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Follow-up strategies for women with endometrial cancer after primary treatment (Protocol)

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[Intervention Protocol]

Follow-up strategies for women with endometrial cancer after primary treatment

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ABSTRACT

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

To assess the clinical effectiveness and cost-effectiveness of different strategies in the follow-up of women with endometrial cancer after completion of primary treatment.

BACKGROUND

Description of the condition

Endometrial cancer is the sixth most common cancer in women (GLOBOCAN 2012). Worldwide there are more than 320,000 new cases of endometrial cancer each year, accounting for around 76,000 related deaths (GLOBOCAN 2012). Compared to many other cancers, the prognosis for survival following endometrial cancer is good (Ferlay 2013). The 10-year survival rate in England and Wales is 77.6% (Cancer Research UK 2012). Early diagnosis explains this high survival rate, as most cases are diagnosed at an early stage and are effectively treated with surgery alone (Amanta 2015). Women who are deemed to be at a higher risk of recurrence may receive postoperative adjuvant radiation therapy in the form of vaginal vault brachytherapy, or pelvic external-beam radiation therapy, with or without additional chemotherapy (NICE 2010). In the UK, despite improvements in overall survival, there has been rise in incidence and mortality related to endometrial cancer (Evans 2011).

Based on histopathology and clinical course, endometrial cancers can be divided into two categories: Type I and Type II (Hecht 2006). Type I are typically low-grade (I to II) endometrioid adenocarcinomas, and are usually associated with unopposed oestrogen stimulation. These are usually diagnosed early and have a favourable prognosis. Type II endometrial cancers are commonly described as oestrogen-independent and are predominantly serous carcinomas (Emons 2000). They have poorer prognoses than Type I tumours, and account for 40% of endometrial cancer deaths, whereas they only account for 10% to 20% of cases (Moore 2011).

After completion of primary treatment, many women undergo long-term follow-up in secondary care (Kew 2006; Leeson 2013). The aim of this follow-up is early detection of cancer recurrence or spread of disease, before the onset of symptoms. Recurrent disease may be more amenable to treatment at this stage, possibly leading to improved survival rates. These follow-up appointments also provide an opportunity for women to discuss any physical or psychological effects post treatment (Roberts 2009).

Description of the intervention

Follow-up care for endometrial cancer usually involves a review of current symptoms and a physical examination. Although not routine, especially for women with a low risk of recurrence, follow-up may include imaging procedures. Use of further investigations for the detection of recurrent endometrial cancer can be used (for example, chest radiology, serum tumour markers and vault cytology), but may detect asymptomatic recurrence without improving survival (Gordon 1997; Sartori 2010). In addition, many women with relapsed disease will not present at routine follow-up, but between scheduled appointments with abnormal symptoms. However, routine imaging procedures (magnetic resonance imaging (MRI)/computed tomography (CT)), vault cytology, serum tumour markers and other laboratory-based tests in the absence of symptoms are used to detect asymptomatic recurrence, whilst able to detect pre-clinical recurrence, have shown conflicting effects upon survival from retrospective data (Berchuck 1995; Carrara 2012; Owen 1996; Ueda 2010).

Recent reports on the strategy for cancer in the UK and USA highlight the importance of designing a patient-centred approach, addressing the needs of service users, exploring women's and carers' perspectives and preferences for gynaecological cancer follow-up services in hospital, or potentially in a primary care setting, led by different professionals (Department of Health 2014; NCI 2010). However, the evidence base for the effectiveness of these approaches in detecting recurrent cancer or spread of disease is not robust (Kew 2005). Studies have reported no survival benefit for women in detection of recurrent disease at an asymptomatic stage for endometrial cancer over and above current standard models of follow-up care. Many of these studies are non-randomised, retrospective and of poor methodological quality (Kew 2005).

