Womb Cancer Alliance Priority Setting Partnership Literature reviews

Summaries of literature reviews in answer to questions submitted by participants of the uncertainty gathering questionnaire 2015

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Aftercare in primary care

Q1 When & how is it best to discharge patients after cancer treatment for GP care?

There are no studies regarding the provision of cancer follow up in primary care in patients with womb cancer. Systematic review of studies including survivors of all types of cancer showed no significant difference in patient wellbeing, recurrence rate, survival, recurrence-related serious clinical events, diagnostic delay, or patient satisfaction with GP led care. Cancer survivors' health care needs in general practice were found to focus mainly on psychosocial support, i.e. discussing the impact of their disease, getting medical help for mostly for non-cancer related problems, and getting general information about their disease. Interventions improving communication between primary and secondary care could lead to greater GP and patient involvement.

Studies are ongoing as to whether patient initiated follow up in endometrial cancer may be more effective to reduce fear of recurrence and improve quality of life than routine hospital based follow up.

Changing demographics of patients diagnosed with womb cancer

Q2 Is there an increase in the incidence of women under the age of 50 diagnosed with endometrial cancer? If so, what are the reasons for this increase?

6% of all women diagnosed with womb cancer in the UK are under 50. There has been an increase in the number of women diagnosed with womb cancer in all age groups over the last 40 years. The steepest increase in womb cancer incidence in last 20 years is actually in women over 50 (Evidence level 1).

In contrast in the US, the proportion of women with endometrial cancer who were under 50 has doubled in the last 40 years. (Evidence level 1). The increase in the US has been suggested to be associated with an increase in obesity in young women.

Being obese, having polycystic ovary syndrome, never having been pregnant and smoking are the most important risk factors for womb cancer in pre-menopausal women.

Q3 Is there an increase in the incidence of diagnosed with high grade endometrial cancer? If so, what are the reasons for this increase?

It is unclear whether there has been an increase in high grade endometrial cancer (i.e. women with Grade 3 endometrioid, clear cell and high grade serous cancers) as this group is not separately recorded by most cancer registries.

There has been an increase in the number of women with endometrioid type womb cancer over the last 40 years. However, the numbers of women with other types of womb cancer have remained quite stable. Improvements in typing of cancers may explain a small increase in numbers of women diagnosed with clear cell or high grade serous cancers, as numbers of women with unclassified cancers have fallen at

the same time. Lifestyle associated risks may be similar in women with high grade disease and those with low grade disease.

Chemotherapy/ Radiotherapy in primary disease

Q4 Is chemotherapy effective in the primary treatment of endometrial cancer?
Most women with womb cancer are diagnosed at early stages before their cancer has spread. These women are treated with surgery. Following surgery, women who are considered at high risk of relapse may be offered additional chemotherapy. Only a small proportion of patients will have disease which is too advanced to consider surgery. These women can be considered for chemotherapy; even with intense treatment consisting of 3 or more chemotherapy drugs only a modest increase in survival is seen (Evidence level 1). This is at the expense of more severe side effects.

The combination of drugs which offers the longest increase in survival still needs to be established. There have been no studies which compare chemotherapy in these patients to hormonal treatments or supportive care.

Q5 What are the biological mechanisms underpinning chemotherapy resistance in endometrial cancer?

Most chemotherapies kill cancer cells by causing irreparable damage to a cell's genetic material. The mechanisms by which womb cancer cells 'learn' to avoid cell death are being investigated in numerous laboratory-based studies. These studies have revealed that resistance to chemotherapy is multi-factorial.

As yet this knowledge is not complete enough to translate this into ways in which the responsiveness of a tumour to a drug can be predicted or develop new treatments which are more effective at treating cancers that are already resistant.

Q6 Are alternative therapies effective in the management of treatment toxicities?
There are few high quality studies to determine whether complementary and alternative therapies are effective ways to manage the side effects of cancer treatment.

The best studied is acupuncture. Acupuncture may be useful in some patients experiencing nausea and vomiting associated with chemotherapy (Evidence level 4). Its use to manage other side effects is undetermined.

Trace element supplementation has also been studied. There is insufficient evidence to suggest that selenium supplementation reduces the side effects of chemotherapy, radiotherapy or after-effects of surgery. Small studies suggest possible benefits for calendula oil in radiation induced dermatitis.

Q7 Is intracavity brachytherapy as effective as surgery for women with low risk stage 1 endometrial cancer who are unfit for surgery?

A review of the records of patients who received brachytherapy instead of surgery for early stage womb cancer in one institution suggested that brachytherapy along with externally delivered radiotherapy resulted in excellent rates of disease control in women who were unfit for surgery (Evidence level 4).

Q8 Does histological subtype influence the efficacy of chemotherapy?
Women with clear cell and serous type womb cancers tend to have a worse outlook than those with endometrioid type cancers (Evidence level 2). Reanalysis of chemotherapy trials suggest that whether a woman responds to conventional chemotherapy is not related to the type of womb cancer she had. Length of time she survives after treatment is however dependent on her cancer type (Evidence level 2). New targeted chemotherapies may work better in some types of womb cancer. Therefore this question will need to be considered each time a new drug is evaluated.

Q9 Which patients will benefit from adjuvant chemotherapy or radiotherapy following surgery?
After hysterectomy, the chance of cancers returning can be stratified into low, intermediate and high risk according features of the cancer which include the depth of invasion of the tumour, the cancer type, its grade and whether tumour is seen in the vessels around the womb (lymphovascular space invasion). Chemotherapy reduces the risk of a cancer returning, lengthens the time between initial treatments and the first signs of spread and improves survival rates in patients with advanced disease (stage 3 and 4)(Evidence level 1). Chemotherapy prolongs survival more than radiotherapy and can be an alternative to radiotherapy. Chemotherapy and radiotherapy can be used together to improve survival even further. However these benefits come at the expense of short term and long term side effects. Women with low risk cancers are usually cured by surgery. Additional treatment would not reduce the chance of their cancer returning and only need to a woman experiencing unnecessary side effects. Some women with intermediate risk will benefit from the reduction in risk of spread that comes with chemo or radiotherapy but this must be offset against the side effects. A significant proportion of women with high risk disease would benefit from chemotherapy/radiotherapy and therefore the risk-reduction of spread or death may be enough for women to tolerate the side-effects. Even in the highest risk groups, only 1 woman in every 10 will benefit from chemotherapy. Better ways to select patients who might benefit from chemotherapy and/or radiotherapy may therefore be useful.

Q10 Would it be better to give chemotherapy for adjuvant treatment, rather than radiotherapy and then leave ERBT for salvage treatment?
There are no studies which address this question.

Q11 Is there a place for neo-adjuvant chemotherapy in high-risk endometrial cancer?
High-risk endometrial cancer is defined as an endometrioid histological type that is at least stage 1B and high grade (G3) or any non-endometrioid endometrial cancer. This terminology therefore encompasses women with a wide range of disease. Neo-adjuvant chemotherapy is giving chemotherapy before surgery to treat the cancer. It is aimed to reduce the size or bulk of the tumour as to make the surgery more straightforward/less extensive. The mainstay of treatment in endometrial cancer is

primary surgery, there has been very little literature about the use of neoadjuvant therapy. Studies to date have mainly consisted of small retrospective case series (Level 4). In total there have only been 106 published cases where the outcomes of neoadjuvant chemotherapy were documented. More studies are required before any recommendations can be made.

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Q12 Does radiotherapy in high risk disease reduce risk of recurrence following surgery?

A meta-analysis of studies looking at the use of radiotherapy in stage 1 endometrial cancer following surgery concluded that external beam radiotherapy significantly reduced recurrence of the cancer around the original cancer site but this did not have an effect on survival (Evidence level 1). The PORTEC 2 study recommended that vaginal brachytherapy should be offered to prevent vaginal recurrence to women at high and intermediate risk (Evidence level 2). It is unclear whether these women would also have reductions in recurrence in the rest of the pelvis.

It remains difficult to bring together the results of different radiotherapy trials due to the inconsistency in the definition of the risk groups considered. Therefore, some women may benefit from increased survival as well as reduced rates of recurrence following radiotherapy.

Q13 Does metformin improve response rates to adjuvant radiotherapy and or chemotherapy?

A relationship between metformin use and better survival in women with womb cancer has been noticed in a number of clinical trials of other agents. Several laboratory based studies have suggested that metformin sensitises cells to chemotherapy treatment (Evidence level 5). There have been no prospective clinical trials that formally assessed whether the addition of metformin to adjuvant treatment improves response rates and survival.

Q14 How can we develop better-tolerated and more effective therapy for patients with advanced endometrial cancer?

The treatment options for women with advanced endometrial cancer are limited. Even with combination chemotherapy time to progression and survival is limited. Further trials of new chemotherapy drugs targeting new blood vessel development (anti-angiogenic) and key cancer pathways (e.g. MTOR inhibitors) may lead to increases in survival.

It is hoped that drugs targeting key drivers of cancer growth will have fewer side effects than conventional chemotherapies. Combining novel treatments with being able to predict those women who might benefit from these therapies, will reduce the number of women who experience side effects without significant benefit (Evidence level 5).

Q15 Can imaging predict which women will benefit from adjuvant radiotherapy?

A number of small studies have evaluated the use of ultrasound, diffusion weighted MRI or PET to predict cervical and myometrial invasion and lymph node metastasis. Sensitivity and specificity of diffusion weighted MRI and ultrasound for invasion was

high. Prediction of lymph node metastasis by imaging was less accurate. Accuracy varies with the location of the lymph node metastasis (Evidence level 4).

There have been no studies which evaluate whether offering adjuvant radiotherapy based on imaging findings rather than histological features (current standard of care) is effective.

Q16 Is concomitant use of vaginal brachytherapy with external beam therapy beneficial compared to external beam therapy alone?
Post-operative radiotherapy reduces local recurrence rates but does not increase survival. PORTEC-2 concluded that women treated with vaginal brachytherapy had similar rates of local recurrence as women treated with external beam radiotherapy but suffered fewer side effects (Evidence level 2).

50% of the patients in the ASTEC/EN.5 trials also received brachytherapy as well as being randomised to either ERBT or no additional treatment (Evidence level 1). Given that vaginal brachytherapy and external beam therapy act locally and do not reduce distant disease recurrence or death from either local or distant disease, vaginal brachytherapy plus additional ERBT is unlikely to be beneficial.

Q17 Is chemoradiotherapy superior to chemotherapy alone as adjuvant treatment?
There have been no randomised control trials which have compared chemoradiotherapy to chemotherapy alone for adjuvant treatment.

Q18 Which is the best sequence for giving chemoradiotherapy; chemotherapy radiotherapy sandwich, radiation followed by chemotherapy, chemotherapy followed by radiation?
There have been no large randomised control trials that compare these three regimens. Existing studies involve very few patients and are inadequately controlled therefore limiting conclusions (Evidence level 4).

Q19 What are the most appropriate chemotherapy agents to use in conjunction with radiation?
There have only been a few high quality prospective studies looking at the combination of radiotherapy and chemotherapy. Each of these have used slightly different chemotherapy regimens and have had different inclusion criteria making it difficult to reach a consensus regarding the best drug regimen. Previous RCTs and retrospective studies have tended to include adriamycin in addition to a platinum based drug +/- paclitaxel whilst the PORTEC3 study (yet to report) looks at the use of platinum and taxol combination.

Comorbidities and associations

Q20 Is endometrial cancer associated with melanoma?
A US census study with over 450,000 participants found that there was an association between womb cancer and melanoma. Women with melanoma or womb cancer had a two fold increase risk of having the other cancer (Evidence Level 2).

A review of Swedish cancer registry found that womb cancer was 40% more common in women who had had melanoma than in the general population (Confidence intervals 1.03-1.88). A similar study in Australia failed to find a significant difference.

It is unclear why this association is seen but this is not thought to be genetic. There have been no studies which explore the common causal mechanisms between these two cancers.

Q21 Should all patients with endometrial cancer have a fasting glucose/GTT performed to exclude the presence of undiagnosed diabetes?
Diabetes is more common in women with womb cancer than in the general population. There have been no large scale studies to determine the rate of undiagnosed diabetes in women with womb cancer. Control of blood sugar is likely to reduce the risk of diabetic complications and cardiovascular disease (Evidence level 5).

Q22 To what extent is survival predicated on early diagnosis against co-morbid condition?
Most women (78%) will present with early stage disease (i.e. Stage 1). 95% of these women diagnosed will survive 5 at least years. Survival rates decrease with increased stage at diagnosis (Evidence level 1).

It is unclear whether BMI, hypertension or diabetes adversely affects womb cancer survival as studies have shown mixed results (Evidence level 3). There have been few systematic reviews on this subject.

Q23 Should endometrial cancer patients be screened for other cancers?
There have been 2 large studies which address whether women with womb cancer are more likely to be affected by a second primary cancer. Data from the Swedish cancer registry suggest that there were 50% more cancers seen in women with womb cancer than the general population. These include cancers of the breast, gastrointestinal tract, female genital tract and urinary tract. Data from the US National Cancer Institute Surveillance (SEER) database suggests that risk of other cancers differs according to race. White Americans were significantly less likely than the general population to have a second cancer whilst Black Americans were more likely to have second cancers (Evidence level 2). Increases in other cancers have been attributed to radiotherapy. It is known that women undergoing radiotherapy are at a higher risk of future cancers to areas exposed to radiation.

There are no studies which address whether screening for these cancers would be beneficial.

Q24 What are risks of developing ovarian cancer following uterine cancer?
The standard treatment for women with womb cancer is a total hysterectomy and bilateral salpingoophrectomy; removing the womb and both tubes and ovaries. The risk of developing ovarian cancer therefore is reduced in women undergoing standard treatment.

Studies of the ovaries removed at the time of surgery suggest that spread to the ovaries is rare (2-4%) and a ovarian cancer unrelated to the womb cancer even rarer. Data from the Swedish cancer registry suggests that even though primary ovarian cancers in association with womb cancer are rare. They are 55 times more common than in the rest of the population. In young women the risk of an ovarian cancer found at the time of surgery is even higher. 10-29% of young women with womb cancer also have ovarian cancers.

Q25 What are the risks developing of breast cancer following uterine cancer?
Data from the Swedish cancer registry suggest that the risk of breast cancers increases following a diagnosis with womb cancer. Breast cancer was 40% more common in women who had had womb cancer. The American study did not show an increase. It is unclear how representative these studies are to the risk of subsequent cancers to women in the UK population.

Q26 What are the risks of developing lymphatic cancers following uterine cancer?
No increase in lymphoma is seen in women with womb cancer (Evidence level 2).

Q27 Are women who have been diagnosed with breast cancer at higher risk of developing endometrial cancer?
Several large cohort studies in women with breast cancer suggest that womb cancer is more common amongst women who have had breast cancer. This equated to approximately an extra 2-4 cases per year for every 10 000 women with breast cancer. (Evidence level 3).

A Dutch study suggested women over 60 who have breast cancer have a 60% increase in their risk of womb cancer if they required hormonal therapy. Studies looking at whether there has been a change in risk over time suggest that there may be a decline in the number of excess cases of endometrial cancer seen in women with breast cancer. This may be associated with a move away from using Tamoxifen.

Criteria for referral for investigation

Q28 At what age should we investigate inter-menstrual bleeding or heavy menstrual bleeding?
Up to 30% of women will seek medical attention for irregular or heavy menstrual bleeding during their reproductive years. The NICE guidelines on heavy menstrual bleeding suggest that women with symptoms suggestive of abnormalities of the womb lining, such as persistent bleeding between periods or failure of hormone based treatments in women over 45 should be investigated by ultrasound and/or biopsy of the womb lining (Based on consensus for good practice).

