocol)

Cheewakriangkrai C, Kietpeerakool C, Aue-aungkul A, Charoenkwan K, Pattanittum P, John D, Lumbiganon P

Cheewakriangkrai C, Kietpeerakool C, Aue-aungkul A, Charoenkwan K, Pattanittum P, John D, Lumbiganon P.
Health education interventions to promote early presentation and referral for women with symptoms of endometrial cancer.
Cochrane Database of Systematic Reviews 2019, Issue 1. Art. No.: CD013253.
DOI: 10.1002/14651858.CD013253.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Health education interventions to promote early presentation and referral for women with symptoms of endometrial cancer

Chalong Cheewakriangkrai[1], Chumnan Kietpeerakool[2], Apiwat Aue-aungkul[2], Kittipat Charoenkwan[1], Porjai Pattanittum[3], Denny John[4], Pisake Lumbiganon[2]

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand. [2]Department of Obstetrics and Gynaecology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand. [3]Department of Epidemiology and Biostatistics, Public Health Faculty, Khon Kaen University, Khon Kaen, Thailand. [4]Campbell Collaboration, New Delhi, India

Contact address: Chumnan Kietpeerakool, Department of Obstetrics and Gynaecology, Faculty of Medicine, Khon Kaen University, 123 Mitraparb Road, Amphur Muang, Khon Kaen, 40002, Thailand. kiet_ji@hotmail.com.

Editorial group: Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group.
Publication status and date: New, published in Issue 1, 2019.

Citation: Cheewakriangkrai C, Kietpeerakool C, Aue-aungkul A, Charoenkwan K, Pattanittum P, John D, Lumbiganon P. Health education interventions to promote early presentation and referral for women with symptoms of endometrial cancer. *Cochrane Database of Systematic Reviews* 2019, Issue 1. Art. No.: CD013253. DOI: 10.1002/14651858.CD013253.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To determine the effectiveness of health education interventions involving healthcare providers or individuals or both to promote early presentation and early referral for women with symptoms of endometrial (womb) cancer.

BACKGROUND

Description of the condition

Endometrial (womb) cancer is a cancer that arises from the endometrium (inner lining of the womb). It is the fifth most common cancer affecting women worldwide, with an estimated 320,000 new cases, and 72,000 endometrial cancer deaths, occurring globally in 2012 (Ferlay 2015). The highest incidence of endometrial cancer is in North America and Europe (Beesley 2010). Endometrial cancer incidence, particularly aggressive subtypes, is increasing across different populations (Beesley 2010; Cote 2015). Predisposing factors for endometrial cancer include high body mass index, diabetes mellitus, nulliparity, infertility, unopposed oestrogen therapy, oestrogen-producing tumours (tumours that can secrete oestrogen), early menarche or late menopause, and hereditary non-polyposis colorectal cancer syndrome (Lynch Syndrome) (Colombo 2016).

After a diagnosis of endometrial cancer has been made, staging is performed to determine the extent of the disease. Staging of endometrial cancer (procedures carried out to determine whether the cancer has spread within the womb or to other parts of the body) is mainly made as a result of surgery (surgical staging). The International Federation of Gynecology and Obstetrics (FIGO) staging system for endometrial cancer is provided in Appendix 1 (FIGO Committee 2014). Staging enables physicians to plan the best treatments after surgery and can help predict long-term survival. The majority of cases of endometrial cancer (70% to 75%) are diagnosed at FIGO stages I or II (Colombo 2016). The 5-year overall survival (OS) of women with endometrial cancer

stages I or II ranges from 75% to 90%. In contrast, the 5-year OS for stages III and IV are only 55% to 65% and 20% to 25%, respectively (Colombo 2016).

Description of the intervention

Timely cancer diagnosis improves survival and quality of life (Neal 2015). Early diagnosis of cancer necessitates the awareness of patients and healthcare providers about the early symptoms and signs of cancer, leading to prompt access to healthcare services and referral to a specialised health centre for further prompt diagnostic work-up and management (WHO 2007). Low cancer awareness (which may include lack of knowledge or false beliefs about cancer symptoms and risk of developing cancer) among individuals can contribute to a delay in their presentation (Allgar 2005). Raising public awareness and education about the early symptoms of cancer have been proposed as the highest priorities for reducing delayed diagnosis of cancer (Car 2016).

Health educational interventions aim to improve knowledge, awareness, attitudes, and skills of a target population (Mansell 2011). In the context of this review, we have defined health education interventions as interventions that facilitate knowledge and awareness of early presentation in the general population and interventions that aim to promote early referral among healthcare providers by increasing their knowledge or influencing their attitudes, using a variety of formats or programmes.

Health education intervention for promoting cancer awareness among individuals can be delivered by either individual-level interventions or community-level interventions (Austoker 2009). Intervention provided in an individual level may include a face-to-face session with a health professional or an educational leaflet given to an identified individual. Community-level educational interventions may include media campaigns, health education website, or leaflets or posters distributed indiscriminately at a public space (Austoker 2009).

Healthcare providers in the primary care setting play a major role in identifying people with symptoms suspicious of cancer, since this is the first point of health care access for most people (NICE 2017; Swann 2018). People who have so-called red flag symptoms are then typically referred to a specialised healthcare centre for further diagnosis and treatment. A previous systematic review reported a trend of poor treatment outcomes among people with symptomatic cancers who had long waiting times for definitive treatment (Neal 2015). Based on these findings, reducing the delay in referral may improve outcomes. Several Cochrane Reviews observed an improvement in professional practice after implementing various educational interventions (Forsetlund 2009; Giguère 2012; O'Brien 2007). These may include lectures, printed educational materials, continuing education meetings, workshops, videos, and Internet triage packages to raise the awareness of red flag symptoms of cancer (Mansell 2011).