The evidence base for routine follow-up in other cancers can provide some guidance for the re-design of follow-up services for endometrial cancer. For example, in gynaecological cancers more generally, the detection of recurrence may be delayed because some women do not present with symptoms until their next routine appointment (Olaitan 2001). However, studies investigating recurrence for breast cancer reported most recurrences presenting between scheduled clinic appointments, which may cause a delay in detection of recurrence, pointing to the need for relatively frequent appointments (Olaitan 2001). A meta-analysis of randomised controlled trials (RCTs) of follow-up after bowel cancer has suggested a benefit from intensive follow-up compared to little or no follow-up (Renehan 2002) although, larger trials are required to identify which components of intensive follow-up are most beneficial. Another meta-analysis of nine observational studies and one RCT reported survival benefits in intensive follow-up of women with lung cancer, although the authors noted that the observed benefit may be due to systematic differences in outcomes rather than intervention effects (Calman 2011). Intensive follow-up is thought to benefit the patient by either detecting recurrence early or offering reassurance and reducing anxiety about recurrence (Kew 2005; Kew 2009). There is little evidence to support this approach, particularly in terms of its effectiveness and cost-effectiveness (Kew 2006). Given the financial pressures on health systems, there are limits to the extent to which provision of interventions for reassurance alone can be affordable.

How the intervention might work

A systematic review assessing the views of women and healthcare professionals about cancer follow-up has shown that fear of recurrence is the prime motivation for attending follow-up appointments (Lewis 2009a). It also highlighted that women found regular follow-up, expertise of specialists and quick access to tests reassuring. A recent study that examined the experiences of a gynaecological cancer diagnosis on women and their families, highlighted that living with the risk of cancer recurrence and spread of disease is a life-long social and psychological challenge, affecting the quality of life for women and their families, with women's approaches to managing that risk also affecting their plans for the future (Roberts 2009).

One retrospective study suggested an improvement in survival when recurrent cervical cancer was detected at routine hospital-based, doctor-led follow-up rather than waiting for symptoms to develop (Bodurka 2000). However, the majority of women relapsed with symptoms that would prompt reassessment, even if the patient did not have a scheduled routine follow-up appointment and had simply accessed primary care as a self-referral (Bodurka 2000; Fung-Kee-Fung 2006; Matsuura 2006; Lanceley 2013). Routine follow-up may also have adverse effects. A trial on the follow-up for ovarian cancer (Rustin 2010) reported that early detection of recurrent ovarian cancer did not improve survival, but did impair quality of life, since chemotherapy was started earlier. A further risk of routine scheduled follow-up is that women may wait for their routine appointment to disclose symptoms, rather than making an urgent appointment with their GP, thereby delaying early detection of recurrence and management of symptoms (Olaitan 2001).

Alternatives to the conventional model of follow-up exist, but evidence as to their efficacy varies. For example, the use of specialist nurse-led follow-up in lung cancer (Moore 2002; Lewis 2009b) or primary care follow-up have been shown to be equally effective (or ineffective) as a secondary care model, but there is weak evidence

suggesting that breast cancer follow-up in primary care is effective (Lewis 2009). Their impact on quality of life has not been assessed.

Why it is important to do this review

A recent UK survey of clinical practice in follow-up of gynaecological cancers revealed wide variation of practice across the country (Leeson 2013). A hospital-based protocol emerged as the standard approach, with only a minority using alternative methods of follow-up care, which included follow-up in primary care, hospital-based nurse-led clinics, telephone review or review only at the request of the patient, known as 'open' or 'patient-initiated' follow-up (Lewis 2009a; Moore 2002). A review of retrospective studies of follow-up for women after treatment for endometrial cancer (Fung-Kee-Fung 2006) outlined an optimal programme for follow-up of women. This included a physical examination, targeted investigation, if symptomatic, and counselling on the potential symptoms of recurrence.