A recent meta-analyses as part of a Health Technology Assessment found that 1 in 50 of women of reproductive age with heavy menstrual bleeding have endometrial hyperplasia with atypia or endometrial cancer that would necessitate surgical treatment (Evidence level 1).

The current recommendation of direct treatment without investigation was found to be less clinically effectively (Patient satisfaction rates of 93% compared to 97%) and only marginally cheaper than treatment after investigation with hysteroscopy (Evidence level 1). Although it is known that the risk of womb cancer increases with age, assessment was not stratified by age. Further analysis would be required to answer the question regarding whether age stratified or universal investigation of women attending with abnormal bleeding would be more effective

Q29 Should all women with postmenopausal bleeding be investigated?
The National Institute of Clinical Excellence guidance on referral for suspected cancer recommends that all postmenopausal women over the age of 55 should be referred for further investigation and that referral should be considered in postmenopausal women under the age of 55. Several cohort studies have shown that the probability of womb cancer in women with postmenopausal bleeding rises with age. It is approximately 1 in 100 in women younger than 50 years but rises to 1 in 4 in women older than 80 years (Evidence level 2). The risk of womb cancer in postmenopausal women under 55 is at least 3 times less a woman over 55 and therefore the recommendation is for a referral to be considered if there are additional risk factors. The incidence of malignancy in women with postmenopausal who are obese is18% and diabetic is 21%.

Q30 What is the incidence of occult endometrial cancer? i.e. women who are asymptomatic and have endometrial cancer?
It is difficult to estimate the number of women who have womb cancers without displaying symptoms as definitive diagnosis is based on examination of the womb after hysterectomy. In one retrospective study of women undergoing hysterectomy for reasons other than cancer, womb cancer was found incidentally in 0.26% (1 in 400) of women despite having no symptoms (Evidence level 4).

Q31 What is the best setting for a biopsy of a patient with suspected endometrial cancer?
There have been no studies looking at the ideal setting or provider for endometrial biopsy. Modelling of the cost-effectiveness of different investigative strategies suggests that selective transvaginal ultrasound for women with additional risk factors is likely to be the most cost effective strategy (Evidence level 5). This needs to be confirmed with randomised control trials but integrating multiple tests would likely best be done in a one-stop clinic.

Q32 What is the optimal cut off for endometrial thickness above which postmenopausal patients should have further investigations for endometrial cancer when a) experiencing postmenopausal bleeding b) do not experience bleeding?
Several meta-analyses on the sensitivity and specificity of different cut-offs for endometrial thickness in women with postmenopausal bleeding have been performed. Very few have used the original data from studies during their analysis. The most recent to be performed using original data suggests that a cut-off of 3mm is likely to give the best balance between a low false positive rate and the lowest possible false negative rate. In this study using 3mm as a cut off gave a sensitivity of 98% with a specificity of 51%. This means that 98% of women with womb cancer

will be picked up by this test but 1 in 2 women who are told they have a thickened endometrium will not have a womb cancer.

Similar meta-analysis in postmenopausal women without bleeding found that transvaginal ultrasound was far less effective at detecting womb cancer in women who had no evidence of bleeding. Women without bleeding are inherently less likely to have womb cancer and therefore any test would have to have very low false negative rates to provide any degree of reassurance. With a cut off of 5mm sensitivity was found to be 72% in this meta-analysis. This equates to 3 out of 10 women with womb cancer being missed if this test was used. However, the confidence intervals for the estimate of sensitivity are very wide suggesting that the level of certainty surrounding this estimate is low.

Q33 Does it take longer and are women diagnosed later in their disease course if they present with irregular or heavy menstrual bleeding rather than postmenopausal bleeding?
There is very little research in this area.

A small retrospective study found that women with the longest delays in diagnosis had the longest survival. It is suggested that this phenomenon is seen due to the triaging of referrals by GPs and hospital consultants i.e. those with the highest risk of the most aggressive disease are often seen first. Whilst those more likely to have earlier disease may have to wait longer or undergo a number of tests and treatment before a diagnosis is made (Evidence level 5)

In a second retrospective study of Spanish women with womb cancer, younger age at diagnosis was associated with lower grade, well differentiated tumours with less invasion of the muscle wall. Although longer periods between the time of first symptom to diagnosis may not affect survival, delay does have a negative impact on quality of life and social functioning for women with womb cancer.

Q34 What is the optimal threshold level for endometrial thickness which further investigations are warranted in a premenopausal woman?
The value of ultrasound evaluation of endometrial thickness in premenopausal women is controversial. In pre-menopausal women the endometrial thickness varies throughout the menstrual cycle. One study suggested that a cut-off of 8mm had a sensitivity of 85% and specificity of 56.4% (Evidence level 4). Transvaginal ultrasound in premenopausal women may instead be a useful tool to assess for the presence of polyps and submucosal fibroids which make biopsies of the whole womb cavity difficult.

Q35 When should re-investigation be performed in woman who has a normal biopsy and hysteroscopy but has recurrent or persisting post-menopausal bleeding?
There is very little evidence upon which to base specific guidance but recurrence rates of postmenopausal bleeding after normal investigation findings are in the region of 10%; between 4-8% of these women, will be found to have womb cancer after further investigation (Evidence level 4).

Most guidelines suggest that there is a low threshold for further investigation in women with persistent bleeding given that all investigations are associated with false negative rates of between 3-4%. The SIGN guidelines (withdraw as not updated since 2002) previously suggested women should be reinvestigated after 6months.

Diagnostic accuracy

Q36 What is the negative predictive value of TVUSS for women with suspected endometrial cancer?

Systematic reviews of this subject suggest that when using a cut-off of 5mm, a postmenopausal woman with bleeding with a womb lining measurement of less than 5mm will have a 1% chance of having womb cancer (Evidence level 1). If she has a womb lining of over 5mm, the chance that she has womb cancer is 57%. Transvaginal ultrasound is not a discriminative test in premenopausal women.

Q37 What are the relative diagnostic test accuracy characteristics of pipelle, hysteroscopy and transvaginal ultrasound with regards to endometrial cancer?

Systematic reviews suggest endometrial biopsy and hysteroscopy have similar sensitivities for diagnosing endometrial hyperplasia/cancer. Sensitivity and specificity for both tests was 78% and 96% respectively. (Evidence level 1)
Systematic reviews of transvaginal ultrasound suggest a sensitivity of 96% and specificity of 80% in postmenopausal women. (Evidence level 1)

Q38 What is the negative predictive value of a combination of TVUSS and endometrial sampling?

There have been no studies which have formally reported the negative predictive value of the tests used sequentially. Meta-analysis suggests that transvaginal ultrasound has a false negative rate of 8%, whilst endometrial biopsies have a false negative rate of 5-15%. The combination of both tests will reduce the false negative rate further but at the expense of many more women without cancer having to undergo biopsy than currently where transvaginal ultrasound is offered in the first instance and biopsy only performed if abnormality is seen (Evidence level 5).

Q39 Is pelvis USS a valid screening test for endometrial cancer (in those over 40)?

See answer to Q208

Q40 If a woman has had postmenopausal bleeding investigated with hysteroscopy which is normal, what is their subsequent risk of developing endometrial cancer in the future if they represent with further postmenopausal bleeding?

Rates of postmenopausal bleeding after normal investigation findings are in the region of 10%; between 4-8% of these women, will be found to have womb cancer after further investigation (Evidence level 4).

Q41 Is pipelle sampling as accurate as hysteroscopy in women with ET 3-5mm?

Pipelle sampling is known to only sample about 4% of the womb lining. Meta-analyses of these studies suggest a sensitivity of approximately 99.6% and a specificity of 98%. Inadequate sampling can occur in up to 65% of postmenopausal women (Evidence level 1). Failed hysteroscopy are a lot less common and offer opportunities for visual inspection as well as directed biopsies.

Q42 Are dedicated postmenopausal bleeding and menstrual dysfunction clinics more clinically and cost effective than a general gynaecology service?
A recent Health Technology Assessment and several published service evaluations have found that one stop clinics are more cost effective and convenient for patients undergoing assessment and treatment for postmenopausal bleeding and menstrual dysfunction (Evidence level 2)

Q43 In pre-menopausal women with abnormal bleeding, what is the most accurate method of diagnosing endometrial cancer?
A Health Technology Assessment found that the most clinically and cost-effective investigative procedure for a pre-menopausal woman with abnormal bleeding is outpatient hysteroscopy and biopsy. (Evidence level 1)

Q44 What are the factors associated with missed diagnosis of endometrial cancer?
There are no specific studies which address this in womb cancer but a number of studies across a range of types of cancer suggest that there a many reasons for missed opportunities to diagnose patients in a more timely manner. Broadly they can occur at any of the three phases of the diagnostic process; initial assessment, diagnostic test performance and follow-up. Missed opportunities can involve patients, care team and/or the health system often in combination. More cross disciplinary research is needed to identify and address the factors that lead to a delay in diagnosis.

Q45 What techniques are available to distinguish between endometrial endometrioid adenocarcinoma with synchronous ovarian primary / endometrial endometrioid adenocarcinoma metastatic to ovary?
For accurate differentiation of a synchronous or metastatic cancer, several clinicopathologic criteria have been proposed. The criteria for identification of the synchronous primary cancers include either different histologic types (major criterion) or all of the following minor criteria: (1) both tumours confined to primary sites, (2) no direct extension between tumours, (3) no lymphovascular tumour emboli, (4) no or only superficial myometrial invasion, and (5) distant metastasis. Molecular diagnostic techniques have been less successful at distinguishing the two types of cancer.

Q46 Does a normal USS in pre-menopausal women exclude cancer?
The value of ultrasound evaluation of endometrial thickness in premenopausal women is controversial. In pre-menopausal women the endometrial thickness varies throughout the menstrual cycle. There are no consensus values for a normal endometrial thickness in a pre-menopausal woman. Therefore heterogeneity of the studies have made pooled estimates difficult.

Q47 Is hysteroscopy or pipelle the most cost effective initial investigation in postmenopausal women with thickened endometrium?
A Health Technology Assessment found that the most cost effective initial investigation for postmenopausal women after a finding of a thickened endometrium is an endometrial biopsy rather than an outpatient hysteroscopy (Evidence level 1). However the modelling is focussed on achieving the most improvement in cancer survival for given expenditure rather than on patient satisfaction and improvement of symptoms. Women with non-malignant causes of a thickened endometrium may benefit from treatment of these other causes.

Q48 Can measuring intratumoral resistive indices and Doppler velocimetry of the uterine arteries distinguish benign from malignant processes?
There have been several small single centre studies looking at the ability of ultrasound to distinguish benign from malignant thickening of the womb lining (Evidence level 4). They suggest that due to new vessel formation there is a drop in the resistance of the arteries in the wombs of women with cancer. It is unclear whether the difference is large enough to be able to distinguish normal from abnormal wombs.

Q49 Is 3D ultrasound superior to 2D ultrasound in detecting malignant lesions?
A systematic review concluded that there was some evidence that 3D assessment of the volume of the womb lining may be more specific than measuring a thickness alone. Sensitivity ranged from 63-100% whilst specificity was between 36-99%. It was not possible to pool these findings to provide an estimate of the accuracy of this test due to the very different cut-offs that were chosen in the studies (Evidence Level 2).

Q50 Is diffusion weighted MRI useful in differentiating benign from malignant lesions?
Several single centre studies have looked at the utility of diffusion weighted MRI to differentiate benign from malignant lesions. As with the other imaging modalities no consensus of the cut-off between abnormal and normal has been reached. Studies have determined their accuracy based on cut-offs based on the distribution of readings from scans at their institution leading to a potential for overestimation of sensitivity and specificity (Evidence level 3). As yet there has been no comparison with other imaging modalities.

Q51 Is transvaginal ultrasound acceptable in older women?
A HTA study found that the majority of women (94%) were glad that they had had investigations. Very few women (1%) described ultrasound as being ‘markedly unpleasant’ (Evidence level 3).

Q52 What is the predictive value of the different presenting features (e.g. abnormal vaginal bleeding) of endometrial cancer in a large primary care population?
A study of the 12,269 women presenting to their GP found that 9.6% of women with persistent postmenopausal bleeding will have womb cancer. 1% of postmenopausal women with vaginal discharge and 0.7% of postmenopausal women with blood in their urine will also have womb cancer (Evidence level 2).

Fertility sparing

Q53 Are premenopausal patients aware of the fertility sparing options available to them?

There are no studies which look at whether young women with womb cancer are aware and are seeking fertility sparing options. In non-gynaecological cancers, a retrospective survey found that whilst 61% of women were counselled about fertility sparing options, less than 4% of women took steps to preserve their fertility.

Q54 Are premenopausal patients being offered counselling about their fertility and fertility sparing options?

There are no studies which have examined the proportion of premenopausal women who were counselled about their fertility and where appropriate had fertility sparing options discussed.

Q55 Does imaging predict in those younger women who wish to preserve fertility whether hormonal or surgical treatment may be effective?

Between 40-80% of women with early stage disease offered progesterone therapy will respond. The ideal candidates for conservative management are thought to be women with well differentiated endometrioid cancers with no myoinvasion and no evidence of a concurrent ovarian tumour. Good quality histology is necessary to determine whether the first criteria is met. Imaging should be used to inform decisions about the degree of muscle wall invasion and whether ovarian masses are present. MRI has a sensitivity of between 80-100% for assessing muscle wall invasion and over 90% for diagnosing ovarian tumours. Thinning of the womb lining on ultrasound after a period of treatment with progesterones has been associated with a favourable response to treatment (Evidence level 4) Follow-up biopsies however remain the gold standard for determining response.

Genetics

Q56 Is there a genetic predisposition amongst sufferers of serous endometrial carcinoma?

Uterine serous cancer is currently not part of any recognised hereditary cancer syndrome. One study showed that 1 in 20 women with serous womb cancers will have inherited a germline mutation in BRCA1, CHK2 and TP53. A further study confirmed that women who carry the BRCA1 mutation were more likely to develop high grade serous cancer. They estimated that the increase in risk was approximately 2% over 10 years. There was no increase in risk of the more common endometrioid womb cancer (Evidence level 4).

The majority of women with serous uterine cancers will develop mutations in the cells of their uterus which will then go on to form high grade serous cancers. Studies of tumours from women with serous uterine cancers have found that mutations of TP53 (90.7%), PIK3CA (41.9%), FBXW7 (30.2%) and PPP2R1A (27.9%) are common.

Q57 Who should be screened for Lynch syndrome/Cowden syndrome?

Lynch Syndrome is the most common hereditary cancer syndrome affecting about 1 in 700 to 1 in 2000 people. Those women with this syndrome will have a 40-60% lifetime risk of womb cancer.

A number of countries have adopted testing for Lynch Syndrome in patients recently diagnosed with bowel cancer. No such policy has been implemented in the UK. A recent cost-effectiveness analysis by the National Institute of Health Research (HTA) suggests that testing for Lynch Syndrome for people diagnosed with bowel cancer under the age of 50 and possibly up to 70 may be cost-effective. No such analysis has been done in womb cancer. There are a few local studies to suggest that screening all women with womb cancer for Lynch Syndrome may be cost effective (Evidence level 3) but these are small.

Q58 What is the prevalence of Lynch syndrome amongst women with endometrial cancer?
There are few high quality studies to determine the exact prevalence. Prospective studies in different populations suggest that the prevalence may be between 2-9% of women with endometrial cancer (Evidence level 3).