How the intervention might work

Early diagnosis of endometrial cancer, ideally before disease spreads, is clinically applicable and relatively straightforward, as most women with the disease experience abnormal vaginal bleeding (either postmenopausal bleeding or abnormal pre-menstrual bleeding) (Jamison 2013; Saso 2011). Women with endometrial cancer typically present with postmenopausal bleeding (PMB), which is defined as unexplained vaginal bleeding more than 12 months after menstruation has stopped due to menopause and in those who are not taking hormone replacement therapy (NICE 2017). The probability of endometrial cancer in women presenting with PMB varies from 8% to 11% (Bani-Irshaid 2011; Escoffery 2002; Gredmark 1995; Lee 1995). The risk of endometrial cancer among women with PMB increases with age (Gredmark 1995). The UK National Institute for Health and Care Excellence (NICE) recommends the urgent referral of women with PMB, ensuring an appointment within 2 weeks for further evaluation if they have PMB and are aged 55 or over (NICE 2017). The guidelines also recommend consideration of a referral for an appointment within 2 weeks for endometrial cancer evaluation in women aged under 55 with PMB (NICE 2017). Other suspicious symptoms of endometrial cancer include an abnormal vaginal discharge or heavy or prolonged periods in premenopausal women. Presentation with a pelvic or abdominal mass or pelvic pain is relatively rare and may be associated with advanced cancer (Jamison 2013; Saso 2011).

Promoting recognition of possible warning symptoms and signs of endometrial cancer among individuals and healthcare providers remains a critical goal. However, primary healthcare providers encounter endometrial cancer comparatively rarely, which could lead to low levels of knowledge and awareness. Educational intervention may therefore enhance the appreciation of the need for early referral by improving knowledge and awareness of providers about red flag symptoms of cancer (Rose 2001). A previous systematic review indicated that educational interventions delivered to individuals may increase cancer awareness (Austoker 2009). Educational interventions delivered to individual people or communities may enhance awareness and early cancer presentation (Austoker 2009).

Why it is important to do this review

Delay in the management of endometrial cancer patients is not uncommon (Dolly 2016; Elit 2014; O'Leary 2013; Strohl 2016). Dolly 2016 observed that the mean interval time from diagnosis of endometrial cancer to treatment was 47.5 days. Recently, Strohl 2016 reported that approximately 25% of women with endometrial cancer experienced a surgical delay, which was defined as a surgical wait time greater than 6 weeks. Delay in the management of women with endometrial cancer has a negative impact on survival (Dolly 2016; Elit 2014; Strohl 2016). Survival for women

with surgical wait times more than six weeks was worse than for those treated within six weeks of diagnosis, when controlling for women's age, ethnicity, insurance status, level of education attainment, and comorbidity (Strohl 2016).

Delayed presentation and referral becomes a factor contributory to a delay in management for gynaecologic cancer patients, leading to unfavourable treatment outcomes (Rose 2015; Shalowitz 2015; Shalowitz 2017). To ensure the best possible outcomes for women with endometrial cancer, timely presentation, diagnosis, and referral to an experienced healthcare setting is mandatory. Our aim is to conduct this Cochrane Review with the goal of evaluating the effectiveness of health education interventions for promoting early presentation and referral for women with suspected symptoms of endometrial cancer.

OBJECTIVES

To determine the effectiveness of health education interventions involving healthcare providers or individuals or both to promote early presentation and early referral for women with symptoms of endometrial (womb) cancer.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs), both individually randomised (trials in which individuals were randomised to either the intervention or the control arm of the experiment, or randomised to receive different interventions) and cluster-RCTs (trials that have as the unit of randomisation a group or community level, or where clusters of professionals or groups of professionals are implementing interventions). A cross-over trial (a trial in which participants receive a sequence of different interventions) is not feasible for this review. If we identify no RCTs, we will include non-randomised studies (NRS) with a parallel comparison. We will only include NRS that have analysed results for intervention effects adjusted for baseline characteristics.

Types of participants

Participants of this review may be individuals, healthcare providers, or both. We will include any woman of any age, and in any setting who experienced suspicious symptoms of endometrial cancer. We will include any healthcare providers of any age, gender, or profession (e.g. nurse, doctor, allied staff), in any public or private healthcare facility. In addition, as we plan to recruit cluster-randomised trials to this review, participants may thus be communities or healthcare institutions or other units. We will perform a separate analysis for different types of participants (individuals who experienced suspicious symptoms of endometrial cancer and healthcare providers).

Types of interventions

Any health education interventions performed with the aim of promoting the early presentation and referral of women with symptoms suspected of endometrial cancer compared with the standard or usual care or as specified in the included studies. Interventions may target individuals, healthcare providers, or both. We will include studies regardless of their level of delivery of the intervention (individual or public or community). Interventions aimed at the individual level may be health education outreach visits, meeting, or printed educational materials. Community-based health education interventions may be mass media campaigns, health education website, or posters distributed indiscriminately in public areas.

Types of outcome measures

Primary outcomes

- Overall survival (OS): defined as survival of endometrial cancer patients until death from all causes
- Disease-free survival (DFS): defined as survival of endometrial cancer patients until the appearance of a new lesion of disease

Secondary outcomes

- Delayed referral: defined as time from primary care first appointment to time of primary care referral to secondary care of longer than 14 days (NICE 2017)
- Delayed presentation: defined as time from symptom of postmenopausal bleeding to the first appointment with a responsible specialist of longer than 14 days and longer than 3 months for irregular bleeding if premenopausal
- Referral time: defined as time from primary care first appointment to time of primary care referral to secondary care (days)
- Presentation time or time of help-seeking: defined as time from symptom onset to arrival at primary care hospital (days)
- Conversion rate: defined as the proportion of referrals for suspected cancer who were then shown to have endometrial cancer
- Detection rate: defined as the proportion of endometrial cancers that were detected
- Delayed treatment: as defined by the authors

- Time from presentation to receiving definite treatment (days)
- Cancer-related mortality (death from cancer)
- Proportion of women diagnosed with stage III-IV endometrial cancer
- People satisfaction with the referral process: using visual analogue scale or as defined by the authors
- Physician satisfaction with the referral process: using visual analogue scale or as defined by the authors
- Quality of life: evaluated among women with endometrial cancer after treatment using a scale that has been validated through reporting of norms in a peer-reviewed publication, i.e. European Organisation for Research and Treatment of Cancer (EORTC) QLQ-EN24 endometrial-specific quality of life questionnaire (Greimel 2011)
- Cost-effectiveness of the intervention: using a validated scale, i.e. European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) (Cherny 2015). If data permit, we will analyse either cost per case of endometrial cancer detected or incremental cost-effectiveness ratio (ICER)

We will present a 'Summary of findings' table to report the following outcomes listed in order of priority (see Appendix 2).