The costs for follow-up by the hospital-based protocol or these other alternative methods of follow-up have not been assessed using prospective randomised studies (Kew 2009). A review of retrospective studies in Canada concluded that mean cost of routine follow-up for each women with an endometrial cancer recurrence was CAD$ 19,200 (price year 1995/96) equating to £16,097 (converted to pounds sterling and inflated to price year 2014/2015) (Agboola 1997). Importantly, this review also concluded that there was no difference in overall survival between women with symptomatic and asymptomatic recurrences, or between women with recurrences detected during routine follow-up visits or in the interval between routine visits. Another review of retrospective studies calculated the costs of follow-up for women with endometrial cancer in Belgium. They concluded that the cost for follow-up over five and 10 years ranged between EURO127.68 and EURO2,028.78 (price year: 2002/2003), equating to between £111.57 and £1,773.00 (converted to pounds sterling and inflated to price year 2014/2015) (Curtis 2005; Curtis 2014) and between EURO207.48 and EURO2,353.48 (price year: 2002/2003), equating to £181.32 and £2,056.76 (converted to pounds sterling and inflated to price year 2014/2015), respectively. They also concluded that there was little evidence of routine follow-up improving rates of survival (Tjalma 2004). In the UK there has not been a robust comparison of the costs to NHS commissioners of the different potential models for gynaecological cancer follow-up (NICE 2010).

The aim of this review is to provide an up-to-date evaluation of the available evidence for the different models of endometrial cancer follow-up service delivery and their costs to commissioners.

OBJECTIVES

To assess the clinical effectiveness and cost-effectiveness of different strategies in the follow-up of women with endometrial cancer after completion of primary treatment.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Research looking at patients and their informal caregivers is being carried out as part of another study (Timmis 2015) and will form part of the 'Discussion' in the full review.

Types of participants

Women (18 and above) who have been diagnosed with endometrial (uterine) cancer. This will include type 1 (endometrioid) and type 2 tumours (Moore 2011), and any FIGO (FIGO 2015) stage according to the criteria in Appendix 1.

All women must have completed primary treatment and be in the follow-up phase of care. We will exclude studies which focus on palliative treatment.

Types of interventions

We will consider any of the following comparisons.

Intensive follow-up

Protocol driven follow-up using various interventions including symptomatology, physical examination, serum tumour markers and radiological investigations. This could be either doctor-led or nurse-led in primary care or secondary care.

Non-intensive follow-up

- Follow-up of symptoms that are initiated by the patient and where further intervention and investigations are used as a response to the patient's initial report.
- Clinical needs driven follow-up using various interventions including symptomatology, physical examination, serum tumour markers and radiological investigations. This could be either doctor-led or nurse-led in primary care or secondary care.

The types of intervention will be categorised as follows: care setting, professional responsible, and components of follow-up.

Types of outcome measures

Primary outcomes

- **Overall survival (OS)**: survival until death from all causes (survival from the time when women were randomly assigned). Recurrence-free survival (RFS): defined by inclusion of recurrence or relapse of endometrial cancer (recurrence from the time when women were randomly assigned).

Secondary outcomes

- **Quality of Life**: We will report health-related Quality of Life (QoL) using validated QoL indices/scales, for example the cancer generic EORTC QLQ-C30 questionnaire (Fayers 2002a) in combination with FACT-En for endometrial cancer (McAlpine 2014).
- **Cost-effectiveness:** We will include studies that explore the relative cost-effectiveness of models of follow-up of women with endometrial cancer (economic evidence of follow-up after treatment for gynaecological cancer: cost-effectiveness, cost-utility, cost-consequences, cost-minimisation, cost-benefit or cost-analysis studies).
- **Adverse events:** applicable to endometrial cancer follow-up: increased anxiety, possibility of false-positive findings at follow-up resulting in further investigations.

Search methods for identification of studies

Electronic searches

The following electronic databases will be searched for published literature using strategies that combine search terms relating to endometrial cancers and synonyms for follow-up:

- Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library, latest issue);
- MEDLINE (1946 to present date);
- Embase (1980 to present date); DARE (Database of Abstracts of Reviews of Effects);
- NHS EED (National Health Service Economic Evaluation Database) and;
- HTA (Health Technology Assessment) database.