Q59 What is the incidence of somatic LS gene mutation in womb cancer?
Grouping of womb cancers by the genetic patterns they display, suggest that up to a quarter of tumours display a pattern referred to as microsatellite instability. This is the same pattern of changes seen in the tumours of women with Lynch syndrome. It is unclear how many of these may be due to somatic mutations of the mismatch repair genes which are defective in Lynch. One study suggested that 50% of Lynch-like bowel and womb cancers can be explained by mutations of mismatch repair genes (Evidence level 4).

Q60 What is the relative risk of finding a cancer associated gene mutation in women with endometrial cancer who have a family history of cancer?
Several computer based risk calculators have been developed to work out the likelihood of finding a mutation in one of the genes associated with Lynch syndrome based on a woman's family history (Evidence level 3). These models were developed in specific populations and focus mainly on families with an inherited tendency for bowel cancer. The performance of these models in predicting Lynch syndrome in womb cancer patients needs to be further evaluated.

Q61 What is the psychological impact of being tested for and having being diagnosed with an endometrial cancer associated gene mutation e.g. Lynch syndrome/Cowden syndrome?
A systematic review of the consequences of genetic testing for cancer susceptibility found that both carriers and non-carriers showed decreased distress after testing. This effect was more marked in people found to be non-carriers. How individual felt prior to the test was the most predictive of subsequent distress. The studies all suggest that those undergoing predictive genetic testing do not experience adverse psychological consequences. (Evidence level 1)

Q62 Should we refer all young women with endometrial cancer for genetic screening even when there are other risk factors e.g obesity which may be more important in its development'?

There are no studies which directly answer this question. The development of cancer is multifactorial and as yet there are no models which can accurately integrate environmental factors and inherited factors to predict whether the influence of one of these factors is greater.

Q63 Is there a genomic association with response to treatment?
Studies of the tumour samples from patients are ongoing to determine if there is a genetic signature which can predict response to treatment (Evidence level 5). As yet none of these have been validated for clinical use.

Identifying recurrence

Q64 What is the predictive value of patient reported symptoms in determining likelihood of recurrence?
There are no published RCTs that have addressed this. One randomised control trial, ENDCAT, compared nurse-led follow up with standard hospital-based follow up and found no difference in time to detection of recurrence in the two groups, as most recurrences were symptomatic. This study has not been published yet. Another randomised control trial comparing self referral with routine follow up in womb cancer is ongoing. Published studies have been retrospective or prospective audits that in general suggest that most recurrences are symptomatic. (Evidence level 3)

Q65 What is the ideal length of clinical follow up following treatment for patients with endometrial cancer?
The Japanese Society of Medical Oncology has published follow up guidelines – 3 monthly for the first two years and 6 monthly thereafter. They do not reference these statements with any evidence. They say most recurrences occur in the first three years after treatment. There are no randomised control trials or prospective studies that have addressed this issue. Most retrospective audits suggest that recurrence is usually symptomatic and therefore routine follow up may not expedite detection of recurrence. (Evidence level 4)

Q66 Is telephone-based follow up effective in women treated for endometrial cancer?
One RCT has randomised women to receive standard hospital-based follow up or telephone follow up following treatment of their endometrial cancer. This trial has not yet reported. It is powered to detect non inferiority of telephone-based follow up for endometrial cancer in terms of effectiveness (clinical outcome, psychological morbidity, quality of life) but superiority in terms of satisfaction. It is not possible to rate the quality of this RCT before it is published. There are no other data that specifically address this issue.

Q67 What is the sensitivity/ specificity of pelvic examinations to detect recurrence?
There are no RCTs that have addressed this issue. Most published data relate to retrospective audits and suggest that the majority of recurrences are detected by symptoms and/or signs and that the utility of other routine follow up interventions (imaging, CA125) is not clear. (Evidence level 4)

Q68 How can we better engage primary care in the effective follow up of patients?
Suggestions that have been piloted and assessed are few. A 90 minute workshop to ease transition from specialist oncology services to primary care was well received in a small study in Canada. In California, primary care was just as good as specialist oncology care for follow up so long as a main care provider was identified and specialist oncology services were involved. Most follow up strategies currently in place involve hospital-based care but alternatives appear to be acceptable to patients. (Evidence level 5)

Q69 How useful is 5 year follow up post treatment?
There is no evidence for the 5 year follow up programme in womb cancer. Some retrospectives studies have found traditional 5 year follow up programmes to be inefficient/expensive because most recurrences are symptomatic. Others found that recurrences detected whilst still asymptomatic by pelvic exam, CA125, vault cytology or imaging conferred survival advantage over symptomatic recurrences. One retrospective study suggested routine follow up care was harmful because patients waited for their scheduled appointment to report new symptoms. (Evidence level 5)

Q70 Which group of health care professionals are the most apropriate to offer long term follow up to patients following treatment for endometrial cancer? e.g oncology/surgeons, specialtist nurses, GPs
Nurse led follow up appears to be an acceptable alternative to hospital based follow up for endometrial cancer surviviors (ENDCAT study, RCT not yet published). (Evidence level 5)

Q71 Is the routine use of imaging post treatment effective at detecting recurrence and improving outcomes?
In a small retrospective Korean study, PET CT detected recurrence in 15% of womb cancer survivors who did not show evidence of disease (by symptoms or examination). (Evidence level 5)

Q72 Is Ca125 monitoring effective to detect recurrence?
Most recurrence is detected by symptoms or examination. One retrospective review found 28% of recurrences by CT or CA125 that were not picked up by symptoms/examination. A retrospective Korean study showed that CA125 could detect asymptomatic recurrence but that 839 CA125 tests were required to detect one. Another retrospective, US-based study found that CA125 could detect recurrence in type 2 womb cancers. One retrospective study suggested that routine CA125 testing in follow up of type 2 womb cancers did not detect local or potentially salvageable recurrences. Another retrospective study suggested that routine CA125 testing could detect recurrence before it became symptomatic even in patients whose CA125 was not elevated pre-op. (Evidence level 5)

Q73 Are scheduled or patient triggered follow up appointments most appropriate in the follow up setting?
There is a multicenter RCT ongoing in Denmark to assess the value of scheduled follow up versus self-referral with symptoms. A retrospective Welsh study suggested routine follow up care was harmful because patients waited for their scheduled appointment to report new symptoms. (Evidence level 5)

Q74 Why do endometrial cancers recur?
Apparently low grade womb cancers that recurred had certain mutations (p53, KRAS or Lynch) in two retrospective studies. There is no evidence that the use of uterine manipulators during hysterectomy increases recurrence risk. Age and tumour characteristics predict recurrence. (Evidence level 5)

Q75 What is the most cost-effective strategy to identify cancer recurrence?
A retrospective study found that routine vaginal cytology was ineffective and expensive at detecting recurrence and benefited just 1% of patients. In another retrospective study, routine imaging detected most recurrences but was expensive, and routine CA125 testing was least expensive. There is no evidence for cost effectiveness of routine follow up in womb cancer. (Evidence level 4)

Q77 What is the ideal venue for follow up?
Two systematic reviews have not found evidence for primary care versus secondary care or nurse-led versus physician-led follow up – but these do not relate to endometrial cancer, in which there are no RCTs to assess this question. (Evidence level 4)

Q78 What novel therapies may be useful in women with high-risk endometrial cancer i.e. grade 3/uterine serous/clear cell?
There are reviews written about potential novel treatments but no evidence to demonstrate their efficacy in patients – these include metformin, GnRH antagonists, anti-angiogenesis treatments, mTOR inhibitors. (Evidence level 5)

Impact of cervical screening

Q79 How many endometrial cancers are detected by abnormal endometrial shed on smears?
This appears to be a very promising area of research but it is still in its early stages and not ready to be applied to clinical practice. A recent small study suggests that 100% of endometrial tumours (24/24) (and some ovarian cancers) can be detected on routine cervical smear through detection of tumour DNA using liquid based cytology. Previous studies show that atypical endometrial cells can be detected in routine cervical smear tests. Liquid based cytology has the potential to detect more endometrial cancers than conventional smear tests. Vault smears are somewhat less helpful in detecting endometrial cancer recurrence. Benign endometrial cells in a postmenopausal woman may also indicate womb cancer. (Evidence level 4)

NHS policy and commissioning

Q80 Is the amount of funding into womb cancer research proportional to the burden of disease?
Funding to mortality ratio is US is highest in cervical cancer (40:1) and lowest for uterine cancer (7:1). Breast cancer and prostate cancer are overfunded when disability-adjusted life years and mortality are used to predict funding in the US. Overfunding for breast cancer is 3.6 times higher than for prostate cancer. No

published data for UK spending on endometrial cancer-specific research. (Evidence level 5)

Q81 What will the impact of the increasing rate of womb cancer have on the provision of care provided by the NHS?
Key recommendations have been set out in UK policy documents to safeguard against deficiencies in funding related to changes in patterns of incidence.

Q82 Can earlier identification of womb cancer be achieved through easier access to definitive tests in the future?
This relates to cancer service provision and is not a question that can be answered by research. Access to diagnostic services is all about funding.

Q83 Is there a conception among sponsors of medical research that endometrial cancer usually presents in early stage and has good prognosis and hence we should be focusing on other, more sinister and aggressive types of cancer?
There is a discrepancy in the amount of research funding available for different cancers. Funding to mortality ratio is US is highest in cervical cancer (40:1) and lowest for uterine cancer (7:1). Breast cancer and prostate cancer are overfunded when disability-adjusted life years and mortality are used to predict funding in the US. Overfunding for breast cancer is 3.6 times higher than for prostate cancer. No published data for UK spending on endometrial cancer-specific research. The reasons for this are not known. (Evidence level 5)

Q84 Do women who see the same gynaecologist regularly get diagnosed with a) womb cancer, b) womb cancer recurrences earlier?
In a large retrospective US-based study, women with high risk womb cancer who were cared for by a gynaecological oncologist had survival advantage over those who were cared for gynaecologists or general surgeons. Extrapolation of data suggests that having a long term relationship with your GP increases the likelihood that women will be screened for medical conditions including cancers. (Evidence level 4)

Q85 How do we ensure funding bodies and the pharmaceutical industry prioritise endometrial cancer?
A paper was published in Australia ‘Towards a national cancer research plan’ in 2012 that calls for improved funding of poorly funded cancer types and more funding for screening, prevention and early detection. Data indicates that womb cancer is relatively underfunded when taking into account incidence, deaths from disease, years of life lost and all other metrics. Identifying the research priorities in womb cancer and lobbying for funding to address the questions may help. There are no studies that have addressed this issue.

Q86 Are patients with abnormal uterine bleeding who are referred to private hospitals diagnosed with womb cancer at an earlier stage than those who go via the GP gatekeeper to secondary care?
A US based study found womb cancer patients treated in the private health care sector had better performance status, less aggressive disease, shorted delays from diagnosis to treatment, more likely to have complete staging and laparoscopic

surgery but there was no evidence that any of these factors conferred survival advantage. A Finnish study found no evidence for better patient outcomes if private gynaecologists were used. There are no UK-based studies of this kind. (Evidence level 4)

Non-endometrioid cancers

Q87 What is the best management for carcinosarcoma?
A 2013 Cochrane meta-analysis of three RCTs found combination chemotherapy with ifosfamide and cisplatin to be associated with a lower risk of death than single agent ifosfamide in women with advanced or recurrent uterine carcinosarcoma. Abdominal irradiation did not improve survival. (Evidence level 1). Novel agents like T-DM1, await testing in appropriately controlled RCTs.

Q88 Are platinum and taxol based chemotherapy regimes effective in uterine papillary serous carcinomas?
Small retrospective studies indicate that adjuvant treatment with platinum and taxol based chemotherapy reduces recurrence and improves survival in stage 2+ UPSC. (Evidence level 4)

Q89 Should mixed Mullerian gynae cancer to be studied on its own, or does it belong under the overall womb cancer umbrella?
Current thinking is that MMMTs are metaplastic carcinomas derived from monoclonal origins rather than sarcomas. Treatments should be directed at carcinomatous element since behavior of these tumours is not dissimilar to UPSC and grade 3 endometrioid endometrial tumours.

Q90 Does serous cancer of the uterus share a common origin with other pelvic high grade serous cancers?
These tumours types are probably distinct entities. Little evidence for increased risk of UPSC in BRCA1/2 mutation carriers who have had risk reducing BSO. Distinct immunoprofile distinguishes ovarian (tubal) HG serous cancers (>90% are ER+/WT1+ and >70% are ER+/WT1+/p53+/p16+/IMP3+) from endometrial HG serous cancers (wide immunotypic diversity, only 15% ER+/WT1+). (Evidence level 4)

Q91 What are the predictors of relapse in endometrial stromal sarcoma?
This is a rare tumour. Oophorectomy at the time of hysterectomy reduces relapse according to a small retrospective study. These tumours are hormonally responsive, so progestin therapy may be appropriate. (Evidence level 4)

Q92 Do leioyosarcomas arise de novo or do they originate in leiomyomas?
These are rare malignant tumours of the myometrium. They are believed to arise de novo rather than from a pre-existing fibroid due to characteristics of the tumour and its surrounding tissues at the time of hysterectomy. (Evidence level 4)

Obesity and Physical Activity

Q93 What is the risk of death in morbidly obese patients undergoing hysterectomy for endometrial cancer?
In a prospective study of 120,000 US people undergoing major surgery for non bariatric reasons, the odds ratio of dying for morbidly obese people (men and women) was 1.3 compared to normal weight people. There are no womb cancer-specific data. Studies are unanimous in reporting higher peri-operative complication and post-operative morbidity rates in morbidly obese compared to normal weight women. (Evidence level 4)

Q94 Can hysterectomy for endometrial cancer be safely delayed to accommodate bariatric surgery/ hormone treatment?
One small uncontrolled US-based study found no adverse effect of delaying surgery to allow weight loss whilst on progesterone treatment for grade 1/2 stage 1a EEC with no myometrial invasion (n=24). One case report found that a young woman (age 24) whose surgery was delayed for fertility sparing reasons whilst she was treated with progesterone treatment presented 6 years later with stage IV grade 1 EEC suggesting that delaying surgery without strict follow up procedures may be dangerous. Another found 6 cases of untreated endometrial cancer, who lived for 5 months to 12 years without any treatment, before dying from their womb cancer (Evidence level 4)

Q95 Can surgery be safely omitted if replaced by bariatric surgery/ hormone therapy?
The case has been made for hormone therapy for some women with atypical hyperplasia or low grade stage 1a endometrial tumours (approx. 60% response rate). There is a systematic review of RCTs (Level 1). There are only case reports to show that bariatric surgery can be used with hormone therapy to treat hyperplasia/endometrial cancer (Evidence level 5).

Q96 Does weight loss improve outcomes following treatment for endometrial cancer?
One study found that women who lost weight after treatment for endometrial cancer actually had the worst prognosis, casting doubt on the notion that weight loss in obese endometrial cancer survivors will improve outcomes. No other RCTs have assessed the impact of weight loss on survival in women previously treated for endometrial cancer. But lots of RCTs are completed or in progress that show that weight loss/lifestyle interventions can help obese endometrial cancer survivors lose weight. (Evidence level 4)

Q97 Does time between diagnosis / treatment affect prognosis?
A large retrospective study (n=9417) in Canada found that delays between diagnosis and hysterectomy of >6 weeks and particularly >12 weeks was associated with significantly poorer 10 year survival than surgery between 2-6 weeks following diagnosis (Evidence level 4). Another smaller study found no such association (n=435).

