



# Interventions for weight reduction in obesity to improve survival in women with endometrial cancer

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## Interventions for weight reduction in obesity to improve survival in women with endometrial cancer (Protocol)

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[Intervention Protocol]

# Interventions for weight reduction in obesity to improve survival in women with endometrial cancer

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## ABSTRACT

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

To determine the impact of weight loss interventions, in addition to standard management of endometrial cancer, on overall survival and the frequency of adverse events. Secondary objectives include an assessment of weight loss interventions on endometrial cancer-specific survival, cardiovascular event frequency, and QoL, stratified according to patient BMI, and patient and tumour characteristics.

## BACKGROUND

### Description of the condition

Endometrial cancer is a cancer of the lining of the womb and is the fourth most common cancer in women in the developed world ([Cancer Research UK 2014a](#)). Each year, 9000 new cases of endometrial cancer are diagnosed in the UK, and 60,000 in the USA ([Cancer Research UK 2014a](#); [NCI 2016](#)). The incidence of the disease has doubled in the last twenty years, and this trajectory is expected to continue. Endometrial cancer has a generally good prognosis, with eight out of ten women still alive at five years after diagnosis ([Cancer Research UK 2014b](#)). With more women than ever surviving initial treatment for endometrial cancer, interven-

tions aimed at reducing the risk of disease recurrence and optimising general health in the long term (at least 5 to 10 years following diagnosis) are required.

Endometrial cancer has a strong link with obesity and it is this relationship that is thought to underpin the rising number of cases ([Renehan 2008](#)). As the percentage of the female population who are obese has increased, so has the number of diagnoses of endometrial cancer. Three biological mechanisms, or themes, have been proposed to explain this association: unopposed oestrogen, insulin resistance, and the presence of an inflammatory milieu (tumour environment).

Oestrogen is a potent stimulator of endometrial cell proliferation or turnover, an effect that is normally counteracted by progesterone during the menstrual cycle. Unopposed oestrogen occurs

in two different scenarios; if progesterone levels are low because of absent ovulation (anovulation), such as in polycystic ovary syndrome, or if oestrogen levels exceed progesterone levels. This occurs in obese postmenopausal women, when the ovaries no longer produce progesterone, but testosterone, secreted by the ovaries and adrenal glands, is converted into oestrogen by excess fat (adipose) tissue. Unopposed oestrogen is associated with an increased risk of endometrial cancer. It increases the rate of endometrial cell proliferation and thus the accumulation of mutations within key tumour-promoting genes. Epidemiological studies have confirmed an increased risk of endometrial cancer in women with high oestrogen levels (Dossus 2013).

Insulin is also able to stimulate endometrial cell proliferation, activating many of the pathways shown to be critical to endometrial cancer development. Obese women have higher insulin levels than their normal-weight counterparts; excess fat tissue reduces the responsiveness of the body to the effects of insulin, so levels increase to compensate. Elevated serum insulin levels have been shown to be present in women with endometrial cancer, compared with those without the disease (Dossus 2013).

Third, fat tissue produces inflammatory and carcinogenic (cancer promoting) proteins, hence obese women have elevated levels compared with normal-weight women. Any, or all of these proteins, may be responsible for the increase in endometrial cancer rates seen in this population (Dossus 2013).

Obesity plays an important role in promoting the development of endometrial cancer, and potentially affects treatment and subsequent survival. The mainstay of treatment for endometrial cancer is surgery to remove the uterus (womb), cervix, fallopian tubes, and ovaries. This may be followed by radiotherapy, chemotherapy, or both in some women. Obese women often have other health problems, which can adversely affect their medical fitness to undergo an operation, and increase the risk of complications associated with surgery and radiotherapy. This may lead to compromises in treatment (Papadia 2006). There is debate in the literature as to whether being overweight or obese has a negative impact on survival. Results from two large cohort studies, in which groups of women with endometrial cancer were followed up, have suggested that obese women, with a body mass index (BMI) of 30 or more, are twice as likely to die during this period as women of a healthy weight. This increases to a six-fold elevation in risk if their BMI is over 40 (Calle 2003; Reeves 2007). However, these studies did not take into account differences in the cancer grade (how abnormal the cells appeared), stage (how far the disease had spread), or the type of treatment received.