All databases will be searched to the present date.
We will use a search strategy developed and piloted in MEDLINE (see Appendix 2) and subsequently modified for use in the remaining databases.
We are fairly confident that NHS EED is comprehensive for cost-effectiveness studies to the end of December 2014 when its role changed. Hence, we will also run wider searches on MEDLINE and Embase for full economic evaluations from December 2014 to present date (Appendix 3)

Searching other resources

Reference lists

We will conduct backward and forward citation tracking for all relevant studies and reviews in the field for further possible titles.

Unpublished and grey literature

Grey literature will be limited to practice guidelines published in the UK and will exclude posters, leaflets or abstracts unless these refer to relevant empirical studies. The relevant studies will then be sought and assessed according to our inclusion/exclusion criteria. We will search for ongoing trials in the following sources: Metaregister, Physicians Data Query, www.controlled-trials.com/, www.clinicaltrials.gov, www.cancer.gov/clinicaltrials, NHMRC Clinical Trials Register, UKCCCR, Register of Cancer Trials and Gynaecologic Oncologists of Canada.

Handsearching

Reports of conferences will be handsearched from the following sources.

- Meetings of the International Gynaecologic Cancer Society
- British Cancer Research Meetings
- Annual Meeting of European Society of Medical Oncology (ESMO)
- Annual Meeting of the American Society of Clinical Oncology (ASCO)
- American Association for Cancer Research (AACR) conferences
- European Society of Gynecological Oncology (ESGO) conferences

Data collection and analysis

Selection of studies

The database will be managed in EndNote X7. All titles and abstracts retrieved from the electronic searches will be downloaded to the reference management database and all duplicates will be removed. Two review authors will examine the remaining references in line with the inclusion/exclusion criteria, with one review author examining sections from each for quality control. Any studies that do not meet the inclusion criteria will be excluded. Remaining studies will be obtained as full-text articles and these will be independently assessed for eligibility by at least two review

authors. A third review author will make the final decision on inclusion/exclusion should disagreement occur between the first and second review authors.

Data extraction and management

Two review authors will extract the following data using a pro forma, and a third review author will check a proportion of the studies for consistency.

- Characteristics of women (inclusion criteria, age, grade of cancer, co-morbidities, previous treatment, and whether there is residual disease at the start of follow-up).
- Number enrolled in each study arm, number enrolled at specific follow-up care time points, number lost to follow-up and how this was accounted for.
- Exact description of the follow-up protocols received by experimental and control groups (including whether clinician or patient initiated, care setting and frequency, use of investigations, timing of follow-up events; decision to give further treatment).
- Risk of bias, duration of follow-up, and outcomes and deviations from protocol.
- Recurrences which are patient-reported or clinician-detected.
- Economic evidence of follow-up care after treatment for gynaecological cancer (cost-effectiveness, cost-utility, cost-consequences, cost-minimisation, cost-benefit or cost analysis studies).
- For time to event (survival and recurrence) data, the log of the hazard ratio [log(HR)] and its standard error will be extracted from trial reports; if these are not reported, the log (HR) and its standard error will be estimated. (Parmar 1998).
- For dichotomous outcomes (e.g. adverse events or deaths, if it is not possible to use an HR), we will extract the number of women in each intervention arm who experienced the outcome of interest and the number of women assessed at end point, in order to estimate a risk ratio (RR).
- For continuous outcomes (e.g. QoL measures), the final value and standard deviation of the outcome of interest, and the number of women assessed at the endpoint in each intervention arm at the end of follow-up, will be extracted in order to estimate the mean difference (MD) between intervention arms and its standard error.

Both unadjusted and adjusted statistics will be extracted (Egger 2008), and where possible, all data extracted will be those relevant to an intention-to-treat analysis, whereby participants will be analysed in the groups to which they were assigned. Any disagreements will be resolved through discussion or by appeal to a third review author if necessary.

Assessment of risk of bias in included studies

We will assess the risk of bias in the included RCTs using Cochrane's 'Risk of bias' tool according to the following criteria as specified in Chapter 8 of the *Cochrane Handbook for Systematic Reviews for Intervention* (Higgins 2011, Appendix 4).