- Overall survival
- Disease-free survival
- Delayed referral
- Delayed presentation
- Referral time
- Presentation time

Search methods for identification of studies

We will search the following sources, irrespective of the language of publication, publication status, or sample size.

Electronic searches

We will search the following electronic databases:

- the Cochrane Central Register of Controlled Trials (CENTRAL; latest issue), in the Cochrane Library;
- MEDLINE via Ovid (1946 to present date);
- Embase via Ovid (1980 to present date).

All relevant articles will be identified on PubMed, and we will conduct a further search for newly published articles using the 'related articles' feature. The Ovid MEDLINE search strategy is presented in Appendix 3. We will adapt the search strategy accordingly for databases other than MEDLINE.

Searching other resources

Ongoing studies

We will search the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (www.who.int/ictrp/en/) and the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov) to identify any ongoing trials. If we identify any ongoing unpublished trials, we will approach the principal investigators and major co-operative groups active in this area to ask for relevant data.

Grey literature

We will search the OpenGrey (www.opengrey.eu/) and Index to ProQuest Dissertations & Theses: UK & Ireland databases for grey literature.

Handsearch

We will handsearch within reference lists of all included studies and within previous systematic reviews on the same topic. We will also handsearch the reports of conferences in the following sources: Annual Meeting of the American Society of Gynecologic Oncologists; Annual Meeting of the International Gynecologic Cancer Society; Annual Meeting of the European Society of Medical Oncology (ESMO); Annual Meeting of the American Society of Clinical Oncology (ASCO); Annual Meeting of the British Gynaecological Cancer Society (BGCS); Biennial Meeting of the Asian Society of Gynecologic Oncology (ASGO); Biennial Meeting of the Asia and Oceania Federation of Obstetrics and Gynaecology (AOFOG); Biennial Meeting of the European Society of Gynaecologic Cancer (ESGO); and Biennial Meeting of the International Gynecologic Cancer Society (IGCS).

Data collection and analysis

Selection of studies

We will download all titles and abstracts retrieved by the electronic searching to a reference management program. After removal of duplicates, we will transfer these data to Covidence 2019 (www.covidence.org). Two review authors (CC and CK) will independently examine the remaining references. We will exclude those studies which clearly do not meet the inclusion criteria and obtain full-text copies of potentially relevant references. Two review authors (CC and CK) will independently assess the eligibility of the retrieved reports/publications. Any disagreements will be resolved through discussion or by consulting a third review author (KC, PL, or AA) if necessary. We will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review.

We will use the details obtained from the selection process in Covidence to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Liberati 2009).

Data extraction and management

Two review authors (CC and CK) will independently extract the study characteristics and outcome data from the included studies using Covidence. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. Any disagreements will be resolved by consensus or by involving a third review author (KC, PL, or AA). A second review author (PP) will check the study characteristics for accuracy against the trial report.

We will extract the following data from the included studies.

- Author, year of publication, and journal citation (including language)
- Country
- Setting
- Study designs and study methodology: individual RCT/cluster-RCT/NRS
- Inclusion and exclusion criteria
- Operation definitions of delay in referral and delay in treatment
- Study population, characteristics, and outcomes: sample size, detailed characteristics including levels of healthcare settings, and types of professionals
- Intervention details: any health education interventions performed with the aim of promoting early referral to a specialised centre, single or multifaceted intervention, level of intervention given
- Comparison: standard/usual care/as specified in the included studies
- Risk of bias (see Appendix 4)
- Outcomes: for each outcome, we will extract the outcome definition and unit of measurement (if relevant). For adjusted estimates, we will record variables adjusted for in analyses. Unit of analysis will depend on the type of RCT (see Unit of analysis issues).
- Results: we will extract the number of participants allocated to each intervention group, the total number analysed for each outcome, and missing participants. For NRS, we will extract the number of participants categorised in the group to which the intervention was received.
- Notes: funding for the trial, and notable conflicts of interest of trial authors.

If we find more than one publication of the same study, we will use the most recent publication for data extraction and collate multiple reports of the same study.

We will extract results as follows.

- For time-to-event data (survival outcomes), we will extract the log of the hazard ratio (log(HR)) and its standard error from the trial reports. If these are not reported, we will attempt to estimate the log(HR) and its standard error using the methods cited in Parmar 1998.
- For dichotomous outcomes (e.g. delayed referral, delayed presentation, and delayed treatment), we will extract the number of people in each treatment arm who experienced the outcome of interest and the number of people assessed at endpoint, in order to estimate a risk ratio (RR).
- For continuous outcomes (e.g. referral time and presentation time), we will extract the final value and standard deviation (SD) of the outcome of interest and the number of people assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference (MD) between treatment arms.

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

Assessment of risk of bias in included studies

We will assess and report on the methodological quality and risk of bias of the included RCTs in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), which recommends the explicit reporting of the following individual elements for RCTs (Appendix 4).

- Selection bias: random sequence generation and allocation concealment
- Performance bias: blinding of participants and personnel (participants and treatment providers)
- Detection bias: blinding of outcome assessment
- Attrition bias: incomplete outcome data (i.e. incomplete follow-up outcomes and treatment-related complications)
- Reporting bias: selective reporting of outcomes
- Other potential sources of bias

Two review authors (CC and CK) will independently apply the 'Risk of bias' tool, resolving any differences by discussion or by appeal to a third review author (KC, PL, or AA). We will judge each item as being at high, low, or unclear risk of bias as set out in the criteria presented in Appendix 4 (Higgins 2011).

We will assess the following biases in cluster-RCTs:

- recruitment bias;
- baseline imbalance;
- loss of clusters;
- incorrect analysis; and
- comparability with individually randomised trials (Higgins 2011).

If we identify no RCTs, we will include NRS. We will assess risk of bias in NRS according to the Cochrane Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool, and we will record results in the template (Stern 2016). We will classify

NRS as at high risk of bias when they are at 'serious' risk according to the Cochrane ROBINS-I tool.