When women with endometrial cancer received similar, or standardised treatment, in the context of a randomised controlled trial (RCT), researchers were able to demonstrate that BMI had no impact on the risk of recurrence or overall survival. This was despite a high proportion of obese women having poorer general health (Crosbie 2012). The extra deaths observed in obese women with endometrial cancer may well be unrelated to their cancer. Women

with early stage disease are twice as likely to die from cardiovascular disease, for example heart attacks and strokes, as they are to die from their endometrial cancer (Ward 2012). Excessive weight gain following diagnosis, and indeed, significant weight loss, may be more important than body mass per se. Data from observational studies demonstrate that large weight gains have a detrimental effect on survival, even after adjustment for other factors that influence prognosis, such as cancer grade and stage (El-Safadi 2012; Matsuo 2016). Therefore, measures taken to reduce body weight following treatment for endometrial cancer may be beneficial in improving survival, either by reducing the risk of death from endometrial cancer, or by lowering the chance of dying from other causes, in particular cardiovascular disease.

## Description of the intervention

This review will focus on interventions designed to promote weight loss as their primary goal, and will include non-pharmacological, pharmacological, and surgical interventions. These may be used alone, or in combination. Non-pharmacological or 'lifestyle' interventions are those aimed at reducing nutrient intake and increasing physical activity, through diet and exercise, and may be used alongside psychological interventions such as stress management, stimulus control, and problem solving to induce permanent changes in behaviour. Pharmacological interventions include drugs that act to either reduce fat absorption, the most widely used of which is orlistat, or suppress appetite. Bariatric surgery encompasses procedures designed to limit food intake (e.g. gastric banding), cause malabsorption (e.g. intestinal bypass), or both (e.g. gastric bypass; Figuls 2013).

## How the intervention might work

Weight loss interventions may improve survival by influencing any, or all of the pathways described above that link obesity and endometrial cancer, and have already been shown to be beneficial for survivors of other obesity-related cancers, including breast and colorectal cancer (Morey 2009; Rock 2015; Stolley 2009). Like endometrial cancer, breast cancer also appears to be hormonally driven, and weight loss interventions that have been associated with a loss of 5% or more body weight have been shown to reduce total and free oestradiol levels in women following treatment for this cancer type, which may reduce the risk of disease recurrence (Rock 2013). Similarly, weight loss interventions have already been shown to lower levels of both insulin and adiponectin (a marker of insulin resistance), and improve insulin sensitivity in women following treatment for breast cancer (Rock 2013; Swisher 2015). They have also been associated with a reduction in the expression of inflammatory and cancer-promoting proteins, and this may explain why they reduce the risk of disease recurrence (Irwin 2015).

In addition to potential improvements in cancer-specific outcomes, weight loss interventions may also improve overall survival by reducing the risk of cardiovascular disease. This shares many of the same risk factors with endometrial cancer, including obesity and high blood pressure, both of which were improved when individuals with breast and colorectal cancer underwent intentional weight loss following treatment (Rock 2015). A previous Cochrane review concluded that physical activity may have a positive effect on quality of life (QoL) in multiple different cancers, with reductions in anxiety, fatigue, sleep disturbance, and improved emotional well-being. These results should be interpreted cautiously, as included studies were at risk of considerable bias (Mishra 2012). In particular, there was a high risk of performance bias (significant differences between groups beyond simply which intervention they received), as due to the nature of the intervention (i.e. exercise), it was not possible to conceal the treatment allocation from the participants and researcher. A proportion of the included studies were also assessed to be at high risk of selectively reporting only some of the outcomes (reporting bias), failing to be transparent in their allocation of participants to treatment groups (allocation bias), and not managing incomplete outcome data appropriately (attrition bias). The differences in exercise regimes tested, meant it was difficult to combine the results to give an overall conclusion.

### Why it is important to do this review

The impact of obesity on women's health has recently been highlighted in a number of high-profile publications, including the UK Chief Medical Officer's report in December 2015 (Department of Health 2015), and the publication of the British Journal of Obstetrics and Gynaecology's themed issue, *Obesity and Reproductive Health*, in January 2016 (Crosbie 2016). The impact of lifestyle changes, including weight loss, on outcomes following treatment for endometrial cancer was also identified as one of the top ten research priorities in endometrial cancer in the recent James Lind and Womb Cancer Alliance Priority Setting Partnership (Womb Cancer Alliance 2016). Therefore, this review is timely in its aim to establish the availability of evidence about the effects of weight loss interventions on survival and QoL following treatment for endometrial cancer. There have been no previous reviews of this topic, and such information will set the scene for high quality research to assess the feasibility, effectiveness, and cost-effectiveness of such interventions.