Two review authors will independently apply the 'Risk of bias' tool and we will resolve disagreements by consensus or arbitration with a third author. We will summarise the results in both a 'Risk of bias' graph and a 'Risk of bias' summary. We will interpret the results of meta-analyses in the light of the findings with respect to risk of bias.

Quality Appraisal for economic studies: We will use the Drummond checklist (Drummond 1996, Appendix 5) to assess the methodological quality of any economic studies included in the review.

Measures of treatment effect

We will use the following measures of the treatment effect.

- Hazard ratio (HR) for time-to-event data, if possible.
- Risk ratio (RR) for dichotomous outcomes.
- Mean difference (MD) between treatment arms and standard error for continuous outcomes.

Unit of analysis issues

We do not anticipate there will be any unit of analysis issues.

Dealing with missing data

Missing outcome data will not be imputed for any outcomes. Where we have missing or unclear data or information, we will contact the investigators of the primary research on the outcomes only for those participants who were assessed.

Assessment of heterogeneity

We will assess heterogeneity between studies by forest plots, by estimation of the percentage of heterogeneity between trials which cannot be ascribed to sampling variation (Deeks 2011), by a formal statistical test of the significance of the heterogeneity and, if possible, by subgroup analyses. If there is evidence of substantial heterogeneity, we will investigate this and report the reasons for it.

Assessment of reporting biases

Funnel plots corresponding to meta-analysis of the primary outcome will be examined to assess the potential for publication bias. If these plots suggest that treatment effects may not be sampled from a symmetrical distribution, we will perform further meta-analyses using a fixed-effect model.

Data synthesis

Clinically similar studies will be pooled in meta-analyses. If available, we will use adjusted summary statistics, otherwise we will use unadjusted results.

For time-to-event data, we will pool HRs using the generic inverse variance facility in RevMan 5.

For any dichotomous outcomes, we will calculate the RR for each study and pool the results.

For continuous outcomes, if all trials measured the same outcome on the same scale, we will pool the MDs between the treatment groups at the end of follow-up; otherwise we will use the standardised mean difference (SMD) to pool results.

If any trials have multiple treatment groups, the 'shared' comparison group will be divided into the number of treatment groups and comparisons between each treatment group and the split comparison group will be treated as independent comparisons. We will use a random-effects model with inverse variance weighting for all meta-analyses.

'Summary of findings' for assessing the quality of the evidence

Two review authors (RA and KP) will independently rate the quality of evidence for each outcome. We will provide a source and rationale for each assumed risk cited in the table(s) and we will use the GRADE system to rank the quality of the evidence using the GRADEprofiler Guideline Development Tool (GRADEproGDP) software (GRADEPro 2014) and the guidelines provided in Chapter 12.2 of the *Cochrane Handbook for Systematic Reviews for Intervention* (Schünemann 2011). *W*e will present a summary of the evidence in a 'Summary of findings table' (Appendix 6), which provides key information about the best estimate of the magnitude of the effect, in relative terms and absolute differences for each relevant comparison of alternative management strategies, numbers of participants and studies addressing each important outcome and the rating of the overall confidence in effect estimates for the comparisons of each major primary outcomes, including potential harms, as outlined in the Types of outcome measures section.

If meta-analysis is not possible, we will present results in a narrative 'Summary of findings' table format, such as that used by Chan 2011.

Subgroup analysis and investigation of heterogeneity

Where possible, subgroup analyses will be performed to explore:

- effect of disease status - residual versus no residual disease at commencement of follow-up;
- whether the intervention is modified by the caregiver - doctor versus nurse;
- effect of care setting: primary care versus secondary care;

factors such as age, stage of disease, type of intervention, length of follow-up, adjusted/unadjusted analysis will be considered in interpretation of any heterogeneity.

Sensitivity analysis

We will perform sensitivity analyses in order to identify the effect of any assumptions on results, excluding studies at high risk of bias.