We will assess the included studies for their risk of bias based on the following seven domains in the ROBINS-I tool (Appendix 5).

- Bias due to confounding
- Bias in selection of participants into the study
- Bias in classification of interventions
- Bias due to deviations from the intended intervention
- Bias due to missing data
- Bias in measurement of outcomes
- Bias in selection of the reported result

We will provide a quote from the study report or a statement, or both as justification for the judgement for each item in the 'Risk of bias' table. When interpreting treatment effects and meta-analyses, we will take into account the risk of bias for the studies that contribute to that outcome. Where information on risk of bias relates to unpublished data or correspondence with a trial author, we will note this in the table.

Measures of treatment effect

We will use the following measures for the effect of treatment.

- For time-to-event outcomes (e.g. overall and disease-free survival), we will use the hazard ratio (HR) with 95% confidence interval (CI).
- For dichotomous outcomes (e.g. delayed referral, delayed presentation, delayed treatment, and death (if not possible to treat as a time-to-event outcome and obtain an HR)), we will analyse data based on the number of events and the number of people assessed in the intervention and comparison groups. We will use these to calculate the RR and 95% CI.
- For continuous outcomes (e.g. quality of life measures, cost-effectiveness, and satisfaction score), we will analyse data based on the mean, SD, and number of people assessed for both the intervention and comparison groups to calculate the MD between treatment arms with a 95% CI. If the MD is reported without individual group data, we will use this to report the study results. If more than one study measures the same outcome using different tools, we will calculate the standardised mean difference (SMD) and 95% CI using the inverse-variance method.

Unit of analysis issues

We plan to include studies where individual people were randomised and cluster-randomised studies. For individual RCTs, the unit of analysis will be per woman randomised. As we plan to recruit cluster-randomised trials to this review, we will avoid unit of analysis errors by performing meta-analysis (if appropriate) using effect estimates and their standard errors (SEs) where the trial has been correctly analysed.

On the other hand, for a trial without appropriate adjustment of clustering, we will approximate the correct analyses based on the 'inflating standard error' approach cited in (Higgins 2011), as follows.

- Calculating the design effect, which is 1 + (M − 1) ICC, where M is the average cluster size and ICC is the intracluster correlation coefficient (note: for unknown ICC, the estimated ICC will be (a) yielded from either a similar study, or (b) assume an ICC of 0.10 (Campbell 2001))
- Multiplying SE of the effect estimate by the square root of the design effect (note: we will apply the natural log form for dichotomous and time-to-event outcomes)
- Performing meta-analysis using the generic inverse-variance method in Review Manager 5 (RevMan 2014)

In NRS, the unit of analysis is the participant(s) receiving the intervention. We will follow the methods stated in the *Cochrane Handbook for Systematic Reviews of Interventions* for carrying out the calculations or determining the statistical outcomes (Higgins 2011). In a study with multiple intervention groups, where possible, we will combine all relevant experimental intervention groups into a single group to create a single pair wise comparison (Higgins 2011).

Dealing with missing data

We will report the percentage of observations with missing data in each included study. We will contact the original investigators to request missing data. If we cannot contact the investigators or are unable to obtain the missing data, we will analyse only the available data and will not impute missing outcome data for any of the outcomes.

Assessment of heterogeneity

We will clinically assess heterogeneity by visual inspection of the forest plots. We will also assess statistical heterogeneity in each meta-analysis using the I^2 statistic and Chi^2 test (Higgins 2003). We will regard heterogeneity as substantial if the I^2 statistic is greater than 50%, or there is a low P value (< 0.10) in the Chi^2 test for heterogeneity (Deeks 2001; Higgins 2011). If there is substantial statistical heterogeneity, we will carry out subgroup analyses to assess the differences between the included studies. However, if there is clinical, methodological, or considerable statistical heterogeneity (I^2 greater than 75%) across included studies (Higgins 2011), we will not report pooled results from meta-analysis, but will instead use a narrative approach to data synthesis.

Assessment of reporting biases

We will examine funnel plots corresponding to the meta-analysis of the primary outcome to assess the potential for small-study effects such as publication bias if we identify more than 10 studies. We plan to assess funnel plot asymmetry visually; if we identify

asymmetry of funnel plots, we will perform exploratory analyses to investigate the possible impact (Sterne 2011).

Data synthesis

We will use the random-effects model with an inverse variance weighting for all meta-analyses (DerSimonian 1986). We will perform statistical analysis using Review Manager 5 (RevMan 2014).

- For time-to-event outcome (e.g. overall and disease-free survival), we will pool HRs using the generic inverse-variance method.
- For any dichotomous outcome (e.g. delay in referral or delay in treatment), we will calculate the RRs for each study, which will then be pooled.
- For continuous outcome (e.g. satisfaction score), we will pool the MDs between the treatment arms if all trials measure the outcome on the same scale; otherwise, we will pool SMDs.

Main outcomes of 'Summary of findings' table for assessing the quality of the evidence

A 'Summary of findings' table is presented in Appendix 2, which is prepared to summarise the results of the meta-analysis based on the methods described in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011). We will present the results of the meta-analysis for the outcomes as outlined in the Types of outcome measures section.
We will present the overall quality of the evidence for each outcome according to the GRADE approach, which takes into account issues not only related to internal validity (risk of bias, inconsistency, imprecision, and publication bias) but also to external validity such as directness of results (Langendam 2013). We will create a 'Summary of findings' table based on the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), employing GRADEpro GDT (GRADEpro GDT). We will use the GRADE checklist and GRADE Working Group quality of evidence definitions (Meader 2014). We will downgrade the evidence from 'high' quality by one level for each serious limitation (or by two levels for each very serious limitation), as follows.

- ***High-certainty: We are very confident that the true effect lies close to that of the estimate of the effect.***
- ***Moderate-certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.***
- ***Low-certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.***
- ***Very low-certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.***

Subgroup analysis and investigation of heterogeneity

When data are available, we will carry out subgroup analysis for the following factors to assess the impact
of the following variables on the effect size.