## OBJECTIVES

To determine the impact of weight loss interventions, in addition to standard management of endometrial cancer, on overall survival and the frequency of adverse events. Secondary objectives include an assessment of weight loss interventions on endometrial cancer-

specific survival, cardiovascular event frequency, and QoL, stratified according to patient BMI, and patient and tumour characteristics.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We will only include randomised controlled trials (RCTs), which are considered the highest level of evidence in clinical trials, to maximise the quality of included studies. We will include studies reported as full text, those published as abstract only, and unpublished data, to ensure all relevant trials are incorporated.

#### Types of participants

We will include trials that enrol women of all ages, who are either overweight (BMI more than 25 kg/m<sup>2</sup>) or obese (BMI more than 30 kg/m<sup>2</sup>), and who are currently undergoing, or have been previously treated for endometrial cancer, of any grade, stage, or histological type. Trials will be included regardless of primary treatment modality, i.e. surgery, radiotherapy, hormonal treatment, or a combination. When studies of participants with mixed BMI are identified but subgroup data are not provided, we will contact the study authors to request the subgroup data for overweight and obese participants only. If authors are unable or unwilling to provide these data, the study will not be included in the meta-analysis.

#### Types of interventions

We will include studies reporting on interventions designed to promote weight loss as one of their primary stated goals, in any healthcare setting, including community based studies. These will include:

- Lifestyle interventions, including dietary and physical activity regimes;
- Behavioural strategies to improve adherence to treatment, which may include self-monitoring of eating habits and physical activity, stress management, or stimulus control;
- Pharmacological interventions (such as, but not limited to, appetite suppressants, drugs that cause fat malabsorption or serotonin receptor antagonists of any dose, route of delivery, or duration);
- Surgical interventions (gastric band, sleeve, or bypass procedure).

Any of these interventions will be compared with any other intervention, usual care, or placebo.

## Types of outcome measures

Primary and secondary outcome measures will be described in terms of the effect of the weight loss intervention on survival, body mass index, or QoL, important measures that will help determine whether these interventions should be included in routine clinical practice. Inclusion of these outcomes in the study design will not determine eligibility of the trial for this review.

## Primary outcomes

The primary outcomes of this review will be:

- Overall survival; determined as the time from randomisation until death from any cause;
- Frequency of adverse events, of any nature.

## Secondary outcomes

Secondary outcomes will include:

- Recurrence-free survival; length of time from randomisation to recurrence of the disease or death
- Cancer-specific survival; length of time from randomisation to death from endometrial cancer
- Weight loss; amount of weight lost between randomisation and end of study
- Cardiovascular and metabolic event frequency; particularly the number of strokes, myocardial infarctions, and hospitalisations for heart failure
- QoL as measured on any validated scale

## Search methods for identification of studies

We will impose no language restrictions on our searches. Where necessary, we will translate the reports.

## Electronic searches

We will search the following electronic databases:

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

The MEDLINE search strategy is shown in [Appendix 1](#). We will adapt the search strategy for other databases accordingly.

## Searching other resources

We will handsearch the citation lists of included studies and previous systematic reviews and contact experts in the field to identify further reports of trials. Where additional information is required, we will contact the principal investigator of the trial.

## Unpublished and grey literature

We will search the following for ongoing clinical trials:

- International Standard Randomised Controlled Trial Number (ISRCTN) - metaRegister of Controlled Trials ([www.isrctn.com/](http://www.isrctn.com/))
- [www.controlled-trials.com/rct](http://www.controlled-trials.com/rct)
- Physicians Data Query ([www.cancer.gov/publications/pdq](http://www.cancer.gov/publications/pdq) [www.nci.nih.gov](http://www.nci.nih.gov))
- [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

## Handsearching

We will also handsearch the reports of conferences in the following sources:

- *Gynecologic Oncology* (Annual Meeting of the American Society of Gynecologic Oncologist)
- *International Journal of Gynecological Cancer* (Annual Meeting of the International Gynecological Cancer Society)
- *British Journal of Cancer*
- NCRI Cancer Conference
- Annual Meeting of European Society of Medical Oncology (ESMO)
- Annual Meeting of the American Society of Clinical Oncology (ASCO)

We will search for other conference abstracts and proceedings using [ZETOC](#) and [WorldCat Dissertations](#).