Q98 Are cancers associated with obesity different in their pathogenesis?
The epidemiological profiles of type I and type II womb cancers suggest that this is so. Type I tumours develop on a background of atypical hyperplasia, for which unopposed oestrogen, insulin resistance, PCOS, reproductive factors and obesity

are key risk factors. Type II tumours arise in atrophic endometrium and are believed to be driven by mutations in oncogenic signaling pathways. These tumours are less associated with the risk factors described above and tend to be more aggressive tumours with worse prognosis. (Evidence level 4)

Q99 Can diagnostic imaging predict in older/obese women which patients may benefit from radiotherapy over surgical treatment as a primary treatment?
This has not been answered by research. In general hysterectomy is the preferred treatment for womb cancer but when risks of surgery are high, this must be weighed against the risks of inadequate treatment (and subsequently more difficult surgery) if radiotherapy alone is used. Radiotherapy is also more challenging in obese women. (Evidence level 5)

Q100 What is the optimal timing and nature of lifestyle interventions to promote healthier lifestyles in obese women diagnosed with endometrial cancer?
There are several RCTs ongoing in this area and one or two have been published that show obese endometrial cancer survivors can lose weight using various technologies and weight loss programmes. There is no meta-analysis or systematic review of these studies. Furthermore, the RCTs are small RCTs with short follow up durations and do not demonstrate an impact of these interventions on recurrence or survivorship. (Evidence level 2)

Pain issues

Q101 Is analgesia needed routinely for outpatient hysteroscopy? If so what is the best method?
Early studies failed to find conclusive evidence for routine analgesia administered during outpatient hysteroscopy in terms of pain scores and the need to abandon the procedure due to pain. A Cochrane review (2010) later found that the use of analgesia significantly reduced pain score during and after outpatient hysteroscopy and significantly reduced the number of procedures abandoned due to pain. Routine practice varies considerably throughout the UK, with one-quarter of gynaecology departments offering no analgesia routinely for outpatient hysteroscopy. Subsequent studies have variously shown that vaginal misoprostol given 4-6 hours before procedure significantly decreases or does not increase pain scores during outpatient hysteroscopy. Thinner, flexible hysteroscopes reduce pain associated with the procedure. The vaginoscopic procedure is associated with less pain. Some centres are using conscious sedation with good effect to perform operative outpatient hysteroscopy. A 2010 conference presentation that analysed the results of 7 systematic reviews concluded that best practice to reduce pain during hysteroscopy were the use of injectable (paracervical or intracervical) anaesthetics and a vaginoscopic approach (Evidence level 1 – needs updating).

Q102 What is the incidence of musculoskeletal problems after hysterectomy and what methods are clinically and cost effective for treatment?
No RCTs have specifically examined this. Risks of musculoskeletal pain after hysterectomy would appear to be reduced by laparoscopic approach.

Personalised and targeted treatment

Q103 Do vitamin levels predict response to treatment?

There are as yet no studies which have investigated this.

Q104 How can we individualise treatments for patients with endometrial cancer?

Molecular studies from TCGA and recent publications show that common molecular alterations in endometrial tumours define subgroups of patients with good and poor prognosis and offer hope for individualization of treatment. These so-called prognostic biomarkers are not used currently to define optimal treatment strategies for individual patients or to direct cytotoxic drug therapy. RCTs that direct treatment based on prognostic or predictive biomarkers in endometrial cancer are urgently needed. (Evidence level 5)

Q105 Is immunotherapy potentially of use in endometrial cancer?

There is in vitro evidence for an immunotherapy-based treatment for high grade serous uterine cancer against human trophoblast cell surface marker Trop-2, which is highly expressed in these tumours, using hRS7, a monoclonal antibody directed against it. Laboratory studies suggest that an immunotherapy-based approach using HLA A2-restricted peptides E75 and E39 may be able to generate anti-tumoural immunity in endometrial cancer patients. No clinical trials have yet been conducted in this area (Evidence level 4)

Q106 Are stem cell treatments potentially of use in endometrial cancer?

Endometrial cancer stem cells have been found in laboratory studies involving endometrial cancer cell lines and endometrial cancer patients. No trials have harnassed endometrial cancer stem cell technology for treatment yet.

Q107 Is incidence and pathogenesis of endometrial cancer affected by ethnicity?

There certainly appears to be variation in womb cancer rates based on ethnicity. In a large British study of 38984 women with endometrial cancer published in 2014, lowest rates were seen in women of Bangladeshi origin, next highest rates in white British women, followed by Indian and Pakistani women, and highest rates in Black African and Black Caribbean women. Studies in the US show that mortality from womb cancer was two-fold higher in Black American women than White American women in one study. Poorer outcomes for Black women may be due to later diagnosis, treatment disparities, comorbid conditions and/or genetic differences in tumours. (Evidence level 3).

Q108 Can we predict the patients who would benefit from adjuvant treatment?

Although there are many studies looking at the benefits of chemotherapy/radiotherapy following surgery in different groups of patients, no personalised tests to predict benefit are available at present. A Cochrane review is in progress to assess the role of adjuvant radiotherapy in stage 2 endometrial cancer. A Cochrane review (2013) found that uterine carcinosarcoma (advanced or recurrent disease) responded to combination chemotherapy with ifosfamide and paclitaxel (Evidence level 1). The same review found no evidence for abdominal radiation therapy. A large trial to investigate the benefit of chemotherapy in post-surgical high

risk endometrial cancer patients has completed recruitment and will report in 2016 (PORTEC3). A 2014 Cochrane review updated the 2011 review and found moderate quality evidence to support adjuvant chemotherapy in post-surgical stage 3/4 endometrial cancer patients (25% increase in survival time). An (updated) 2015 Cochrane review found that adjuvant radiotherapy following hysterectomy for endometrial cancer reduces locoregional recurrence but did not impact on survival from endometrial cancer (Evidence level 1). A 2011 Cochrane review failed to establish a role for adjuvant progestogen therapy in the primary treatment of endometrial cancer. The use of targeted molecular therapies have not been reliably tested in endometrial cancer.

Q109 How can we improve long term outcomes for women with locally advanced endometrial cancer, stage III disease?

A Cochrane review (2013) found that uterine carcinosarcoma (advanced or recurrent disease) responded to combination chemotherapy with ifosfamide and paclitaxel (Evidence level 1). The same review found no evidence for abdominal radiation therapy. A large trial to investigate the benefit of chemotherapy in post-surgical high risk endometrial cancer patients has completed recruitment and will report in 2016 (PORTEC3). A 2014 Cochrane review updated the 2011 review and found moderate quality evidence to support adjuvant chemotherapy in post-surgical stage 3/4 endometrial cancer patients (25% increase in survival time). An (updated) 2015 Cochrane review found that adjuvant radiotherapy following hysterectomy for endometrial cancer reduces locoregional recurrence but did not impact on survival from endometrial cancer (Evidence level 1).

Q110 Does being progesterone receptor positive predict women who would respond better to progesterone based treatments?

Stromal expression of progesterone receptor appears to be important for endometrial tumour response to hormonal therapies from in vitro and work in mouse models. This has also been shown in several trials in humans which were collated in a 2007 systematic review of RCTs. (Evidence level 1)

Q111 Is there any value for anti-angiogenic drugs in endometrial cancer?

Bevacizumab plus concurrent radiation therapy provided excellent local control and survival for women with recurrent endometrial cancer, according to a small, uncontrolled clinical trial. (Evidence level 4)

Q112 What can we learn from those women with advanced cancer who do well to help improve treatment for all women with advanced cancer?

Lessons can be learnt in many contexts e.g. from patient to patient in the clinic and from trial to trial in the context of research. These should be applied in an individualised way as no one patient is alike. In general however, further research is needed to help define guidelines for the management of advanced endometrial cancer to ensure that decisions made about each woman's care are based on the best evidence.

Q113 What are the most important druggable molecular aberrations in endometrial cancer?

There are number of laboratory based studies looking into the genetic alterations which are commonly found in endometrial cancer. Some of the more promising such

as p53, PTEN, PI3K-AKT-mTOR signaling, DNA repair pathways and BRCA2 are also found in many other cancers as well. Endometrial cancers also show defects in Wnt signaling and KRAS. Further research is required to investigate how best to exploit these defects with new cancer therapies.

Q114 What percentage of endometrial cancer harbours defective homologous recombination and what is the implication of this for treatment prediction?
Cancers occur as a result of multiple genetic mutations which allow cells to evade the normal fail safe mechanisms which prevent them from growing out of control and accumulating mutations. One of the mechanisms which is commonly defective is a mechanism that repairs gene mutations known as homologous recombination. Homologous recombination deficiency is conferred by BRCA1/2 mutations. A recent conference abstract found 16% of 499 endometrioid womb cancers had BRCA1 and/or BRCA2 mutations. Laboratory studies suggest Olaparib (a PARP inhibitor, against which tumours with homologous recombination deficiency are particularly sensitive) may be effective against certain types of womb cancer. Ongoing studies are looking at whether certain markers can detect women with tumours with DNA repair deficiency and whether this predict poor prognosis in endometrial cancer. (Evidence level 4)

Q115 Can we predict the patients who would benefit from lymphadenectomy?
This is a very contentious issue. There are widespread differences in practice in the UK and across the world with respect to pelvic and para-aortic lymphadenectomy in endometrial cancer patients. A 2010 Cochrane review of two large RCTS found no survival benefit for lymphadenectomy in apparent Stage 1 disease. A large multicenter international lymphadenectomy trial (STATEC) is due to start soon to investigate whether lymphadenectomy improves survival in women with apparent stage 1 high risk endometrial cancer. (Evidence level 1)

Q116 Can diffusion weighted imaging be used to determine tumour response to treatment?
There have been a number of studies which have looked at whether modern MRI imaging techniques are better for diagnosing womb cancers and whether they have invaded into the muscle layer (myometrium). (Evidence level 1). No documented studies have looked at the role of diffusion weighted MR imaging to determine tumour response to treatment.

Prevention of primary disease

Q117 Does metformin prevent endometrial cancer in non diabetic patients at increased risk of developing the disease?
There is very little data regarding whether metformin may be useful to prevent womb cancer in high risk women. Long term follow up studies looking at cancer risk factors suggest that women using metformin have lower rates of womb cancer and better survival. However, these types of studies should be interpreted with caution as the associations seen here could have arisen for many reasons and do not necessarily mean that metformin was directly responsible for the difference in cancer rates and survival. There have been a few small studies in women with risk factors for womb cancers such as polycystic ovary syndrome (PCOS) and endometrial hyperplasia

but there currently is not enough evidence to recommend use of metformin to prevent womb cancer (Evidence level 4).

Q118 What is the incidence of endometrial cancer developing in benign polyps and do they need removal?
The prevalence of atypical hyperplasia or invasive cancer in endometrial polyps is around 5% (Evidence level 1). Malignancy is more common in postmenopausal women with symptoms. Removing polyps in premenopausal women improves fertility. Asymptomatic polyps, especially in premenopausal women do not need to be removed. Removal of polyps should be done during hysteroscopy where possible and if accompanied by resection of the endometrium, is associated with less recurrence (Evidence level 1). Prophylactic mirena intrauterine system prevents tamoxifen-associated endometrial polyps.

Q119 Should we recommend the Mirena intrauterine system as prophylaxis to high risk patients (obese and insulin resistant)?
There is evidence for a 50% reduction in endometrial cancer risk in women using the Mirena intrauterine system. There is no evidence for the Mirena in women who are at risk by virtue of insulin resistance or obesity. (Evidence level 2)

Q120 Which women would get the most benefit from a risk reduction strategy?
High risk women include those with Lynch syndrome and/or a strong family history of womb cancer, obese women with type 2 diabetes, PCOS or metabolic syndrome with prolonged lifetime exposure to oestrogen or relative lack of progesterone. There is evidence for endometrial protection from weight loss (Evidence level 2), exercise (Evidence level 4), the combined oral contraceptive pill or mirena coil (Evidence level 1) and hysterectomy (Evidence level1).

Q121 In uterine serous cancers, what is the earliest pre-invasive endometrial lesion that can be recognised histologically?
Endometrial glandular dysplasia is seen preceding the development of uterine serous carcinomas and clear cell carcinomas (Evidence level 3).

Q122 How can we predict which lesions will evolve into invasive cancer and which will resolve spontaneously?
Not enough is known about the natural history of early precancerous cells and early cancer to be able to answer this question. At the present time, conventional thinking is to treat all premalignant and malignant disease of the endometrium whenever possible (Evidence level 5).

Q123 Is there a role for progesterone contraceptives in nulliparous women once they get to their 40's to prevent endometrial cancer?
A large case control study found that risk of endometrial cancer was reduced for women taking the combined oral contraceptive pill (COCP) in a duration-dependent manner (COCP use for 4, 8 and 12 years, was associated with 56%, 67% and 72% reduction in cancer risk, respectively). There is no specific evidence to recommend COCP use after the age of 40; indeed, this is associated with higher risks of deep vein thrombosis, heart attacks, stroke and breast cancer. There is also a reduction in endometrial cancer risk in Depo-Provera (Evidence level 2) and Mirena coil users (Evidence level 1).

Q124 Is there a reduction in life-time risk of endometrial cancer in women who use the Mirena for abnormal bleeding?
The Mirena may offer similar protection against endometrial cancer as the combined oral contraceptive pill and Depo-Provera. A systematic review found that the Mirena offers endometrial protection in women taking oestrogen-only hormone replacement or tamoxifen treatment. In a prospective Finnish study, the risk of endometrial cancer in women who used the Mirena coil for up to 5 years was half and for women using it for up to 10 years, a quarter of that seen in non users. The risks of ovarian, pancreatic and lung cancer were also lower, but the risk of breast cancer slightly increased (by one fifth). Several large RCTs have shown that the Mirena causes regression of endometrial hyperplasia. (Evidence level 1)

Q125 Are progestin-impregnated intrauterine devices as effective at preventing womb cancer as oral contraceptives?
There is a reduction of endometrial cancer risk associated with oral contraceptive use, which is higher with longer duration of use according to a 2015 systematic review with meta analysis published in the Lancet. These data have been around much longer than the data for Mirena coil protection against endometrial cancer but the magnitude of effect does appear to be similar. The two treatments are often used in different settings and are therefore not directly comparable with each other. (Evidence level 1)

Q126 Are the risks of breast cancer in women using progestin intrauterine devices long term for prophylaxis less than that associated with oral contraceptive use?
COCP use is associated with a modest increase in premenopausal breast cancer risk (of the order of 10-15%). One prospective study in Finland found an increased risk of breast cancer in mirena coil users but this finding has not be corroborated by other studies (Evidence level 3).

Q127 Can we identify a population of women at sufficiently high risk of endometrial cancer who might benefit from a prevention strategy?
Women at high risk of womb cancer include women with hyperplasia, particularly complex atypical hyperplasia, women with Lynch syndrome, women with a strong family history of womb cancer, morbidly obese women, elderly women and tamoxifen users. Other risk factors include type 2 diabetes, PCOS and metabolic syndrome. However, there have been no studies that have addressed this issue specifically.

Q128 Does endometrial ablation prevent womb cancer?
One study described two patients who developed endometrial cancer some months or years following endometrial ablation. They conclude that endometrial ablation is not recommended for women at risk of endometrial cancer because ablation can hinder early diagnosis by causing scarring which closes the cervix (cervical stenosis) and preventing blood loss into the vagina. Another small, uncontrolled study prospectively treated women prior to tamoxifen treatment with microwave endometrial ablation and found no subsequent abnormal bleeding or endometrial changes on tamoxifen. Some studies have ablated/resected tamoxifen-induced endometrial polyps successfully and without reporting subsequent recurrent abnormalities (Evidence level 3).