Ensuring relevance to decisions in health care

We will discuss the relevance to healthcare and delivery of services in the discussion section of the full review, This discussion will use guidance from national and international bodies as well information from qualitative studies which discuss the challenges facing women and the healthcare system.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. FIGO staging uterine carcinoma

Stage I Tumour confined to the corpus uteri
a* No or less than half myometrial invasion
b* Invasion equal to or more than half of the myometrium
Stage II* Tumour invades cervical stroma, but does not extend beyond the uterus**
Stage III* Local and/ or regional spread of the tumour
a* Tumour invades the serosa of the corpus uteri and/ or adnexae#
b* Vaginal and/ or parametrial involvement#
c* Metastases to pelvic and/ or para-aortic node lymph nodes#
c1* Positive pelvic nodes
c2* Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV Tumour invades bladder and/ or bowel mucosa, and/ or distant metastases
a* Tumour invasion of bladder and/ or bowel mucosa
b* Distant metastases, including intra-abdominal metastases and/ or inguinal lymph nodes
* Either G1, G2 or G3.
**Endocervical glandular involvement only should be considered as stage I and no longer as stage II.
Positive cytology has to be reported separately without changing the stage.

Appendix 2. MEDLINE search strategy 1

1. exp endometrial Neoplasms/
2. exp uterine Neoplasms/
3. Or/1-2
4. ((endometri$ or uter$) adj5 (cancer$ or tumor$ or tumour$ or neoplas$ or malignan$ or carcinoma$ or adenocarcinoma$)).mp.
5. 3 or 4
6. Follow-Up Studies/
7. (follow-up or "follow up" or followup).mp.
8. (check-up$ or "check up$" or checkup$).mp.
9. Aftercare/
10. ("after care" or after-care or "after treatment$" or aftercare).mp.
11. surveillance.mp.
12. (post-therap$ or "post therap$" or posttherap$).mp.
13. ("post treatment$" or post-treatment$ or posttreatment$).mp.
14. recur$.mp.
15. Continuity of Patient Care/
16. Or/6-15
17. 5 and 16
18. randomized controlled trial.pt.
19. controlled clinical trial.pt.
20. randomized.ab.
21. placebo.ab.
22. Clinical Trials as Topic/
23. randomly.ab.
24. trial.ab,ti.
25. Or/18-24
26. exp animals/ not humans/
27. 25 not 26
28. 17 and 27

key: mp=title, original title, abstract, name of substance word, subject heading word, unique identifier, pt=publication type, ab=abstract

Appendix 3. MEDLINE search strategy 2

1. exp endometrial Neoplasms/
2. exp uterine Neoplasms/
3. Or/1-2
4. ((endometri$ or uter$) adj5 (cancer$ or tumor$ or tumour$ or neoplas$ or malignan$ or carcinoma$ or adenocarcinoma$)).mp.
5. 3 or 4
6. Follow-Up Studies/
7. (follow-up or "follow up" or followup).mp.
8. (check-up$ or "check up$" or checkup$).mp.
9. Aftercare/
10. ("after care" or after-care or "after treatment$" or aftercare).mp.
11. surveillance.mp.
12. (post-therap$ or "post therap$" or posttherap$).mp.
13. ("post treatment$" or post-treatment$ or posttreatment$).mp.
14. recur$.mp.
15. Continuity of Patient Care/
16. Or/6-15
17. 5 and 16
18. Economics/
19. exp "costs and cost analysis"/

20. Economics, Dental/
21. exp economics, hospital/
22. Economics, Medical/
23. Economics, Nursing/
24. Economics, Pharmaceutical/
25. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
26. (expenditure$ not energy).ti,ab.
27. value for money.ti,ab.
28. budget$.ti,ab.
29. Or/18-28
30. ((energy or oxygen) adj cost).ti,ab.
31. (metabolicadj cost).ti,ab.
32. ((energy or oxygen) adj expenditure).ti,ab.
33. or/30-32
34. 29 not 33
35. letter.pt.
36. editorial.pt.
37. historical article.pt.
38. or/35-37
39. 34 not 38
40. exp animals/ not humans/
41. 39 not 40
42. bmj.jn.
43. "cochrane database of systematic reviews".jn.
44. health technology assessment winchesterengland.jn.
45. or/42-44
46. 41 not 45
47. 17 and 46
48. limit 47 to Dec 2014-Current
key: mp=title, original title, abstract, name of substance word, subject heading word, unique identifier, pt=publication type, ab=abstract