## Data collection and analysis

### Selection of studies

We will download all titles and abstracts retrieved by electronic searching to a reference management database ([EndNote](#)) and remove duplicates. Two review authors (SK and NR) will independently examine the remaining references. We will exclude studies that clearly do not meet the inclusion criteria, and obtain full-text copies of potentially relevant references. Two review authors (SK and NR) will independently assess the eligibility of the retrieved reports and publications. We will resolve any disagreement through discussion, or if required, we will consult a third person (MM). We will identify 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 record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table ([Liberati 2009](#)).

### Data extraction and management

Two review authors (SK and NR) will independently extract study characteristics and outcome data from included studies onto a pre-



piloted data collection form. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable format. We will resolve disagreements by consensus or by involving a third person (MM). One review author (SK) will transfer data into the Review Manager file (RevMan 2014). We will double-check that data are entered correctly, by comparing the data in the RevMan file with the study reports. A second review author (MM) will spot-check study characteristics for accuracy against the trial report. In the case where an included study has multiple reports, we will collate the available data to ensure maximal information yield and give priority to the publication with the longest follow-up associated with our review's primary and secondary outcomes.

We will extract the following data:

- Author, year of publication, and journal citation (including language)
  - Country
  - Setting
  - Inclusion and exclusion criteria
  - Study design, methodology
  - Study population (total number enrolled; baseline patient characteristics: age, co-morbidities (e.g. diabetes, cardiovascular disease); European Cooperative Oncology Group (ECOG) performance status; BMI; type of endometrial cancer; grade and stage of disease; timing of intervention in relation to treatment of endometrial cancer (i.e. before or after definitive treatment, nature of primary endometrial cancer treatment (e.g. surgery, radiotherapy, hormonal)).
    - Intervention details (type of intervention; dose, route of administration; duration of treatment; additional information as appropriate)
    - Comparison (nature of intervention; dose, route of administration; duration of treatment; additional information as appropriate)
      - Risk of bias in study (see below)
      - Duration of follow-up
      - 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 the analyses.
        - Results: We will extract the number of participants allocated to each intervention group, the total number analysed for each outcome, and the missing participants.
        - Notes: Funding for trial, and notable conflicts of interest of trial authors.

We will extract the results as follows:

- For time-to-event data (survival and disease progression), we will extract the log of the hazard ratio [log(HR)] and its standard error from trial reports. If these are not reported, we will attempt to estimate the log (HR) and its standard error using the methods of Parmar 1998.
  - For dichotomous outcomes (e.g. adverse events, cardiovascular events or deaths), if it is not possible to calculate a

hazard ratio, we will estimate a risk ratio; we will extract the number of patients in each treatment arm who experienced the outcome of interest and the number of patients assessed at endpoint. .

- For continuous outcomes (e.g. QoL measures, weight loss), we will estimate the mean difference between treatment arms and its standard error; we will extract the final value and standard deviation of the outcome of interest and the number of patients assessed at endpoint in each treatment arm at the end of follow-up. .

If reported, we will extract both unadjusted and adjusted statistics. Where possible, we will extract data relevant to an intention-to-treat analysis, in which case participants will be analysed in groups to which they were assigned.

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

### Assessment of risk of bias in included studies

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

- Selection bias: random sequence generation and allocation concealment
- Performance bias: blinding of participants and personnel (patients and treatment providers)
- Detection bias: blinding of outcome assessment
- Attrition bias: incomplete outcome data
- Reporting bias: selective reporting of outcomes

Two review authors (SK and NR) will independently apply the 'Risk of bias' criteria; we will resolve differences by discussion, or by appealing to a third review author (MM). We will check clinical trial registries for a priori primary and secondary outcome measures to assess the risk of selective reporting. We will judge each item as being at high, low, or unclear risk of bias, as set out in the criteria provided by Higgins 2011 and Higgins 2011a. We will provide a quote from the study report and a statement to justify the judgement for each criteria. We will summarise results in both a graph and a narrative summary. When interpreting treatment effects and meta-analyses, we will take into account the risk of bias for the studies that contributed to that outcome. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

### Measures of treatment effect

We will use the following measures of the effect of treatment:

- For time-to-event data, we will use the hazard ratio (HR), if possible.