Q129 How should postmenopausal women found to have proliferative endometrium on biopsy be managed?
We do not know whether a proliferative postmenopausal endometrium is a risk factor for endometrial cancer because there are no studies which have followed such women up over a period long enough to see whether cancers occur. In general, simple hyperplasia of the endometrium ('disordered proliferation') is not considered to be a risk factor for endometrial cancer, whilst complex atypical hyperplasia is. Currently, simple hyperplasia would be treated with progestagens, if symptomatic. Atypical hyperplasia is treated by hysterectomy or progesterone treatment if hysterectomy is contraindicated/not desired. (Evidence level 4)

Q130 How effective are conservative treatments for atypical hyperplasia?
A number of medical treatments have been investigated as alternatives to hysterectomy in women diagnosed with the precancerous condition, atypical hyperplasia. In 2013, a Cochrane review did not find any RCTs of sufficient quality to recommend Mirena over oral progesterone treatment for atypical endometrial hyperplasia. Other conservative treatments such as letrozole, GnRH analogues and metformin have not been robustlyexamined.

Q131 Is oral or intrauterine progesterone more effective for prevention of endometrial cancer in those with hyperplasia with and without atypia?
A recent systematic review (2015) found that intrauterine progesterone was more effective than oral progesterone at inducing regression of non-atypical endometrial hyperplasia. A second systematic review found that this was also the case in atypical endometrial hyperplasia; however the quality of the studies included was low. (Evidence level 1)

Q132 What monitoring is best in women with atypical hyperplasia treated with Mirena?
Recurrence appears to be common after conservative management of atypical endometrial hyperplasia. Regular monitoring by transvaginal ultrasound scan, endometrial biopsy and/or an assessment of bleeding symptoms is appropriate; although, there is no evidence base to recommend one particular surveillance strategy over another. (Evidence level 5)

Q133 Does the Mirena coil reduce the risk of endometrial cancer in women with Lynch syndrome?
This is unknown. A clinical trial investigating this question was discontinued due to poor recruitment (POET). (no evidence)

Q134 What are the risks and benefits of prophylactic hysterectomy in obese women after they have finished their family?
This has not been answered by research. Those women most at risk of endometrial cancer are those who are morbidly obese (Body mass index >40) and diabetic. These women are also at higher risk of surgical and anaesthetic complications. Prophylactic surgery to reduce endometrial cancer risk has only been shown to be useful in women with Lynch syndrome. (Evidence level 5)

Q135 What interventions have been shown to be effective at preventing endometrial cancer? (e.g. intrauterine progestins, oral progestins, weight loss, metformin, vitamin D, hysterectomy, endometrial ablation, endometrial curettage, physical activity, COCP)

Hysterectomy protects against endometrial cancer (Evidence level 1). There is convincing evidence from RCTs and/or systematic reviews that the risk of developing endometrial cancer in women taking the COCP and using the mirena coil; women who drink coffee; women who exercise in childhood, mid adulthood and late adulthood; and those who breastfeed their babies is lower (Evidence level 1). There is retrospective data to suggest a protective impact of massive weight loss in morbidly obese women undergoing bariatric surgery (Level 4). There is retrospective data to suggest a reduced incidence of endometrial cancer in diabetic women taking metformin (Evidence level 4).

Q136 Should women with HNPCC syndrome be offered prophylactic hysterectomy to prevent endometrial cancer?

Hysterectomy is protective against endometrial cancer. Women with hereditary non-polyposis colorectal cancer (HNPCC)/Lynch syndrome have an increased risk of endometrial cancer. The risk of endometrial cancer during the lifetime of a women with HNPCC/Lynch syndrome is reported as being between 40-60. This forms the basis of exploring risk-reducing options.

One study has explored prophylactic hysterectomy in women with HNPCC. This study found that none of the women who had a prophylactic hysterectomy went on to get endometrial cancer (Evidence Level 4). The authors concluded that women with HNPCC should be offered a prophylactic hysterectomy after the age of 35 years or once childbearing has been completed.

Q137 Should women with Lynch Syndrome/Cowden's syndrome be offered risk reducing hysterectomy and bilateral salpingoophrectomy to reduce their risk or endometrial surveillance to reduce their risk of endometrial or ovarian cancer related mortality?

As reported in Q136, hysterectomy is recommended in women with Lynch syndrome after the age of 35 or once childbearing is completed to prevent endometrial cancer. Removing both fallopian tubes and ovaries at this operation (bilateral salpingoophrectomy), has been shown to reduce the risk of ovarian cancer (Evidence Level 4).

Current evidence does not support a role for regular ultrasound and/or biopsy of the endometrium (i.e. endometrial surveillance) in women with Lynch syndrome to prevent endometrial cancer (Level 3). In some studies no cancers were detected by this method. There was no clear improvement in survival. The addition of endometrial sampling through a biopsy taken blindly or at the time of hysteroscopy does improve endometrial cancer detection (Level 3). If surveillance is used, it is generally thought that this should be done annually but it is unclear as at what age this should start (Evidence Level 3).

Prevention of recurrence

Q138 Is there a role for aspirin in prevention/reducing progression?
There is conflicting data about the role of aspirin in the prevention of endometrial cancer. A systematic review and meta-analysis incorporating eight studies showed a reduced risk of developing endometrial cancer in ever users compared with never users of aspirin (OR 0.87, 0.79-0.96). In particular, the authors found that obese women benefited from exposure to aspirin, with an 18% reduction in incidence of endometrial cancer, an effect which was not seen in non-obese women (Evidence level 2). In contrast, a large case-control study of >70,000 Danish women found a similar risk of endometrial cancer in users and non-users of aspirin, but did note that it appeared to be protective in nulliparous women (OR 0.82, 95% CI 0.70-0.95) (Evidence level 3). Any interaction between obesity and aspirin use was not investigated in this study and low dose aspirin only was considered, as exposure relied on prescriptions for the drug rather than self-reporting of use as in other studies. The dose of aspirin appears to be important, with a stronger, albeit not significant, reduction in endometrial cancer risk with regular compared with low dose aspirin (Evidence level 2). Aspirin does not appear to have an effect on overall or progression free survival in diabetic users with endometrial cancer (Evidence level 2).

Q139 Can the risk of endometrial cancer recurrence be reduced by changing lifestyle factors?
There are no studies of the effect of lifestyle changes on the risk of endometrial cancer recurrence. A survey of patients previously diagnosed with endometrial cancer indicated that they would be interested in taking part in a weight loss programme. As most women with endometrial cancer are likely to die of cardiovascular disease, improved weight, hypertension and diabetic control would be anticipated to result in improved overall survival of endometrial cancer sufferers, even if it did not impact on disease recurrence (Evidence level 5).

Q140 Does adjuvant metformin as maintenance therapy reduce the risk of disease recurrence in patients at high risk for relapse?
There are no studies investigating the use of metformin as an adjuvant treatment with the aim of preventing disease recurrence. All of the available data is derived from retrospective cohort studies of patients taking metformin for the treatment of diabetes. Metformin use is associated with an improvement in overall and disease free survival, but there are differing results as to whether it has any effect on disease recurrence (Evidence level 2). In studies that have controlled for age, grade, stage, histology and adjuvant treatment, metformin use was associated with a decreased risk of tumour recurrence in high grade tumours but not endometrioid type, where any benefit is likely to arise from improvement in general health (Evidence level 2). Prospective, randomised studies of metformin in the non-diabetic population are warranted.

Q141 Can alternative treatments improve the efficacy of adjuvant chemotherapy?
There have been no studies of alternative treatments to improve the efficacy of adjuvant chemotherapy in endometrial cancer.

Q142 Can lifestyle changes and weight reduction reduce risk of recurrence?

There are no studies into the effect of lifestyle changes and weight reduction on risk of recurrence. A cohort study following 705 women with endometrial cancer found no benefit of weight loss on recurrence free survival, but did not specifically look at recurrence (Evidence level 2).

Professional awareness

Q143 How can the experience of diagnosis, examinations, etc. be improved with regards to preserving patient dignity, modesty and comfort?
There is little available information on how to promote patient dignity, modesty and comfort during the diagnosis of endometrial cancer. Most studies evaluating patient experience have focussed on post-treatment symptoms, particularly sexual function. Focus groups and in-depth interviews with patients with endometrial cancer in Andalusia in Spain identified humane treatment, continuity of care and attention to psychosexual aspects as being of particular importance (Evidence Level 3).

Q144 What percentage of GPs/nurses recognise that obesity is a risk factor for endometrial cancer?
Over 95% of primary care physicians surveyed in a single American state were aware that obesity increased the risk of developing endometrial cancer but only 36.8% counselled patients about this. A significantly greater proportion of obstetricians and gynaecologists reported discussing the risks of obesity on endometrial cancer risk with their patient in the same survey (Evidence level 3). There are no published studies documenting awareness of the association between obesity and endometrial cancer risk in other countries or specifically in the nursing profession.

Q145 What is the most effective educational intervention to improve primary healthcare professionals' ability to detect endometrial cancer?
There are no published studies evaluating the most effective educational intervention to improve primary healthcare professionals' ability to detect endometrial cancer. A retrospective audit performed in Dunedin in New Zealand identified delays in referral from primary into secondary care services, particularly in rural areas, which they postulated may be related to socioeconomic factors. They also noted longer referral times in younger patients and those who repeatedly failed to attend appointments; assumed to be related to a low suspicion of cancer in the doctor and patient, respectively (Evidence level 5). A cancer risk assessment tool has been devised to help assess cancer risk in primary care, but this has not been validated for endometrial cancer.

Prognosis (Predicting outcome)

Q146 Are any serum markers effective for informing prognosis in endometrial cancer?
Retrospective studies have associated high serum levels of Ca125, calprotectin and growth differentiation factor (GDF) 15 with aggressive phenotype, but have yet to determine whether they have any clinical value in stratifying treatment decisions and determining response to therapy (Evidence level 4). Human epididymis protein 4 (HE4) is the most promising serum prognostic marker, with levels correlating with

known pathological prognostic variables. It is also an independent prognostic factor for overall survival with a HR of 2.4-2.78 (Evidence level 2). Published studies, however, have used differing methodologies to determine levels preventing assessment of the specificity and sensitivity of the test and the provision of optimal cut-off values.

Q147 What molecular or other markers are available/under evaluation to predict adverse outcome in women with low stage low grade endometrial carcinoma?

Multiple prognostic markers have been or are currently being evaluated in endometrial cancer, including serum and tumour proteins and cervical cytology. The most promising are hormone receptor status, Ca125 and HE4. A single prospective, multicentre study showed that oestrogen and progesterone receptor negative tumours independently predicted lymph node metastasis (OR 2.0) and poor survival (HR 2.3) (Evidence level 3). Ca125 and HE4 have been evaluated both singularly and in combination and have both been shown to predict myometrial invasion and lymph node metastases, with HE4 demonstrating superior sensitivity, specificity and a higher negative predictive value (Evidence level 4). There are no prospective studies using HE4 levels to guide decisions about the extent of surgery.

Q148 Does pre-operative MRI predict outcomes in endometrial cancer?

No studies have specifically evaluated whether pre-operative MRI predicts outcome in endometrial cancer, although it is routinely performed in many countries. Several cohort studies and a systematic review and meta-analysis have shown that MRI is able to accurately assess the depth of myometrial invasion and presence of lymph node metastases, with sensitivity up to 86% and specificity up to 82% (Evidence level 2). This information is useful in assigning a provisional stage and, therefore, influences surgical management.

Q149 What predictive biomarkers can be used to assess risk of relapse?

Several biomarkers have been evaluated and found to predict endometrial cancer relapse, including circulating steroid levels, particularly estrone sulphate, heparin-binding EGF-like growth factor, Ca125, PARP and ANXA2 (Evidence level 3-4). HE4 has also been evaluated in this setting and shown to be an independent predictor of recurrence free survival (Evidence level 3). Larger prospective studies are required to validate these potential biomarkers.

Q150 Is colonisation of the cervical epithelium without cervical stromal invasion (i.e. old stage 2a) by endometrial cancer of prognostic significance?

There is no published data evaluating whether endometrial cancer colonisation of the cervical stroma without invasion is of prognostic significance.

Q151 Is neuroendocrine differentiation in endometrial cancer of prognostic significance?

There is contradictory evidence about the prognostic significance of neuroendocrine differentiation in endometrial cancer, with one paper identifying a significantly poorer outcome for patients with neuroendocrine differentiation and another finding no difference between groups (Evidence level 3). Both studies included only 40-50 patients, of which approximately half had neuroendocrine differentiation as determined by positive staining for synaptophysin and chromogranin by

immunohistochemistry. Larger, prospective studies are required to address this question.

Q152 Is transvaginal ultrasound useful in determining if there is cervical extension, parametrial extension or lymphadenopathy?
Transvaginal ultrasound is of some value in assessing the stage of endometrial cancer. When compared to final histopathological findings, it had a sensitivity, specificity and negative predictive value of 19-100%, 83-100% and 80-100% for determining whether cervical invasion has occurred (Evidence level 2-3). There is no published data evaluating transvaginal ultrasound in the assessment of parametrial spread or lymph node metastases. Transvaginal ultrasound is cheap and easily available, but is highly operator dependent. MRI has greater sensitivity and sensitivity and is also able to assess nodal status (Evidence level 2-3).

Q153 Is contrast enhanced ultrasound useful to diagnose myometrial invasion?
Combined 2D and 3D contrast enhanced ultrasound is able to correctly assess the depth of myometrial invasion with a sensitivity of 75-85%, specificity 77.8-95% and accuracy of 68-82.8%, when compared with the gold standard, histopathology. (Evidence level 2). No studies have evaluated the accuracy of contrast enhanced ultrasound in comparison with MRI or clinical assessment.

Q154 Is multidetector CT useful for staging EC?
A single centre study of 21 patients was conducted to assess the accuracy of multidetector CT in staging endometrial cancer. They found that this radiological investigation was able to correctly diagnose myometrial and cervical invasion with sensitivity, specificity and accuracy of 100%, 80% and 95% and 78%, 83% and 81%, respectively (Evidence level 2). Larger studies, allowing direct comparison with MRI scans, are required to fully address this question.

Psychological aspects

Q155 What are the support and information needs of patients when endometrial cancer is suspected and referral instigated?
Family support is particularly important to women with gynaecological cancers and being able to talk about the problem is beneficial. Women have highlighted a need for information about workshops, support meetings and alternative therapies to help them through their treatment (Evidence level 4). Patients report receiving inadequate information about their diagnosis and the practicalities of the treatment they are likely to need. A sense of loss of control, due to being in an unfamiliar environment, and subsequent vulnerability were also frequently identified (Evidence level 4). The specific needs of patients prior to confirmation of a diagnosis of endometrial cancer have not been addressed to date.

Q156 What measures can reduce the psychological distress of patients faced with losing their fertility as a result of treatment for endometrial cancer?
There are no studies investigating means of reducing psychological distress in patients faced with losing their fertility as a result of treatment for endometrial cancer.

Public awareness

Q157 Is a NHS funded awareness campaign a cost-effective measure of raising public awareness of womb cancer?
There are no published studies addressing this question. Mass media campaigns have evoked change in behaviour in other health spheres, but there has been no research into raising public awareness of endometrial cancer.

Q158 Is there a stereotypic image of a woman with endometrial cancer?
There are no studies of the stereotypic image of a woman with endometrial cancer. Obesity has the strongest link with endometrial cancer of any cancer type, however, this cannot be the sole explanation, as not all obese women will develop endometrial cancer and the disease also occurs in normal weight individuals (Evidence level 2).