- Single or multifaceted/integrated intervention
- Income status of the country (e.g. low- and middle-income countries versus high-income countries)
- Characteristics of population (e.g. disadvantaged or advantaged population or general population versus minority groups)

We will assess subgroup differences by interaction tests available within Review Manager 5 (RevMan 2014). We will report the results of subgroup analyses quoting the Chi² statistic and P value, the interaction test, and I² statistic value.

Sensitivity analysis

We will perform a sensitivity analysis in order to assess the effect of the following factors on the primary outcomes.

- Repeating the analysis excluding unpublished studies (if any)
- Repeating the analysis excluding RCTs judged to be at high or unclear risk of bias for allocation concealment (in case of RCT available)
- Repeating the analysis excluding studies that were not originally adjusted for clustering (in case of cluster-RCT available)
- Repeating the analysis excluding NRS judged to be high risk of bias according to the Cochrane ROBINS-I tool (in case of no RCT available)

ACKNOWLEDGEMENTS

We thank Gail Quinn, Clare Jess, and Tracey Harrison for their contribution to the editorial process; Jo Platt for designing the search strategy; and Jo Morrison for clinical and editorial advice.

This project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to the Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service (NHS), or the Department of Health.

We would like to thank the referees for their many helpful suggestions and comments, including Andrew Bryant, Katharine Tylko-Hill, Stuart Rundle, and Hans Nagar.

REFERENCES

Additional references

Allgar 2005

Allgar VL, Neal RD. Delays in the diagnosis of six cancers: analysis of data from the National Survey of NHS Patients: Cancer. *British Journal of Cancer* 2005;**92**(11):1959–70.

Austoker 2009

Austoker J, Bankhead C, Forbes LJ, Atkins L, Martin F, Robb K, et al. Interventions to promote cancer awareness and early presentation: systematic review. *British Journal of Cancer* 2009;**101**(Suppl 2):S31–9.

Bani-Irshaid 2011

Bani-Irshaid I, Al-Sumadi A. Histological findings in women with postmenopausal bleeding: Jordanian figures. *Eastern Mediterranean Health Journal* 2011;**17**(7):582–6.

Beesley 2010

Beesley VL, Janda M, Eakin EG, Auster JF, Chambers SK, Aitken JF, et al. Gynecological cancer survivors and community support services: referral, awareness, utilization and satisfaction. *Psychooncology* 2010;**19**:54–61.

Campbell 2001

Campbell MK, Mollison J, Grimshaw JM. Cluster trials in implementation research: estimation of intracluster correlation coefficients and sample size. *Statistics in Medicine* 2001;**20**(3):391–9. [PUBMED: 11180309]

Car 2016

Car LT, Papachristou N, Urch C, Majeed A, El-Khatib M, Aylin P, et al. Preventing delayed diagnosis of cancer: clinicians' views on main problems and solutions. *Journal of Global Health* 2016;**6**(2):020901.

Cherny 2015

Cherny NI, Sullivan R, Dafni U, Kerst JM, Sobrero A, Zielinski C, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). *Annals of Oncology* 2015;**26**(8):1547–73.

Colombo 2016

Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, et al. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up. *International Journal of Gynecological Cancer* 2016;**26**(1):2–30.

Cote 2015

Cote ML, Ruterbusch JJ, Olson SH, Lu K, Ali-Fehmi R. The growing burden of endometrial cancer: a major racial disparity affecting black women. *Cancer Epidemiology, Biomarkers & Prevention* 2015;**24**(9):1407–15.

Covidence 2019 [Computer program]

Veritas Health Innovation. Covidence. Version accessed 21 January 2019. Melbourne, Australia: Veritas Health Innovation, 2019.

Deeks 2001

Deeks J, Altman D, Bradburn M. *Statistical Methods for Examining Heterogeneity and Combining Results From Several Studies in Meta-Analysis*. 2nd Edition. London: BMJ, 2001.

DerSimonian 1986

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**(3):177–88.

Dolly 2016

Dolly D, Mihai A, Rimel BJ, Fogg L, Rotmensch J, Guirguis A, et al. A delay from diagnosis to treatment Is associated with a decreased overall survival for patients with endometrial cancer. *Frontiers in Oncology* 2016;**6**:31.

Elit 2014

Elit LM, O'Leary EM, Pond GR, Seow HY. Impact of wait times on survival for women with uterine cancer. *Journal of Clinical Oncology* 2014;**32**(1):27–33.

Escoffery 2002

Escoffery CT, Blake GO, Sargeant LA. Histopathological findings in women with postmenopausal bleeding in Jamaica. *West Indian Medical Journal* 2002;**51**(4):232–5.

Ferlay 2015

Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *International Journal of Cancer* 2015;**136**(5):E359-86.

FIGO Committee 2014

FIGO Committee on Gynecologic Oncology. FIGO staging for carcinoma of the vulva, cervix, and corpus uteri. *International Journal of Gynecology & Obstetrics* 2014;**125**(2):97–8.

Forsetlund 2009

Forsetlund L, Bjørndal A, Rashidian A, Jamtvedt G, O'Brien MA, Wolf F, et al. Continuing education meetings and workshops: effects on professional practice and health care outcomes. *Cochrane Database of Systematic Reviews* 2009, Issue 2. DOI: 10.1002/14651858.CD003030.pub2

Giguère 2012

Giguère A, Légaré F, Grimshaw J, Turcotte S, Fiander M, Grudniewicz A, et al. Printed educational materials: effects on professional practice and healthcare outcomes. *Cochrane Database of Systematic Reviews* 2012, Issue 10. DOI: 10.1002/14651858.CD004398.pub3

Gredmark 1995

Gredmark T, Kvint S, Havel G, Mattsson LA. Histopathological findings in women with postmenopausal bleeding. *British Journal of Obstetrics and Gynaecology* 1995;**102**(2):133–6.

Greimel 2011

Greimel E, Nordin A, Lanceley A, Creutzberg CL, van de Poll-Franse LV, Radisic VB, et al. Psychometric validation of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Endometrial Cancer

Module (EORTC QLQ-EN24). *European Journal of Cancer* 2011;**47**(2):183–90.