Appendix 4. Classification scheme for risk of bias

Type of bias	Description	Relevant domains in the Collaboration's 'Risk of bias' tool
Selection bias.	Systematic differences between baseline characteristics of the groups that are compared	• Sequence generation. • Allocation concealment.
Performance bias.	Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest	• Blinding of participants and personnel. • Other potential threats to validity.
Detection bias.	Systematic differences between groups in how outcomes are determined	• Blinding of outcome assessment. • Other potential threats to validity.
Attrition bias.	Systematic differences between groups in withdrawals from a study	• Incomplete outcome data

(*Continued*)

Reporting bias.	Systematic differences between reported and unreported findings	• Selective outcome reporting

Source: Higgins 2011

Appendix 5. Drummond checklist

Drummond's check-list for assessing economic evaluations Drummond 1996is in the following table. Response for each item can be Yes, No, Not clear or Not appropriate.

Study design

1. The research question is stated
2. The economic importance of the research question is stated
3. The viewpoints of the analysis are clearly stated and justified
4. The rationale for choosing the alternative programmes or interventions compared is stated
5. The alternatives being compared are clearly described
6. The form of economic evaluation used is stated
7. The choice of form of economic evaluation is justified in relation to the questions addressed

Data collection

8.The sources of effectiveness estimates used are stated
9.Details of the design and results of effectiveness study are given (if based on a single study)
10.Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)
11.The primary outcome measure(s) for the economic evaluation are clearly stated
12.Methods to value health states and other benefits are stated
13.Details of the subjects from whom evaluations were obtained are given
14.Productivity changes (if included) are reported separately
15.The relevance of productivity changes to the study question is discussed
16.Quantities of resources are reported separately from their unit costs
17.Methods for the estimation of quantities and unit costs are described
18.Currency and price data are recorded
19.Details of currency or price adjustments for inflation or currency conversion are given
20.Details of any model used are given
21.The choice of model used and the key parameters on which it is based are justified

Analysis and interpretation of results

22.Time horizon of costs and benefits is stated
23.The discount rate(s) is stated
24.The choice of rate(s) is justified
25.An explanation is given if costs or benefits are not discounted
26.Details of statistical tests and confidence intervals are given for stochastic data
27.The approach to sensitivity analysis is given
28.The choice of variables for sensitivity analysis is justified
29.The ranges over which the variables are varied are stated
30.Relevant alternatives are compared
31.Incremental analysis is reported
32.Major outcomes are presented in a disaggregated as well as aggregated form
33.The answer to the study question is given
34.Conclusion follow from the data reported
35.Conclusions are accompanied by the appropriate caveats

Appendix 6. Draft 'Summary of findings' table

Title: Follow-up strategies for women with endometrial cancer after primary treatment

Patient or population: Women who have been diagnosed with endometrial cancer
Settings: Specialist hospital/outpatient
Intervention: Intensive follow-up
Comparison 1: Non-intensive follow-up
Comaprison 2: Patient-initiated

Outcomes	Illustrative comparative risks*		Relative effect (95% CI)	No of participants (studies)	Quality of evidence (GRADE)	Comment
	Assumed risk	Corresponding risk				
Overall survival						
Cost-effectiveness						
Adverse event: anxiety						
Adverse effect: false-positive findings						

*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; **HR:** hazard ratio; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

WHAT'S NEW

Date	Event	Description
13 October 2016	Amended	Serach strategy error corrected.

CONTRIBUTIONS OF AUTHORS

RWA developed the protocol with KP and TR. BH developed the search strategy with the reviewers, LJT and STY provided economic input and SL is a holder of the grant and provided the clinical input for the protocol. All authors commented and approved the final draft of the protocol for publication.

DECLARATIONS OF INTEREST

Rabeea'h W Aslam: None known.

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