Q159 What is the level of public awareness of endometrial cancer?
There have been no UK studies of public awareness of endometrial cancer. An observational study in Australia found 96% of women attending gynaecology clinics in two rural areas had no awareness of endometrial cancer and almost half were unable to identify common risk factors for the disease (obesity, diabetes and hypertension) (Evidence level 3). In a similar American study, 58% of respondents were unaware of the link between obesity and endometrial cancer (Evidence level 1).

Q160 What are the most effective methods of raising public awareness of endometrial cancer?
There are no studies into raising public awareness of endometrial cancer.

Q161 What interventions are effective at reducing the psychological distress associated with waiting for a diagnosis?
There are no studies of interventions to reduce psychological morbidity associated with waiting for a diagnosis of endometrial cancer.

Q162 Do women ignore erratic bleeding confusing it with the menopause?
There are no studies assessing women's perception of erratic bleeding and its relationship to the menopause and endometrial cancer risk.

Q163 Are women aware that postmenopausal bleeding should be investigated?
There are no studies of awareness of postmenopausal bleeding and the need for investigation. The small numbers of published observational studies on women's preferences in the evaluation of postmenopausal bleeding have been conducted in gynaecological outpatient clinics after women have already been referred.

Q164 What is being done to raise awareness of womb cancer?
There is no published information on raising awareness of endometrial cancer.

Q165 What can be done to get women to present earlier for diagnosis?
There are no studies comparing different techniques to encourage women to present with symptoms earlier.

Q166 How can we raise awareness in the population with regards to weight and the risk of endometrial cancer?
There are no studies of interventions to raise public awareness of the link between weight and risk of endometrial cancer.

Q167 What are the barriers to presentation of women with post-menopausal bleeding?
Lack of knowledge about the causes of postmenopausal bleeding and need to seek medical attention have been highlighted as reasons for women failing to present in a study of Maori vs. non-Maori New Zealand women (Evidence level 2). African-American women and those with a low income were more likely to present with advanced stage disease, suggesting that access to healthcare is a priority; certainly within the American healthcare system (Evidence level 2). No studies about the barriers to presentation of women with postmenopausal bleeding in the UK have been conducted.

Q168 What key symptoms should patients report to their doctors to trigger investigation for a possible womb cancer?
Postmenopausal bleeding (PMB) is a key symptom of endometrial cancer and warrants referral for further investigation using the two-week suspected cancer pathway referral (Evidence level 2). Any bleeding symptom, however, can be associated with endometrial cancer (Evidence level 2).

Q169 Should awareness of womb cancer be taught within schools?
There are no studies addressing whether awareness of endometrial cancer should be taught within schools, however, it would seem advisable to counsel children about the risks of obesity and, in particular, its association with the disease (Evidence level 5).

Q170 Are obese women aware that they are at increased risk of endometrial cancer and would they be prepared to engage in risk reducing strategies?
Obese women are no more aware of increased body mass index as a risk factor for endometrial cancer than their normal weight counterparts (Evidence level 2). There is no data available regarding whether they would be willing to participate in risk reducing strategies; however, increased perception of obesity as a risk factor for the disease is warranted before intervention will be effective.

Risk factors and causation

Q171 Does testosterone increase the risk of endometrial cancer?
Any association between free testosterone and endometrial cancer risk is no longer significant after adjusting for BMI, estrone and estradiol (types of the female hormone, oestrogen) (Evidence level 3-IV). Exogenous testosterone used as part of hormone replacement therapy in postmenopausal women has not been shown to cause an increase in the number of cases of endometrial cancer (Evidence level 2).

Q172 Does vaginal (unopposed) oestrogen treatment increase endometrial cancer risk?
A systematic review of studies evaluating vaginal oestrogen for the treatment of genitourinary symptoms found no increase in risk of endometrial cancer following

exposure to unopposed topical oestrogen (Evidence level 1). In total, 600 women received active treatment, of which only one developed endometrial cancer, giving a prevalence of 0.17% (Evidence level 1). The trials were of variable quality, however, and had limited follow-up periods of 3-6 months.

Q173 Does obesity increase endometrial cancer risk?
The results of several systematic reviews document a 1.6 fold increase in the risk of developing endometrial cancer with every 5kg/m^2 increase in BMI, the strongest association of obesity with any cancer type (Evidence level 2). The effect appears to be non-linear. Women with a BMI of 42kg/m^2 have a 9 times higher risk of developing endometrial cancer compared with those with a normal BMI.

Q174 Does fertility treatment increase endometrial cancer risk?
Whilst infertility and nulliparity are risk factors for the development of endometrial cancer, long term follow-up studies have failed to show any increase in risk following fertility treatment (Evidence level 2).

Q175 What causes endometrial cancer in normal weight women?
Increasing age, exposure to oestrogen only hormone replacement treatment, early menarche (age of first period), late menopause, nulliparity (having no children), infertility and low socio-economic status have all been shown to be risk factors for the development of endometrial cancer (Evidence level 2-4). Mutations in the DNA mismatch repair genes also increase the risk of endometrial cancer as part of Lynch syndrome. An underlying mechanistic pathway in all cases of endometrial cancer has yet to be determined.

Q176 Are particular contraceptive methods (hormonal, intrauterine device or barrier method) associated with endometrial cancer risk?
The combined oral contraceptive pill is associated with a 40-50% reduction in the incidence of endometrial cancer; an effect which persists for up to 10 years after discontinuing use (Evidence level 2). Levonorgesterol intrauterine systems (Mirena® coil) provide endometrial protection when used in conjunction with oral oestrogens or in patients taking tamoxifen (Evidence level 1).Users of inert copper intrauterine devices also have a 30% reduction in the incidence of endometrial cancer, particularly if used for more than 10 years, as a consequence of local hormone changes and induction of a foreign body reaction (Evidence level 2). There is limited evidence to support a beneficial effect from other progesterone only preparations, such as the progesterone only pill or implant, as the number of users in studies has been small (Evidence level 2). No studies have investigated the effect of barrier contraceptives on endometrial cancer risk.

Q177 How does obesity cause endometrial cancer?
Several mechanisms have been proposed to explain the association between obesity and endometrial cancer. These include insulin resistance (change in response to the hormone, insulin), aromatisation of androgens to oestrogen (conversion of naturally occurring hormones into the female hormone, oestrogen), adipokine secretion (particularly adiponectin), chronic inflammation and oxidative stress (Evidence level 3-4). No definitive conclusions have yet been reached and most work in this area has been conducted in laboratory studies of cancer cells grown *in vitro* rather than be demonstrated to occur in animals or humans.

Q178 What environmental factors increase endometrial cancer risk?
Oestrogen exposure (either endogenous or exogenous), obesity, low levels of physical activity, nulliparity, diabetes and adjuvant breast cancer treatment with tamoxifen have been shown to increase the risk of endometrial cancer (Evidence level 2-IV). Small case-control studies have also suggested that exposure to silica dust and pesticides may play a role in endometrial cancer development (Evidence level 4).

Q179 What are the causes of womb cancer?
The causes of endometrial cancer can be divided into genetic and environmental factors. Mutations in the mismatch repair genes increase the risk of endometrial cancer and are collectively referred to as Lynch syndrome (Evidence level 2). Environmental risk factors include obesity, low levels of physical activity, exposure to excess oestrogen (either endogenous or exogenous), diabetes, tamoxifen use, nulliparity and infertility (Evidence level 2-IV). The exact mechanism driving endometrial carcinogenesis has, however, yet to be established.

Q180 Is mode of delivery of children associated with endometrial cancer?
There are no published studies investigating whether mode of delivery is associated with future risk of endometrial cancer.

Q181 Does occupational exposure to radiation cause womb cancer?
There is conflicting evidence about the effect of occupational exposure to radiation on endometrial cancer incidence. Follow-up of Japanese atomic bomb survivors found no increase in number of cases diagnosed, whilst radiation workers at the UK Atomic Energy Authority were shown to have a higher rate of endometrial cancer. No correlation with dose of radiation was noted, however, suggesting other confounding factors may have been present (Evidence level 3). There have been no studies investigating the effect of radiation exposure on endometrial cancer incidence in medical professionals.

Q182 What are the causes of clear cell cancer?
In comparison with women with low grade endometrioid tumours, those with clear cell and serous endometrial cancers are more likely to be older, non-white, smokers and less likely to be obese (Evidence level 4). A family history of breast cancer or Lynch syndrome-associated cancers is more likely in women with clear cell endometrial cancer ,than those with serous or endometrioid tumours (Evidence level 4). Mutations in hepatocyte nuclear factor I beta (HNF1B) are associated with clear cell morphology in gynaecological cancers although the mechanisms driving endometrial carcinogenesis have yet to be elucidated (Evidence level 4). Whilst aneuploidy, p53 and her2 mutations are more common in this histological type, the ‘type 1’ and ‘type 2’ tumour distinction is becoming obsolete as greater prognostic information can be gleaned from genetic profiling of cancers (Evidence level 4).

Q183 Is endometrial cancer caused by stress?
There have been no studies into the effect of stress on the development of endometrial cancer. Mutations in circadian clock genes have been found in endometrial tumours suggesting a link with disruption to the sleep-wake cycle (Evidence level 5).

Q184 Is obesity associated with endometrial hyperplasia?
Obesity is a risk factor for endometrial hyperplasia and is thought to explain disease persistence in women treated with GnRH analogues, which blocks the production of the female hormone, oestrogen (Evidence level 3-4).

Q185 Does the Mirena coil increase or decrease endometrial cancer risk?
The Mirena coil decreases the risk of endometrial abnormalities, including benign polyps, in women taking tamoxifen following breast cancer and those using oestrogen replacement therapy (Evidence level 1). A meta-analysis of patients using a Mirena coil for endometrial protection from tamoxifen showed an 87% reduction in endometrial hyperplasia compared with a control group (Evidence level 1). The studies were not sufficiently powered to comment on whether the INTRAUTERINE SYSTEM decreases the risk of endometrial cancer and did not provide any information on whether it also prevents tumour development in other high risks groups of women, such as the morbidly obese or those with Lynch syndrome.

Q186 Do fibroids increase endometrial cancer risk?
A single case-control study has reported on a 39% increased risk of endometrial cancer in the presence of a fibroid womb (Evidence level 4). The study was retrospective and relied on self-reporting of a diagnosis of fibroids, potentially introducing recall bias. The relationship between the presence of fibroids and risk of endometrial cancer also varied in relation to body mass index, suggesting the presence of confounding factors. No mechanistic information has been postulated to explain any association between the two conditions.

Q187 Does endometriosis increase endometrial cancer risk?
There are conflicting reports in the literature as to whether endometriosis increases the risk of endometrial cancer, with the majority of studies showing no association between the conditions (Evidence level 3-IV). In general, the low number of cases has meant that the studies are underpowered to investigate any relationship.

Q188 Is it possible to attribute a cause in each case of endometrial cancer?
Risk factors for the development of endometrial cancer are well established, with obesity showing the strongest link with endometrial cancer of all cancer types, such that 41% of cases are directly attributable to being overweight or obese (Evidence level 3). Despite this, not all obese women will develop endometrial cancer and there are a proportion of women with the disease who have a normal BMI, suggesting a complex interaction between environmental and genetic factors which has yet to be adequately explained.

Q189 Do lifestyle choices impact the development of womb cancers?
Higher levels of physical activity are associated with a lower risk of endometrial cancer in overweight and obese women, whereas prolonged periods of TV viewing are associated with a higher risk of developing the disease (Evidence level 2). No relationship between alcohol and endometrial cancer risk has been demonstrated (Evidence level 3). Increasing coffee and tea consumption have been shown to reduce the risk of endometrial cancer in meta-analyses, though included studies were small and failed to control for confounding factors (Evidence level 2). The effect of smoking on endometrial cancer risk is still debated, with the most recent analysis

suggesting up to a 27% reduction in risk for women smoking >20 cigarettes per day (Evidence level 2).

Q190 Does HRT increase endometrial cancer risk?
Unopposed oestrogen for 1-3 years in women with an intact uterus is associated with an increased risk of endometrial hyperplasia, whilst the addition of at least 1mg of norethisterone or 1.5mg medroxyprogesterone acetate (synthetic progesterones) reduces the level of risk down to the baseline rate (Evidence level 1). HRT does not appear to increase the risk of endometrial cancer recurrence, though studies have been predominately observational rather than randomised (Evidence level 2).

Q191 Does hysterectomy reduce endometrial cancer risk?
Hysterectomy in women with Lynch syndrome has been shown to prevent endometrial cancer development (Evidence level 2). There are no published papers establishing whether hysterectomy reduces the risk of endometrial cancer in women without Lynch syndrome, but expert opinion would support this hypothesis (Evidence level 5).

Q192 What modifiable risk factors are present for womb cancer?
Obesity, low levels of physical activity and use of oestrogen only HRT are modifiable risk factors for endometrial cancer (Evidence level 2). Bariatric surgery and intentional weight loss of 20 pounds or more may be associated with a reduction in the risk of disease (Evidence level 2). Use of the combined oral contraceptive pill causes a 40-50% reduction in endometrial cancer risk (Evidence level 2).

Q193 Why are women with PCOS (polycystic ovary syndrome) more likely to develop womb cancer?
There are several proposed mechanisms to explain the increased risk of endometrial cancer in women with PCOS, though all are based on mechanistic reasoning rather than as a result of direct evidence from clinical trials. Obesity and PCOS frequently co-exist and obesity is known to be a strong risk factor for endometrial cancer (Evidence level 5). Obesity also causes insulin resistance and women with PCOS have a higher prevalence of the metabolic syndrome than matched controls (Evidence level 4). Insulin stimulates IGF-1 production by the ovaries, a potent growth factor that can promote the development of endometrial cancer (Evidence level 5). Progesterone has been shown to counter the effects of oestrogen on the endometrium in women taking exogenous hormones and as women with PCOS are anovulatory and progesterone resistant; their endometrium is exposed unopposed oestrogen resulting in hyperplasia and a risk of malignancy (Evidence level 5). Further research is required to address this question fully, however, as not all women with PCOS will develop endometrial cancer.

Q194 What is the relationship of womb cancer to oestrogen and progesterone?
Unopposed oestrogen HRT used for 1-3 years increases the risk of endometrial hyperplasia, regardless of dose or preparation. The addition of at least 1mg of norethisterone or 1.5mg of medroxyprogesterone acetate (synthetic progesterones) is sufficient to counteract the stimulatory effect on the endometrium, reducing the incidence of hyperplasia to background levels (Evidence level 1). Levonorgesterol-releasing coils also protect the endometrium from tamoxifen induced proliferation in women with previous breast cancer, though whether this effect is also seen in other

high risk groups, such as the morbidly obese and those with Lynch syndrome, has yet to be investigated (Evidence level 1). The relative importance of endogenous oestrogen and progesterone levels in the pathogenesis of endometrial cancer is currently unknown.

Q195 Are viruses implicated in endometrial cancer development?
The prevalence of HPV is similar in patients with endometrial cancer compared with a control group, suggesting that it is not important in the aetiology of the disease (Evidence level 3). There are no published studies investigating the effect of other viruses on endometrial cancer risk.

Q196 Does hyperemesis gravidarum increase endometrial cancer risk?
Hyperemesis gradivarum (excessive vomiting in pregnancy) is associated with a reduction in the risk of gynaecological malignancies, after adjustment for country of birth and age at childbirth, with a relative risk of 0.84 (Evidence level 3). Scandinavian national cancer registries were used in this nested case-control study to provide follow-up data and did not discriminate between reproductive tract cancer types, meaning that the effect of hyperemesis specifically on endometrial cancer risk could not be addressed.