Higgins 2003
Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327** (7414):557–60.

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Jamison 2013
Jamison PM, Noone AM, Ries LA, Lee NC, Edwards BK. Trends in endometrial cancer incidence by race and histology with a correction for the prevalence of hysterectomy, SEER 1992 to 2008. *Cancer Epidemiology, Biomarkers & Prevention* 2013;**22**:233–41.

Langendam 2013
Langendam MW, Akl EA, Dahm P, Glasziou P, Guyatt G, Schünemann HJ. Assessing and presenting summaries of evidence in Cochrane Reviews. *Systematic Reviews* 2013;**2**: 81.

Lee 1995
Lee WH, Tan KH, Lee YW. The aetiology of postmenopausal bleeding - a study of 163 consecutive cases in Singapore. *Singapore Medical Journal* 1995;**36**(2):164–8.

Liberati 2009
Liberati A, Altman D, Tetzlaff J, Mulrow C, Gotzsche P, Ioannidis J. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *BMJ* 2009;**339**:2700.

Mansell 2011
Mansell G, Shapley M, Jordan JL, Jordan K. Interventions to reduce primary care delay in cancer referral: a systematic review. *British Journal of General Practice* 2011;**61**(593): e821–35.

Meader 2014
Meader N, King K, Llewellyn A, Norman G, Brown J, Rodgers M, et al. A checklist designed to aid consistency and reproducibility of GRADE assessments: development and pilot validation. *Systematic Reviews* 2014;**3**:82.

Neal 2015
Neal RD, Tharmanathan P, France B, Din NU, Cotton S, Fallon-Ferguson J, et al. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review. *British Journal of Cancer* 2015;**112 Suppl 1**:S92–107.

NICE 2017
National Institute for Health and Care Excellence (NICE). Suspected cancer: recognition and referral (NICE guideline [NG12]). nice.org.uk/guidance/ng12 (accessed prior 21January 2019) 2015.

O'Brien 2007
O'Brien MA, Rogers S, Jamtvedt G, Oxman AD, Odgaard-Jensen J, Kristoffersen DT, et al. Educational outreach visits: effects on professional practice and health care outcomes. *Cochrane Database of Systematic Reviews* 2007, Issue 4. DOI: 10.1002/14651858.CD000409.pub2

O'Leary 2013
O'Leary E, Elit L, Pond G, Seow H. The wait time creep: changes in the surgical wait time for women with uterine cancer in Ontario, Canada, during 2000-2009. *Gynecologic Oncology* 2013;**131**(1):151–7.

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.

RevMan 2014 [Computer program]
The Nordic Cochrane Centre. Review Manager (RevMan) Version 5.3. Copenhagen: The Cochrane Collaboration, 2014.

Rose 2001
Rose PW, Watson E, Yudkin P, Emery J, Murphy M, Fuller A, et al. Referral of patients with a family history of breast/ ovarian cancer - GPs' knowledge and expectations. *Family Practice* 2001;**18**(5):487–90.

Rose 2015
Rose PW, Rubin G, Perera-Salazar R, Almberg SS, Barisic A, Dawes M, et al. Explaining variation in cancer survival between 11 jurisdictions in the International Cancer Benchmarking Partnership: a primary care vignette survey. *BMJ Open* 2015;**5**(5):e007212.

Saso 2011
Saso S, Chatterjee J, Georgiou E, Ditri AM, Smith JR, Ghaem-Maghami S. Endometrial cancer. *BMJ* 2011;**343**: d3954.

Schünemann 2011
Schünemann HJ, Oxman AD, Higgins JPT, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Shalowitz 2015
Shalowitz DI, Vinograd AM, Giuntoli RL. Geographic access to gynecologic cancer care in the United States. *Gynecologic Oncology* 2015;**138**(1):115–20.

Shalowitz 2017
Shalowitz DI, Epstein AJ, Buckingham L, Ko EM, Giuntoli RL 2nd. Survival implications of time to surgical treatment of endometrial cancers. *American Journal of Obstetrics and Gynecology* 2017;**216**(3):268.e1–18.

Stern 2016
Sterne JAC, Hernán MA, Reeves BC, Savovi
ć J, Berkman ND, Viswanathan M, et al. ROBINS-I: a

tool for assessing risk of bias in non-randomized studies of interventions. *BMJ* 2016;**355**:i4919.

Sterne 2011
Sterne J, Sutton A, Loannidis J, Terrin N, Jones D, Lau J. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;**343**:d4002.

Strohl 2016
Strohl AE, Feinglass JM, Shahabi S, Simon MA. Surgical wait time: a new health indicator in women with endometrial cancer. *Gynecologic Oncology* 2016;**141**(3): 511–5.

Swann 2018
Swann R, McPhail S, Witt J, Shand B, Abel GA, Hiom S, et al. Diagnosing cancer in primary care: results from the National Cancer Diagnosis Audit. *British Journal of General Practice* 2018;**68**(666):e63–72.

WHO 2007
World Health Organization. *Cancer Control: Prevention*. Geneva: WHO Press, 2007.

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. The International Federation of Gynecology and Obstetrics (FIGO) staging for carcinoma of the endometrium

FIGO stage			Description
I			Tumour contained to the corpus uteri
	IA		No or less than half myometrial invasion
	IB		Invasion equal to or more than half of the myometrium
II			Tumour invades the cervical stroma but does not extend beyond the uterus
III			Local and/or regional spread of tumour
	IIIA		Tumour invades the serosa of the corpus uteri and/or adnexas
	IIIB		Vaginal and/or parametrial involvement
	IIIC		Metastases to pelvis and/or para-aortic lymph nodes
		IIIC1	Positive pelvic nodes
		IIIC2	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
IV			Tumour invades bladder and/or bowel mucosa and/or distant metastases
	IVA		Tumour invasion of bladder and/or bowel mucosa
	IVB		Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

Appendix 2. 'Summary of findings' table

Interventions to promote early presentation and referral for women with symptoms of endometrial cancer (womb cancer)

Patient or population: .....(specify type of population: individuals, healthcare providers, or both)
Settings: .....(specify type of setting)
Intervention: ……(specify type of intervention)
Comparison: standard/usual care or as specified in the included studies

Outcomes	Illustrative comparative risks*		Relative effect (95% CI)	Number of participants (studies)	Quality of evidence (GRADE)	Comment
	Assumed risk	Corresponding risk				
Overall survival[a]						
Disease-free survival[b]						
Delayed referral[c]						
Delayed presentation[d]						
Referral time (days)[e]						
Presentation time (days)[f]						

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)
CI: confidence interval

[a] Survival until death from all causes.
[b] Survival until the appearance of a new lesion of disease.
[c] Time from primary care first appointment to time of primary care referral to secondary care of longer than 14 days
[d] Time from symptom of postmenopausal bleeding to the first appointment with a responsible specialist of longer than 14 days and longer than 3 months for irregular bleeding if premenopausal
[e] Time from primary care first appointment to time of primary care referral to secondary care
[f] Time from symptom onset to arrival at primary care hospital.