- For dichotomous outcomes, 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 risk ratio (RR) and 95% confidence interval (CI).
- For continuous outcomes, we will analyse data based on the mean, standard deviation (SD), and number of people assessed for both the intervention and comparison groups, to calculate mean difference (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 in [RevMan 2014](#).

We will undertake meta-analyses only where this is meaningful, i.e. if the treatments, participants, and the underlying clinical question are similar enough for pooling to make sense. We will describe skewed data reported as medians and interquartile ranges. Where multiple trial arms are reported in a single trial, we will include only the relevant arms and divide the 'shared' comparison group equally between the number of treatment groups, to avoid 'double-counting'.

### Unit of analysis issues

The unit of analysis will be the participant

### Dealing with missing data

We will attempt to contact study authors to obtain missing data (participant, outcome, or summary data). Where possible, we will conduct analysis of participant data on an intention-to-treat basis; otherwise, we will analyse data as reported. We will report on the levels of loss to follow-up, and assess this as a source of potential bias.

We will not impute missing outcome data.

### Assessment of heterogeneity

Where we consider studies similar enough (based on participants, intervention, comparison, settings and outcome measures) to pool the data using meta-analysis, we will assess the degree of heterogeneity by visually inspecting forest plots, by estimating the percentage of heterogeneity ( $I^2$  statistic) between trials that cannot be ascribed to sampling variation ([Higgins 2003](#)), by formally testing the significance of the heterogeneity ( $\text{Chi}^2$  statistic; [Deeks 2001](#)), and if possible, by conducting sub-group analyses. We will use these  $I^2$  statistic levels as a rough guide to assess heterogeneity:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity

We will evaluate the value of the  $I^2$  statistic alongside the magnitude and direction of effects, and the P value for the  $\text{Chi}^2$  test ([Higgins 2011](#)).

If there is evidence of substantial clinical, methodological, or statistical heterogeneity across included studies, we will not report pooled results from meta-analysis, but will instead use a narrative approach to data synthesis. In this event, we will investigate and report the possible clinical or methodological reasons for this.

### Assessment of reporting biases

We aim to minimise reporting bias by systematically searching for all eligible studies, including unpublished data and ongoing clinical trials, and by not including any language restrictions. Updates of this review will deal with any time lag bias.

If we include 10 or more studies that investigate a particular outcome, we will examine funnel plots that correspond to the meta-analysis of the outcome to assess the potential for small study effects, such as publication bias. We plan to visually assess funnel plot asymmetry; if asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

### Data synthesis

If sufficient, clinically similar studies (in terms of participants, intervention, comparison, settings and outcome measures) are available to ensure meaningful conclusions, we will pool their results in meta-analyses using the random effects model in RevMan. Given the number of possible interventions that may be included in the incorporated studies, only the following meaningful comparisons will be performed:

- Lifestyle interventions in addition to usual care versus usual care;
- Behavioural interventions in addition to usual care versus usual care;
- Pharmacological interventions in addition to usual care versus usual care;
- Surgical interventions in addition to usual care versus usual care;
- Lifestyle interventions versus behavioural interventions;
- Lifestyle interventions versus pharmacological interventions;
- Lifestyle interventions versus surgical interventions;
- Behavioural interventions versus pharmacological interventions;
- Behavioural interventions versus surgical interventions;
- Pharmacological intervention versus surgical interventions.

If any trials have multiple treatment groups, we will divide the 'shared' comparison group into the number of treatment groups in the comparison, and treat the split comparison group as independent comparisons.

The specific method for pooling data will depend upon the nature of the outcome measure. If we are unable to pool the data statisti-

cally using meta-analysis, we will conduct a narrative synthesis of results. We will present the major outcomes and results, organised by intervention categories, according to the major types or aims of the identified interventions. Depending on the assembled research, we may also explore the possibility of organising the data by population. Within the data categories, we will explore the main comparisons of the review.