Q197 Does pregnancy reduce endometrial cancer risk?
Nulliparity is associated with a 2-3 fold increase in the risk of developing endometrial cancer (Evidence level 4). In a large Swedish cohort, the risk of the disease decreased with increasing parity, with a 34% reduction in incidence in women with 4 or more pregnancies compared with uniparous women (Evidence level 2). The age of first birth did not affect the risk of endometrial cancer after adjusting for other reproductive factors. The mechanisms underpinning this association have yet to be fully elucidated.

Q198 Does working environment have any influence on the development of endometrial cancer?
Long term exposure (>10 years) to silica dust in the textile industry is associated with a 7.4-fold increase in the risk of developing endometrial cancer, although the numbers included in the analysis were extremely small (Evidence level 4). Exposure to pesticides may also predispose to endometrial cancer development (Evidence level 4). No increase in risk of endometrial cancer was noted with exposure to acrylamide (Evidence level 4). There have been no studies investigating the effect of radiation exposure in the workplace on risk of endometrial cancer.

Q199 Is there an association of endometrial cancer with diet?
Studies have published conflicting data regarding the effect of diet on the risk of endometrial cancer. Large cohort studies conducted in the UK, European Union and USA showed baseline coffee intake to be inversely proportional to risk of endometrial cancer, but no effect of other dietary factors, including fat and carbohydrate (Evidence level 2). In contrast, a study of Mediterranean diet in Italy and glycaemic index in Chinese women demonstrated a reduction in disease risk with higher consumption of vegetables, fruit and nuts, monounsaturated fats and low consumption of meat and high GI foods (Evidence level 3-IV). The limited geographical areas used for these studies, use of a restrictive control group and

failure to adjust for BMI may account for these discrepancies. All studies have relied on patient recall of diet, which has frequently been performed retrospectively.

Q200 What causes type 2 endometrial cancer?
There are similarities in risk factors for both type 1 and type 2 tumours, arguing against the use of this terminology. Obesity, diabetes and nulliparity have been shown to increase the risk of type 2 tumours, albeit the strength of association is lower than that for type 1 cancers (Evidence level 2). Mutations in p53 and her2 genes and aneuploidy, however, are more common in type 2 endometrial cancers, though the mechanisms leading to the development of these cancers have yet to be fully explained (Evidence level 4).

Q201 Can we define a risk signature for endometrial cancer based on demographic, reproductive, genetic and lifestyle factors?
There are no studies defining a risk signature for endometrial cancer based on demographic, reproductive, genetic and lifestyle factors. Data has been published on various genetic mutations which are associated with an impact on survival from the disease (Evidence level 4).

Q202 What is the risk of endometrial cancer in women with mild, moderate and severe atypical hyperplasia?
There are no studies investigating the risk of endometrial cancer in women with mild, moderate and severe atypical hyperplasia. In the published literature, precancerous endometrial lesions are described as simple, complex or atypical hyperplasia. Following a pre-operative diagnosis of atypical hyperplasia, the incidence of endometrial cancer in the subsequent hysterectomy specimen is 17-59% (Evidence level 4). Long term follow-up of patients with atypical hyperplasia showed a significant progression of disease, with 27.5% of women developing endometrial cancer after 19 years (Evidence level 4). Only 42 women with atypical hyperplasia did not undergo hysterectomy immediately after diagnosis and were thus eligible for the study, however, it is unclear whether repeat biopsies were performed during the follow-up period to monitor for disease progression. Given the known high prevalence of co-existing endometrial cancer with atypical hyperplasia, it would be unethical to continue to perform observational studies of conservative management of women with a precancerous lesion.

Q203 Is the association of endometrial cancer and metabolic syndrome stronger than the association with endometrial cancer and obesity?
The relative risk of endometrial cancer for women with the metabolic syndrome is 1.37-2.12 in large cohort studies and meta-analyses (Evidence level 2). With regards to higher BMI, the relative risk of the disease is similar at 2.21 (Evidence level 2). As many studies have included obesity or a high waist: hip ratio in their definition of metabolic syndrome, it is difficult to directly compare the two risk factors. Where both are reported in the same study, adjustment for obesity modifies the impact of the metabolic syndrome on endometrial cancer risk.

Screening

Q204 Are any serum markers effective in early detection of endometrial cancer?
There have been no trials to determine whether looking at the levels of markers in the blood of women can detect cancers at earlier stages than if a woman was to present with symptoms alone.

HE4, CA 125, CEA, S-AA and prolactin are found at higher levels in the blood of women with womb cancer. Of these, prolactin is the most discriminative blood marker for womb cancer (Evidence level 3).

Q205 How can we diagnose endometrial cancer earlier?
There have been a number of studies looking at blood markers which differ between women with womb cancer from women without womb cancer (see q205). As yet none of the blood markers identified have been developed into clinical tests which can definitely discriminate between women with and without cancer. There has been no trials into whether other tests (e.g. scans, urine tests, sampling from the womb or vagina) may be useful tools in diagnosing endometrial cancer earlier.

Q206 Should obese women be screened for endometrial cancer?
There have been no studies which address whether obese women would benefit from screening for endometrial cancer. Womb cancer is more common in obese women but it is unknown whether screening would mean better health outcomes in these women. Computer predictions based on whether screening would save the NHS money have suggested that it is unlikely that screening in obese women would be cost effective (Evidence level 4)

Q207 Is hysteroscopy an effective screening tool for endometrial cancer?
There are no studies which look at whether hysteroscopy on its own is an effective and acceptable tool for screening women in the general population who do not have symptoms of womb cancer. There have however been a few studies looking at whether hysteroscopy could be used to detect womb cancer or pre-cancerous changes before symptoms develop in women at higher risk of womb cancer (e.g. Lynch syndrome, Tamoxifen use).

Studies in postmenopausal women who were being treated with Tamoxifen for breast cancer, found that hysteroscopy is highly accurate at detecting all women with endometrial abnormalities (i.e. sensitivity of the test) and gives very few false positives (i.e. specificity of the test) (Evidence level 3). In comparison, ultrasound is more acceptable as a screening test but is not as effective (Evidence level 4).

Two studies of hysteroscopy in women with Lynch syndrome conclude that hysteroscopy is more sensitive at picking up abnormalities than ultrasound (Evidence level 3).

Q208 What is the value of pelvic ultrasound in the screening of women for endometrial cancer?
Studies have found that ultrasound may be able to distinguish postmenopausal women with a higher risk womb cancer or hyperplasia (pre-cancer) from those with a very low risk of womb cancer on the basis of the thickness of their womb lining (Evidence level 4). These studies suggest that to ensure very few women with

womb cancer were missed, many women with endometrial thicknesses around the cut-off but otherwise normal wombs would have to undergo unnecessary hysteroscopies and biopsies (Evidence level 5). Ultrasound is not a very good tool for assessing the endometrial cancer risk in premenopausal women.

There are no studies which then go on to look at whether women who have treatment for the abnormalities detected by ultrasound screening do better than women who are diagnosed after demonstrating symptoms of womb cancer.

Q209 Is screening for endometrial cancer effective amongst general population or high risk women (e.g. Lynch syndrome, obese)?
There are no studies which determine whether screening is effective at reducing womb cancer rates and/or improving survival in women with womb cancer in the general population.

Long term follow up of women with Lynch syndrome suggests that screening in these women does not detect womb cancer earlier (Evidence level 4). There are no such studies in women with other risk factors such as obesity, diabetes or Tamoxifen use.

Q210 What is the most effective screening modality for endometrial cancer?
The effectiveness of clinical examination, ultrasound, endometrial sampling and hysteroscopy to detect early cancers in women taking Tamoxifen and women with Lynch syndrome has been compared in a small number of studies (Evidence level 3). Hysteroscopy appears to have the highest accuracy at distinguishing normal from abnormal womb linings. However it is the most invasive procedure and therefore may be less acceptable than less invasive procedures, such as ultrasound.

Q211Should annual endometrial pipelles be offered to all women as screening who have BMI >35?
There are no well designed studies looking at whether offering endometrial sampling to all obese women would reduce the number of women developing womb cancer and/or improve survival in these women.

Q212 Does early diagnosis improve outcomes in women with endometrial cancer?
There are no well designed studies which have looked at whether earlier diagnosis improves outcomes in women with womb cancer.

One very small study which compared the records of women with womb cancer found that there was no difference in the stage or survival of women who experienced abnormal bleeding and those who had had no vaginal bleeding before diagnosis (Evidence level 4).

Q213 Is screening with endovaginal ultrasonography and subsequent endometrial biopsy useful in high-risk groups (obesity, diabetes mellitus, known endometrial hyperplasia, hereditary nonpolyposis colorectal cancer syndrome)?

The long term implications of screening in high risk groups has not been studied extensively. It is unknown whether a strategy of screening by ultrasound followed by endometrial biopsy in women with abnormal findings at ultrasound is likely to be more or less effective than a strategy of ultrasound along with endometrial sampling/ hysteroscopy or endometrial sampling/hysteroscopy alone.

Q214 Is endometrial cancer surveillance in women with Lynch Syndrome/Cowden syndrome effective at detecting endometrial cancers earlier and reducing cancer related mortality?

No well designed studies exist to determine whether surveillance of women with Lynch or Cowden's syndrome results in earlier diagnosis and improved survival for those that develop womb cancer.

Two small studies have suggested that when compared to no screening, surveillance for womb cancer in women with Lynch syndrome does not result in the detection of womb cancers at earlier stages (Evidence level 4). No definitive improvement in survival from womb cancer has been seen.

Self help and support

Q215 What support would patients with womb cancer need / like?
Provision of adequate information about the diagnosis, treatment, after-care and effect on social and sexual life have been identified as being important to patients with endometrial cancer and something which they frequently find is not adequately achieved (Evidence level 3). Women have also identified being able to talk, and having support from their gynae-oncologist and nurse as being important, alongside workshops, support meetings and access to alternative therapies. Parking at hospitals has been found to be a cause of stress (Evidence level 3). Family support is of particular importance (Evidence level 3). Every patient will be different, however, and individualised assessments are required to address the specific needs of any particular patient.

Surgical management of disease and its alternatives

Q216 What is the risk of relapse in premenopausal patients who have hysterectomy alone compared to those who have a hysterectomy with bilateral salpingo-ophrectomy?
There are no studies investigating the risk of replace in premenopausal women who have had a hysterectomy alone compared with those who have also had a bilateral salpingo-oophorectomy.

Q217 Is cyberknife radiotherapy cost-effective in patients with recurrent endometrial cancer?
There have been no randomised controlled trials of the effectiveness of cyberknife radiotherapy for the treatment of recurrent endometrial cancer and no cost-effectiveness analysis has been performed. Of the three small case series reporting on the response to cyberknife radiotherapy in recurrent gynaecological cancer, only

17 patients with endometrial cancer were included and results were not available for individual cancer types, limiting the conclusions which can be drawn (Evidence level 4).

Q218 Is the iKnife an effective tool to aid decision making intraoperatively for patients with endometrial cancer?

There have been no studies of the intraoperative value of the iKnife in endometrial cancer.

Q219 Does robotic surgery improve outcomes in endometrial cancer?

Compared with open surgery, a robotically performed operation for endometrial cancer is associated with lower blood loss, shorter hospital stay, fewer major complications and greater lymph node yield at dissection in an unselected cohort (Evidence level 4). The available data is conflicting as to whether robotic procedures are superior to laparoscopic operations. A systematic review of eight observational studies found a reduced length of hospital stay and blood loss for robotic cases compared with historical controls (Evidence level 3). In contrast, a more recent study from a single centre highlighted no difference in short term outcomes and complications in the robotic and laparoscopically treated groups (Evidence level 4). Certainly, morbidly obese women benefit from robotic surgery (Evidence level 4). Disease free survival is similar regardless of surgical approach (Evidence level 4). Surgeon experience is of paramount importance in this situation, highlighting the need for prospective, randomised trials of the two surgical techniques.

Q220 Is pelvic lymph node sampling as effective as systematic dissection of all pelvic nodes at detecting nodal metastasis?

If lymphadenectomy is performed, it should be done systematically rather than by sampling. A randomised controlled trial of lymphadenectomy versus no lymphadenectomy in women with presumed stage I disease allowed grossly enlarged nodes (>1cm) to be removed at the surgeons discretion. The rate of lymph node metastases was four fold higher in the systematic lymphadenectomy arm (13.3% vs. 3.2%, <0.001), as only a proportion of women with metastases will have enlarged nodes (Evidence level 2). Although there was no difference in survival in the two groups, this information is important for staging and will influence decisions about adjuvant treatment (Evidence level 2). Systematic pelvic lymphadenectomy is of therapeutic significance in women with more advanced disease, however, and is associated with improved 5 year survival. This is thought to be related to more accurate staging and removal of micrometastases (Evidence level 3).

Q221 What is the role of pelvic and para-aortic lymphadenectomy?

The role of pelvic and para-aortic lymphadenectomy remains one of the most controversial topics in endometrial cancer management, with divisions across the continents. In theory, removal of lymph nodes has two main advantages; it allows accurate staging so that adjuvant treatment is only given to those likely to derive benefit from it and it ensures removal of micrometastases. A meta-analysis of randomised controlled trials of pelvic in women with disease presumed to be confined to the uterus showed no improvement in overall and disease free survival with lymphadenectomy (Evidence level 1). There have been criticisms of the included trials, however; para-aortic lymph node dissection and adjuvant treatment were not standardised across patients and a low number of lymph nodes were

removed in the lymphadenectomy arm. A retrospective cohort study showed a survival advantage for women with intermediate to high risk endometrial cancer from combined pelvic and para-aortic lymphadenectomy compared with pelvic lymph node dissection alone (HR 0.53, 95% CI 0.38-0.76, p<0.001) (Evidence level 3). The patients were generally young and had predominantly endometrioid type tumours, limiting the applicability of the results to the wider endometrial cancer population. There are no prospective randomised trials to determine the value of para-aortic lymphadenectomy or to define whether lymphadenectomy is of benefit in type 2 tumours, as the numbers included in studies to date have been too small to draw any definitive conclusions. The main difficulty is accurately identifying women with intermediate to high risk tumours pre and intra-operatively so that lymphadenectomy is performed appropriately.

Q222 Is there a survival advantage of omentectomy in women with high grade/ serous or clear cell endometrial cancer?

Experience from the management of ovarian cancer has led to omentectomy being performed in cases of serous and clear cell endometrial cancer. Studies of stage I, none or minimally myoinvasive uterine papillary serous carcinomas noted a survival advantage with full staging, including omentectomy, compared with incomplete staging, although it is difficult to separate out the specific benefit of omentectomy from that associated with pelvic and para-aortic node dissection (Evidence level 3). Omental micrometastases may be present in up to a quarter of women with negative lymph nodes, suggesting omentectomy allows more accurate staging of disease (Evidence level 4). A retrospective analysis of patients undergoing surgery for stage III and IV serous endometrial cancer, however, found no survival advantage for those who underwent omentectomy (Evidence level 3). Only 21 women underwent full staging, though, and the FIGO 1988 staging criteria were used, limiting the applicability of the results to modern practice. Certainly, if macroscopic omental disease is present this should be removed; complete surgical resection of disease is associated with improvement in survival, in line with evidence from ovarian cancer (Evidence level 2). Due to the low morbidity associated with omentectomy, it is likely to continue to be performed even in the absence of prospective, randomised data to support a survival advantage in this patient group.