GRADE Working Group grades of evidence

- ***High-certainty:****We are very confident that the true effect lies close to that of the estimate of the effect.*
- ***Moderate-certainty:****We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.*
- ***Low-certainty:****Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.*

(*Continued*)

- ***Very low-certainty:****We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effec*

Appendix 3. MEDLINE Ovid search strategy

1. exp Uterine Neoplasms/
2. ((uterus or uterine or endometri* or womb or corpus uteri) adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or malignan*)).ti,ab.
3. ((vag* bleed* or discharge* or menstruat*) adj3 (menopaus* or pre-menopaus* or between period* or unusual* or heav* or abnormal* or unexplain*)).ti,ab. 4. (post menopaus* bleed* or PMB).ti,ab.
5. 1 or 2 or 3 or 4
6. exp "Referral and Consultation"/
7. (refer or referral* or referred).ti,ab.
8. consult* or red flag symptom*.ti.ab.
9. ((earl* or urgent*) adj3 (refer* or treat* or manag* or alert* or eval* or suspic*)).ti,ab.
10. 6 or 7 or 8 or 9
11. Health Promotion/
12. Health Knowledge, Attitudes, Practice/
13. Health Education/
14. (health* adj3 (promot* or knowledge* or practice* or educat*)).ti,ab.
15. ((earl* or urgent*) adj3 (warning* or indicat* or sign* or symptom* or interven* or identif* or investigat*)).ti,ab.
16. 11 or 12 or 13 or 14 or 15
17. (seek help* or access* or engage* or attend* or identif* or eval* or present* or explor* or investigat* or pursue* or inquir* or search*).ti,ab.
18. 16 and 17
19. 10 or 18
20. 5 and 19
21. randomized controlled trial.pt.
22. controlled clinical trial.pt.
23. randomized.ab.
24. placebo.ab.
25. clinical trials as topic.sh.
26. randomly.ab.
27. trial.ti.
28. exp case-control studies/
29. exp Cohort Studies/
30. (cohort* or prospective* or retrospective*).mp.
31. ((case adj control*) or (case adj series)).mp.
32. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33. (animals not (humans and animals)).sh.
34. 32 not 33
35. 20 and 34

Appendix 4. 'Risk of bias' assessment in RCTs

We will base the 'Risk of bias' assessment on Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), as follows.

- Random sequence generation
  - Low risk of bias, e.g. participants assigned to treatments on the basis of a computer-generated random sequence or a table of random numbers.
  - High risk of bias, e.g. participants assigned to treatments on the basis of date of birth, clinic ID number, or surname, or no attempt to randomise participants.
  - Unclear risk of bias, e.g. not reported, information not available.
- Allocation concealment
  - Low risk of bias, e.g. where the allocation sequence could not be foretold.
  - High risk of bias, e.g. allocation sequence could be foretold by participants, investigators, or treatment providers.
  - Unclear risk of bias, e.g. not reported.
- Blinding of participants and personnel
  - Low risk of bias if participants and personnel were adequately blinded.
  - High risk of bias if participants and personnel were not blinded to the intervention that the participant received.
  - Unclear risk of bias if this was not reported or unclear.
- Blinding of outcome assessors
  - Low risk of bias if outcome assessors were adequately blinded.
  - High risk of bias if outcome assessors were not blinded to the intervention that the participant received.
  - Unclear risk of bias if this was not reported or unclear.
- Incomplete outcome data: we will record the proportion of participants whose outcomes were not reported at the end of the study. We will determine this domain for each outcome as follows.
  - Low risk of bias, e.g. if less than 20% of participants were lost to follow-up, and reasons for loss to follow-up were similar in both treatment arms.
  - High risk of bias, e.g. if more than 20% of participants were lost to follow-up, or reasons for loss to follow-up differed between treatment arms.
  - Unclear risk of bias, e.g. if loss to follow-up was not reported.
- Selective outcome reporting
  - Low risk of bias, e.g. the study reports all outcomes specified in the protocol.
  - High risk of bias, e.g. it is suspected that the study has selectively reported outcomes.
  - Unclear risk of bias, e.g. it is unclear whether outcomes have been selectively reported.
- Other bias
  - Low risk of bias, e.g. the review authors do not suspect any other source of bias, and the trial appears to be methodologically sound.
  - High risk of bias, e.g. the review authors suspect that the trial is prone to an additional bias.
  - Unclear risk of bias, e.g. the review authors are uncertain whether an additional bias may be present.