### 'Summary of findings' table

We will assess and report the quality of the evidence for each outcome, using the GRADE approach and these domains: study limitations (suggesting a high likelihood of bias), inconsistency (unexplained heterogeneity), imprecision (wide confidence intervals), indirectness of evidence, and publication bias. We will create a 'Summary of findings' table, using GRADEpro GDT software (Appendix 2), and two authors (SK and NR) will independently assess the quality of the evidence, using Chapter 12.2 of the *Cochrane Handbook of Systematic Reviews of Interventions* as a guide (Schünemann 2011). We will use a checklist to maximise consistent GRADE decisions, and the GRADE Working Group quality of evidence definitions (Meader 2014). We will downgrade the evidence from high quality by one level for serious limitations (or by two for very serious limitations) for each outcome, and outline our rationale in the footnotes:

- **High quality:** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate quality:** 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 quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

We will include these outcomes in the 'Summary of findings' table:

1. Overall survival

2. Adverse events
3. Recurrence-free survival
4. Cancer-specific survival
5. Weight loss
6. Cardiovascular and metabolic event frequency
7. Quality of life

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

We will perform subgroup analyses for the following factors:

- BMI
- Histological type, stage, and grade of endometrial cancer

### Sensitivity analysis

If adequate data are available, we will perform a sensitivity analysis comparing studies with high and unclear risk of bias and low risk of bias for attrition and outcome reporting, and allocation concealment (the latter is relevant only to pharmacological interventions).

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\* Indicates the major publication for the study

## APPENDICES

### Appendix 1. 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\*)).mp.
3. 1 or 2
4. body mass index/
5. BMI.mp.
6. exp obesity/
7. exp body weight/
8. Adiposity/
9. (obese or obesity or overweight or weight or adiposity or excess body fat).mp.
10. 4 or 5 or 6 or 7 or 8 or 9
11. randomized controlled trial.pt.
12. controlled clinical trial.pt.
13. randomized.ab.
14. placebo.ab.
15. clinical trials as topic.sh.
16. randomly.ab.
17. trial.ti.
18. 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 3 and 10 and 18

### Appendix 2. Draft 'summary of findings' table

| Title: Interventions for weight reduction in obesity to improve survival in women with endometrial cancer                                                                                                                                                                                                                                                                                      |                                 |                    |                          |                              |                                                                             |                                                                           |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|--------------------|--------------------------|------------------------------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------|
| <p><b>Patient or population:</b> Women of all ages who are either overweight or obese, who are undergoing or have been previously treated, for endometrial cancer</p> <p><b>Settings:</b> In- and out-patient</p> <p><b>Intervention:</b> Interventions designed to promote weight loss</p> <p><b>Comparison:</b> Compared with any other weight loss intervention, usual care, or placebo</p> |                                 |                    |                          |                              |                                                                             |                                                                           |
| Outcomes                                                                                                                                                                                                                                                                                                                                                                                       | Illustrative comparative risks* |                    | Relative effect (95% CI) | No of participants (studies) | Quality of evidence (GRADE)                                                 | Comment<br>Possibly discuss the subgroup findings/ effects in this column |
|                                                                                                                                                                                                                                                                                                                                                                                                | Assumed risk                    | Corresponding risk |                          |                              |                                                                             |                                                                           |
| Overall survival                                                                                                                                                                                                                                                                                                                                                                               |                                 |                    |                          |                              | [Delete as appropriate for each outcome]<br>⊕○○○<br><b>very low</b><br>⊕⊕○○ |                                                                           |

(Continued)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |  | low |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|--|-----|--|
| Adverse events                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |  |  |  |     |  |
| Recurrence-free survival                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |  |  |  |     |  |
| Cancer-specific survival                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |  |  |  |     |  |
| Weight loss                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |  |  |  |  |     |  |
| Car-diovascular and metabolic event frequency                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |  |  |  |     |  |
| Quality of life                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |  |     |  |
| <p>*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).<br/>           CI: confidence interval; HR: hazard ratio; MD: mean difference; RR: risk ratio; OR: odds ratio</p>                                                                                                                                                                         |  |  |  |  |     |  |
| <p>GRADE Working Group grades of evidence<br/>           High quality: Further research is very unlikely to change our confidence in the estimate of effect.<br/>           Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.<br/>           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.<br/>           Very low quality: We are very uncertain about the estimate.</p> |  |  |  |  |     |  |

## CONTRIBUTIONS OF AUTHORS

All authors have contributed to the study conception and design.

Aquisition of data will be undertaken by Kitson, Ryan, Mackintosh, and Duffy.

Analysis and interpretation will be undertaken by Crosbie and Duffy.

Drafting of manuscript will be performed by Kitson, Duffy, and Crosbie and will be reviewed by all authors.

The review update will be undertaken by Crosbie.

## **DECLARATIONS OF INTEREST**

Sarah Kitson: None known

James Duffy: None known

Neil Ryan: None known

Michelle Mackintosh: None known

Emma Crosbie: None known

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