Q223 Does sentinel node surgery accurately predict lymph node metastasis in endometrial cancer?

A systematic review found sentinel lymph node surgery to accurately predict lymph node metastases, with a sensitivity of 95%, negative predictive value of 99% and a false negative rate of 5% (Evidence level 1). Ultrastaging of the sentinel lymph node is required to detect micrometastses.

Q224 Does sentinel node surgery reduce recurrence of endometrial cancer?

Long term follow-up of patients enrolled in the SENTI-ENDO study showed no difference in recurrence free survival between those that had a sentinel lymph node detected and those that did not (Evidence level 2). Similarly, comparison of two units, one who routinely performed sentinel node surgery and another that undertook pelvic and para-aortic node dissection on selected cases at high risk of metastases, showed similar node-free recurrence rates at 3 years (Evidence level 3). Both studies only included patients with early stage endometrial cancer, where the outcome is already excellent, even if lymphadenectomy is not performed. Large

prospective randomised studies are required incorporating all grades, stages and histological types of endometrial cancer in order to determine whether sentinel node surgery has an impact on clinical outcomes.

Q225 Is myoinvasion of >50% an independent prognostic biomarker in endometrial cancer?

The depth of myoinvasion has been shown to be an independent prognostic marker in women with intermediate risk endometrial cancer for disease free survival and, in particular, distant recurrence (Evidence level 2). In a cohort of women with disease confined to the uterus, depth of invasion was associated with disease free and overall survival, but significance was lost in a multivariate analysis (Evidence level 2). There are no prospective studies of the prognostic value of myoinvasion in endometrial cancer and no large studies of women with non-endometrioid histology.

Q226 Which of total abdominal hysterectomy, laparoscopically assisted vaginal hysterectomy or total laparoscopic hysterectomy enable patients to return to normal activity the soonest?

Total laparoscopic hysterectomy is associated with a significantly lower risk of postoperative complications compared with total abdominal hysterectomy (RR 0.57, 95% CI 0.29-0.98, p=0.003) (Evidence level 1). It also results in improved quality of life in the early and late recovery periods (Evidence level 2). The length of hospital stay after a laparoscopically assisted vaginal hysterectomy is, on average, one day shorter and women are quicker to return to work than after a laparotomy (Evidence level 2-IV). There are no studies directly comparing all three surgical techniques or reporting on speed of return to normal activities.

Q227 What is the most effective route and duration of treatment in patients having progestin therapy for endometrial cancer? (i.e. oral vs intrauterine)

There are no randomised controlled trials comparing different routes of progestin treatment for endometrial cancer. A meta-analysis performed to establish response to progestin treatment incorporated 12 low quality studies, of which only 1 evaluated the intrauterine releasing system. The response rate for histological regression to normal endometrium for oral progesterone was 72% compared with 68% for the Mirena coil, suggesting similar efficacy (Evidence level 2).

Q228 Is robotic surgery superior to straight stick laparoscopy for morbidly obese women with endometrial cancer undergoing hysterectomy?

Two case-control studies have compared robotic and conventional laparoscopy for the treatment of endometrial cancer in obese and morbidly obese women. They both found decreased operating time, blood loss, length of hospitalisation, conversion rate and greater lymph node retrieval in the robotically treated group, without any increase in intra or postoperative complications (Evidence level 4). There are no prospective, randomised trials to guide surgical management of morbidly obese women.

Q229 Is apronectomy plus hysterectomy superior to laparoscopic hysterectomy for morbidly obese women with endometrial cancer in terms of outcomes?

There are no studies comparing apronectomy plus hysterectomy with laparoscopic hysterectomy for the treatment of endometrial cancer in morbidly obese women.

Q230 Does cytoreductive surgery have any role in advanced endometrioid endometrial cancer?

A meta-analysis of 14 small, retrospective, non-randomised studies of cytoreductive surery in advanced and recurrent endometrial cancer showed a survival benefit for those women who underwent complete surgical resection of disease. For every 10% increase in the proportion of patients undergoing 'optimal' resection there was a 9.3 month increase in survival (p=0.04) (Evidence level 2) The studies were very different, however, with varying definitions of complete surgical resection and insufficiently powered to allow a multivariable analysis to be performed. More recently, similar improvements in survival have been noted for women with complete resection of advanced disease in a range of endometrial cancer histological types, including carcinosarcoma (Evidence level 4). Standardisation of reporting outcomes of trials, including 'optimal' cytoreduction are required to inform future systematic reviews. Individual patient factors need to be taken into account when considering whether to embark on cytoreductive surgery in this context.

Q231 Is intraoperative macroscopic assessment and/or frozen-section of the hysterectomy specimen of value to define the depth of myometrial invasion?

There have been numerous prospective and retrospective single institutional studies of the value of intraoperative gross assessment of myometrial invasion and/or frozen section compared with the gold standard of postoperative histopathological examination. The diagnostic accuracy of intraoperative macroscopic assessment for depth of myometrial invasion has been found to be 70-99% and for frozen section 86.5-99% (Evidence level 3). When direct comparisons of the two techniques has been performed in the same study, frozen section has been shown to be the more reliable method. Only one study of frozen section specifically documented that the pathologist was blinded during the assessment; a similar level of diagnostic accuracy of 92% was found compared with other studies (Evidence level 2). The accuracy of frozen section in determining myometrial invasion in early stage disease may be lower than this, however, as concordance with final histology was only 61% for women with stage I tumours (Evidence level 3). This study used the 1988 FIGO staging system, which may have affected the results. A systematic review of the available data is required to establish whether gross intraoperative assessment or frozen section are valuable techniques in determining depth of myoinvasion, and comparisons ned to be made with pre-operative imaging, such as MRI. Evaluation of the impact of intraoperative gross examination and frozen section on the extent of surgical staging and clinical outcomes is awaited.

Q232 Do wound complications in obese women with endometrial cancer have more of an economic impact than those in non-obese women?

There are no studies of the economic impact of wound complications in obese women compared with non-obese women. Obesity was a significant predictor of superficial incisional surgical site infections, which in itself was associated with a $5447 increase in 30-day cost (Evidence level 1).

Q233 Is primary radiotherapy as effective as primary surgery in women with local disease and significant comorbidities?

There are no prospective studies comparing primary radiotherapy with primary surgery in women with local endometrial cancer. Three retrospective case series

have been published, incorporating 30-70 patients undergoing primary radiotherapy rather than surgery because of co-morbidities (Evidence level 4). All had short follow-up periods. Only one study commented upon disease specific survival, reporting 93% and 73% survival at 1 and 3 years, respectively; a more useful measure, particularly in this population, than overall survival (Evidence level 4). Given the good prognosis associated with surgery in early stage endometrial cancer it is highly unlikely that adequately powered trials comparing radiotherapy and surgery as primary treatment options will be conducted.

Q234 Is robotic surgery cost effective alternative to laparoscopic or open surgery in obese women?

There are no studies specifically looking at the cost effectiveness of robotic surgery compared with laparoscopic or open surgery for obese women. The published data on the cost effectiveness of each surgical approach within the whole endometrial cancer population is conflicting, with the majority reporting laparoscopy to be the cheapest option, from both a societal and hospital point of view, followed by robotic procedures and laparotomy as the most expensive (Evidence level 2-III). After adjusting for the initial outlay costs, the reduced conversion rate and number of laparoscopic procedures performed, robotic procedures became the most cost effective option (Evidence level 2). All studies to date, however, have been performed in single centres and there is no available data from within the NHS to guide management.

Survivorship

Q235 What is the impact of womb cancer treatment on sexual function?

Following surgery, more patients with endometrial cancer were found to have superficial dyspareunia, sexual desire dysfunction, arousal dysfunction and reduced intensity of orgasm compared with women undergoing a hysterectomy for benign indications or healthy controls (Evidence level 3). Interestingly, endometrial cancer patients reported similar levels of sexual dysfunction pre and postoperatively, suggesting the surgery itself was not to blame. The route used to perform a hysterectomy does not appear to influence the risk of subsequent sexual dysfunction, with equivalent scores being given by patients who were randomised to either laparotomy or laparoscopy as part of the GOGLAP2 study (Evidence level 2). Brachytherapy has not been shown to adversely affect quality of life and sexual function for women undergoing adjuvant radiotherapy for the treatment of endometrial cancer (Evidence level 3). The studies performed to date in this area have generally been small, frequently failed to adjust for pre-treatment sexual morbidity and have not been subjected to a systematic review.

Q236 Does physiotherapy enhance quality of life during treatment and after cancer?

Physical activity, facilitated by a physiotherapist, involving a 12 week walking programme was found to reduce fatigue up to 6 months after treatment in gynaecological cancer survivors (Evidence level 2). Pelvic floor muscle training also improved symptoms of urinary incontinence in women after treatment of their malignancy (Evidence level 2). There are no studies specifically addressing whether

physiotherapy enhances quality of life during and after treatment of endometrial cancer.

Q237 What supportive interventions are most valued by patients and families following a diagnosis of womb cancer?

There are no systematic studies of supportive interventions and their value to patients and their families following a diagnosis of endometrial cancer. Several questionnaire based studies have been conducted of women with endometrial cancer and their spouses about the amount of information they received about their diagnosis and subsequent treatment. Many women reported receiving insufficient information (Evidence level 4). Written information is better than orally given information (Evidence level 2). A survey of younger women recently diagnosed with breast, ovarian or endometrial cancer specifically focussing on social support highlighted socioemotional support as being the most beneficial (i.e. listening or talking to the patient about the disease) (Evidence level 4). Other supportive behaviours differed between individuals depending upon age and marital status, suggesting an individualised approach to supportive care.

Q238 How do patients with womb cancer cope with anxiety and psychological issues?

Whilst there are several cross-sectional studies of the prevalence of anxiety and psychological issues in women who have undergone treatment for endometrial cancer, there is no published information on how such patients cope with their symptoms.

Q239 Is fatigue management effective in patients with womb cancer?

A small, randomised controlled trial has been conducted to test the feasibility and efficacy of a 12 week home based walking programme on fatigue. The study included patients with both ovarian and endometrial cancer, but found a significant reduction in fatigue at 12 weeks and 6 months in the intervention arm (Evidence level 2). This trial has not been subsequently followed up by an adequately powered randomised control trial of physical activity for the treatment of cancer related fatigue. There are no other studies of fatigue management in endometrial cancer.

Q240 When is the optimum time for interventions such as fatigue and anxiety management with patients with endometrial cancer?

There are no studies assessing the optimum time for interventions such as fatigue and anxiety management in patients with endometrial cancer.

Q241 What are the risks and benefits of hormone replacement in premenopausal women who have gone through the menopause as a result of treatment for endometrial cancer?

There are no studies specifically addressing the risks and benefits of hormone replacement in premenopausal women who have had treatment for endometrial cancer. In comparison with women who did not receive HRT following oophorectomy for the treatment of gynaecological malignancies, HRT use was effective in preventing bone loss and had a beneficial effect on lipid metabolism (Evidence level 3). It also improved vaginal dryness and improved quality of life (Evidence level 4). Most of the benefits are assumed from studies of HRT use in women who have undergone oophorectomy for treatment of other conditions.

Q242 What is the best way to support our patients in relation to psychosocial issues after treatment for endometrial cancer?

There are no studies identifying the best way to support patients in relation to psychosocial issues after treatment for endometrial cancer. A national study in America showed that following the introduction of guidelines advising on the management of psychological distress in cancer patients, there were a greater number of referrals to mental health experts and fewer unmet needs in this patient population (Evidence level 4). This would suggest that screening for psychosocial issues and appropriate onward referral would be beneficial.

Q243 Does depression/anxiety or chronic stress have a part to play in the development of endometrial cancer?

There are only two published studies which have evaluated the role of depression and stress in the development of endometrial cancer. A prospective cohort study of women enrolled in the Copenhagen City Heart study found that women who self-reported stress on one occasion had a lower subsequent risk of endometrial cancer; the effect was stronger in patients taking HRT and with a normal BMI (HR 0.77 and 0.73, respectively) (Evidence level 2). In contrast, patients being treated for depression in a psychiatric clinic were found to have a higher incidence of endometrial cancer than expected (Evidence level 2). There are no studies of the effects of chronic stress or lesser degrees of depression and anxiety on endometrial cancer risk.

Q244 What is the psychological impact of womb cancer?

There are no good quality studies of the psychological impact of endometrial cancer on patients. A diagnosis of endometrial cancer appears to be associated with psychological distress, even in the absence of any treatment (Evidence level 4) and social functioning is significantly decreased following radiotherapy (Evidence level 4). Anxiety levels are lower, however, at 3 months after surgery (Evidence level 4).

Treatment of recurrent or metastatic disease

Q245 What is the best first line/ second line/third line chemotherapy regimen for metastatic endometrial cancer?

A systematic review of chemotherapy for locally advanced uterine carcinosarcoma only identified three studies which met the authors' inclusion criteria. Ifofosfamide and pacliataxel combination chemotherapy was associated with a lower rate of death compared with ifofosfamide alone (Evidence level 1). Gynecologic Oncology Group (GOG) trials of chemotherapy for advanced or recurrent endometrial cancer have identified a combination of doxorubicin/cisplatin/paclitaxel as being associated with the highest complete response rate and progression free and overall survival (Evidence level 2). A systematic review of adjuvant chemotherapy following hysterectomy specifically focussed on platinum based regimes and also found a small benefit in survival irrespective of radiotherapy treatment (Evidence level 1). There are no studies comparing carboplatin to cisplatin in this setting to determine which is superior. A recent phase III randomised study of ixabepilone vs. paclitaxel or doxorubicin for women who have had at least one failed line of platinum based chemotherapy was prematurely discontinued due to poorer overall survival in the

ixabepilone arm compared with control (Evidence level 3). The use of chemotherapy in endometrial cancer is under-researched and there are currently no other studies comparing second and third line chemotherapy regimens; most agents are unlicensed and are in phase II and III trials.

Q246 What treatment options are most effective in recurrent uterine serous carcinoma?

There are no randomised trials of treatment options for recurrent uterine serous carcinoma. In a retrospective case series of patients with recurrent uterine serous carcinoma treated with platinum based chemotherapy and paclitaxel, objective response of measurable and/or evaluable disease was seen in 7 out of 11 women treated, with a median progression free interval of 9 months (Evidence level 4). Platinum sensitive disease is associated with a longer progression free interval when platinum based chemotherapy is reintroduced for the treatment of recurrent disease compared with platinum resistant tumours; however, this does not equate to any improvement in overall survival (Evidence level 4). Platinum-taxane combination chemotherapy is more sensitive than platinum-gemcitabine (Evidence level 4). Cisplatin, doxorubicin and cyclophosphamide has also been evaluated, with all women dying of their disease with a median survival of 7 months from chemotherapy, which the authors regarded as being a sign of lack of efficacy (Evidence level 4). No comparisons have been made between chemotherapy and surgery or radiotherapy in this context. Although serous cancers are diagnosed infrequently, they represent a significant proportion of recurrences, highlighting the need for good quality, randomised trials of treatment to guide practice.

Q247 Is chemotherapy effective in recurrence or metastatic uterine cancer?

A systematic review of chemotherapy in the treatment of advanced, recurrent or metastatic endometrial cancer concluded that it may improve overall and progression free survival, but that the available data was insufficient to recommend a specific regime (Evidence level 1). Subsequent GOG trials have supported a combination of doxorubicin/cisplatin/paclitaxel for women who are able to tolerate it (Evidence level 2). There is no available data on the most effective second and third line chemotherapy regimes.