Appendix 5. Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool

Risk of bias judgements in ROBINS-I: pre-intervention and at-intervention domains			
Risk judgement	**Bias due to confounding**	**Bias in selection of participants into the study**	**Bias in classification of interventions**
Low	No confounding expected	All participants who would have been eligible for the target trial were included in the study	Intervention status is well-defined and based solely on information collected at the time of

(*Continued*)

		and start of follow-up and start of intervention coincide for all participants	intervention
Moderate	Confounding expected, all known important confounding domains appropriately measured and controlled for; *and* reliability and validity of measurement of important domains were sufficient, such that we do not expect serious residual confounding	Selection into the study may have been related to intervention and outcome, but the authors used appropriate methods to adjust for the selection bias; *or* start of follow-up and start of intervention do not coincide for all participants, but (a) the proportion of participants for which this was the case was too low to induce important bias; (b) the authors used appropriate methods to adjust for the selection bias; or (c) the review authors are confident that the rate (hazard) ratio for the effect of intervention remains constant over time	Intervention status is well-defined, but some aspects of the assignments of intervention status were determined retrospectively
Serious	Switches in treatment, co-interventions, or problems with implementation fidelity are apparent and are not adjusted for in the analyses	Proportions of missing participants differ substantially across interventions; *or* reasons for missingness differ substantially across interventions; *and* missing data were addressed inappropriately in the analysis; *or* the nature of the missing data means that the risk of bias cannot be removed through appropriate analysis.	The methods of outcome assessment were not comparable across intervention groups; *or* the outcome measure was subjective (i.e. likely to be influenced by knowledge of the intervention received by study participants) and was assessed by outcome assessors aware of the intervention received by study participants; *or* error in measuring the outcome was related to intervention status
Critical	Substantial deviations from the intended intervention are present and are not adjusted for in the analysis	There were critical differences between interventions in participants with missing data that were not, or could not, be addressed through appropriate analysis	The methods of outcome assessment were so different that they cannot reasonably be compared across intervention groups

(*Continued*)

No information	No information is reported on whether there is deviation from the intended intervention	No information is reported about missing data or the potential for data to be missing.	No information is reported about the methods of outcome assessment.

Risk of bias judgements in ROBINS-I: postintervention domains

Judgement	Bias due to deviations from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Low	No bias due to deviation from the intended intervention is expected, e.g. if both the intervention and comparator are implemented over a short time period, and subsequent interventions are part of routine medical care, or if the specified comparison relates to initiation of intervention regardless of whether it is continued	Data were reasonably complete; *or* proportions of and reasons for missing participants were similar across intervention groups; *or* analyses that addressed missing data are likely to have removed any risk of bias	The methods of outcome assessment were comparable across intervention groups; *and* the outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants *or* the outcome assessors were unaware of the intervention received by participants; *and* any error in measuring the outcome is unrelated to intervention status	There is clear evidence (usually through examination of a preregistered protocol or statistical analysis plan) that all reported results correspond to all intended outcomes, analyses, and subcohorts
Moderate	Bias due to deviation from the intended intervention is expected, and switches, co-interventions, and some problems with intervention fidelity are appropriately measured and adjusted for in the analyses. Alternatively, most (but not all) deviations from intended intervention reflect the natural course of events after initiation of intervention	Proportions of missing participants differ across interventions; *or* reasons for missingness differ minimally across interventions; *and* missing data were not addressed in the analysis.	The methods of outcome assessment were comparable across intervention groups; *and* the outcome measure is only minimally influenced by knowledge of the intervention received by study participants; *and* any error in measuring the outcome is only minimally related to intervention status	The outcome measurements and analyses are consistent with an a priori plan; or are clearly defined and both internally and externally consistent; *and* there is no indication of selection of the reported anal-

(*Continued*)

				ysis from among multiple analyses; *and* there is no indication of selection of the cohort or subgroups for analysis and reporting on the basis of the results
Serious	Switches in treatment, co-interventions, or problems with implementation fidelity are apparent and are not adjusted for in the analyses	Proportions of missing participants differ substantially across interventions; *or* reasons for missing participants differ substantially across interventions; *and* missing data were addressed inappropriately in the analysis; *or* the nature of the missing data means that the risk of bias cannot be removed through appropriate analysis	The methods of outcome assessment were not comparable across intervention groups; *or* the outcome measure was subjective (i.e. likely to be influenced by knowledge of the intervention received by study participants) and was assessed by outcome assessors aware of the intervention received by study participants; *or* error in measuring the outcome was related to intervention status	Outcome measurements or analyses are internally or externally inconsistent; *or* there is a high risk of selective reporting from among multiple analyses; *or* the cohort or subgroup is selected from a larger study for analysis and appears to be reported on the basis of the results
Critical	Substantial deviations from the intended intervention are present and are not adjusted for in the analysis	There were critical differences between interventions in participants with missing data that were not, or could not, be addressed through appropriate analysis	The methods of outcome assessment were so different that they cannot reasonably be compared across intervention groups	There is evidence or strong suspicion of selective reporting of results, and the unreported results are likely

(*Continued*)

				to be substantially different from the reported results
No information	No information is reported on whether there is deviation from the intended intervention	No information is reported about missing data or the potential for data to be missing	No information is reported about the methods of outcome assessment	There is too little information to make a judgement (e.g. if only an abstract is available for the study)

Source: Stern 2016

CONTRIBUTIONS OF AUTHORS

Chalong Cheewakriangkrai: conceived the review question; developed, co-ordinated, and completed the protocol

Chumnan Kietpeerakool: conceived the review question; developed and completed the protocol

Apiwat Aue-aungkul: conceived the review question; developed and completed the protocol

Kittipat Charoenkwan: conceived the review question; developed and completed the protocol

Porjai Pattanittum: editing and advisory role

Denny John: editing and advisory role

Pisake Lumbiganon: co-ordinated the development of the protocol, editing and advisory role

DECLARATIONS OF INTEREST

Chalong Cheewakriangkrai: none known

Chumnan Kietpeerakool: none known

Apiwat Aue-aungkul: none known

Kittipat Charoenkwan: none known

Porjai Pattanittum: none known

Denny John: none known

Pisake Lumbiganon: none known

SOURCES OF SUPPORT

Internal sources

- Department of Obstetrics and Gynaecology, Faculty of Medicine, Chiang Mai University, Thailand.
- Department of Obstetrics and Gynaecology, Faculty of Medicine, Khon Kaen University, Thailand.
- Department of Epidemiology and Biostatistics, Faculty of Public Health, Khon Kaen University, Thailand.
- Campbell Collaboration, New Delhi, India.
- Cochrane Thailand, Thailand.

External sources

- Thailand Research Fund (Distinguished Professor Award), Thailand.
- Long-term Institutional Development HUBs (LID-HUBs), the Human Reproduction Programme (HRP) Alliance for Research Capacity Strengthening, Department of Reproductive Health and Research, World Health Organization, Geneva, Switzerland.