## Appendix B: Stakeholder consultation comments table

2019 surveillance of [Menopause: diagnosis and management](2015)

Consultation dates: 13 to 30 August 2019

<table>
<thead>
<tr>
<th>Stakeholder</th>
<th>Overall response</th>
<th>Comments</th>
<th>NICE response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Besins Healthcare UK Ltd</td>
<td>No</td>
<td>An estriol based intravaginal pessary is due to be marketed in UK in 2019 for the indication of managing urogenital atrophy due to oestrogen deficiency.</td>
<td>Thank you for your comment. We identified several studies of intravaginal preparations of oestrogen that support the current recommendation to offer vaginal oestrogen to women with urogenital atrophy. The guideline does not contain recommendations about specific products. However, we have decided to update the section of the guideline on urogenital atrophy to consider the new treatments ospemifene and prasterone in addition to the currently recommended intravaginal oestrogen.</td>
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<tr>
<td>British Acupuncture Council</td>
<td>No</td>
<td>Your (2015-2019) evidence review found 'improvements in sleep quality, vasomotor symptoms, and oestrogen levels, but no effect on luteinising hormone or follicle stimulating</td>
<td>Thank you for your comment.</td>
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hormone levels' from the four non-sham trials. The impact statement says of acupuncture that the new evidence is 'showing little clinically important effect of this treatment', but I think this pertains only to the two sham controlled trials, not the four others.

Looking at the most recent published systematic review (Befus et al 2018), in fact an umbrella review and meta-analysis, there is the same distinction apparent between the sham and non-sham trials. For the latter the SMDs for vasomotor symptoms are -.49 and -.66 (for frequency and severity) and 0.93 for health related QoL. The effect sizes were smaller, or not even statistically significant, with the sham trials.

On the basis that clinical significance should be measured from comparisons of the intervention against real world alternative possibilities, such as no treatment or usual care, then acupuncture is indeed clinically significant. It is less effective than hormone treatment, but the offer of acupuncture in that context would be on the basis of avoiding the possible side effects of HRT for those people for whom that is an issue.

The problem with sham comparator acupuncture trials is the strong possibility of confounding physiological effects from the sham intervention, hence it is unwise to attach much weight to those results.

The authors of the above review concluded that the evidence did favour use of acupuncture for menopause-related vasomotor symptoms. We maintain that there is sufficient evidence to consider acupuncture as a possible alternative treatment for menopausal symptoms.

The study by Befus et al. (2018) does not clearly report systematic search and selection methods so is not eligible for inclusion in surveillance. However, the results are consistent with the evidence identified in surveillance, namely that acupuncture appears to be effective when the control is no acupuncture, but there are no effects when the control is sham.

We agreed that sham acupuncture is likely to have different effects from non-sham control. On that basis, we further considered your conclusion that it is 'unwise to attach weight to those results'.

Randomised controlled trials aim to control the conditions of each group to isolate the effects of the intervention. In the case of acupuncture, this would be the effect of placing needles at specific points in the body.

When comparing acupuncture with usual care, each group is aware of their treatment assignment. Thus, the results may be biased because people who believe acupuncture will help will find an improvement in symptoms but those in the usual care group have no reason to believe their symptoms will improve. This bias would be likely to result in a higher measured effect of acupuncture.

To measure the specific effect of placing needles at specific points in the body patients in both groups should share as much of the process and context in which treatment is delivered. In this way, effects arising from patients' expectations, or from the therapeutic setting and process, will apply equally to both groups.

Therefore, we consider sham-controlled trials of acupuncture to be the most appropriate study design, in accordance with the guideline's protocol, and thus place greater emphasis on those results. An update in this area is not necessary at this time.

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| British Menopause Society (BMS) | No | We do not agree with the proposal not to update the guideline. The British Menopause Society believes there are sufficient new data on cardiovascular mortality, VTE, new products (hormonal, non-hormonal and complementary), testosterone and POI prediction to justify an update of the guideline. There is also a need to clarify the differences and regulatory issues concerning compounded HRT products. In addition, we are approaching 5 years since the publications of the guideline, and as a result there will be a need to address and include the updated evidence on the areas covered in the guideline and review the implementation of the guideline. The literature review of the evidence provided by NICE has captured most of the evidence related to this topic since the publication of the guideline in 2015. However, we do feel that a number of key references have not been included and these have been referred to in the appropriate sections below. The Medical Advisory Council of the British Menopause Society believes that the new data published since 2015 justify an update of the NICE guideline. We have included below our comments on the main areas that the British Menopause Society believes would benefit from an update: |

Thank you for your comment. We recognise that fully up-to-date reviews would be ideal, but we do not recommend updates unless we have sufficient information to indicate that a new review would suggest a need to change the strength or direction of a recommendation. Therefore, the evidence has been considered in terms of whether results suggest an impact on current recommendations. The chapter ‘Ensuring that published guidelines are current and accurate’ in Developing NICE guidelines: the manual has further information on the surveillance process. Because of the table format of this document, your comment ran for many pages, and the text from your comments became separated from our responses. To improve readability, we have separated each issue into a separate cell. Please continue reading each subsequent row, where you will find a detailed response to each of the issues that you have raised. Although several stakeholders have mentioned implementation of the guideline, we did not identify any information or evidence to allow us to explore this issue further. For example, if implementation of recommendations was poor because the recommendations were unclear, we could consider whether an update could improve uptake of those recommendations. |
| British Menopause Society (BMS) | No | 1. Cardiovascular disease:  
The BMS suggests that the following references should be included:  
In addition, while the below reference had been included in the original guideline in 2015, the British Menopause Society feels the level of evidence it included and the Cochrane conclusion from the analysis on cardiovascular benefits should be re-considered in an updated guideline.  
The Cochrane review concluded that women who started HRT within 10 years of their menopause had lower mortality (RR: 0.70; 95% CI: 0.52–0.95) and coronary heart disease, including death from cardiovascular causes and non-fatal myocardial infarction (RR: 0.52; 95% CI: 0.29–0.77). The study by Mikkola et al. (2015a) was not identified in our searches. The data reported in the abstract were reported as ranges of percentages, for example (risk of coronary heart disease death reduced by 18% to 54%). This abstract did not meet our inclusion criteria for this surveillance review because there is no statistical data accompanying these figures.  
However, we included several studies indicating that current or past HRT use is associated with lower cardiovascular and stroke mortality (except in the first year after stopping HRT). Yet, we also found evidence supporting the current guidance on increased risks of stroke and venous thromboembolism.  
We excluded the study by Hodis et al. 2016 because this study reported on the surrogate outcome of atherosclerosis progression, and we identified a large volume of studies that reported on cardiovascular events. Where possible, in this surveillance review we prioritised patient-oriented outcomes over measurements of surrogate outcomes.  
As you note, the study by Boardman et al. (2015) was considered when the guideline was being developed. Therefore, it is not eligible for consideration in this surveillance review. We identified several more recent studies that reported on mortality indicating inconsistent effects of different types of HRT on mortality across studies.  
The study by Vinogradova et al. (2019) is ineligible for consideration in this surveillance because it is a case-control study. The protocol for the evidence review of venous thromboembolism conducted when developing the guideline excluded this study design.  
We recognise the importance of shared decision-making between healthcare professionals and patients. The guideline aims to provide |
0.96) compared to placebo or no treatment. On the other hand, a neutral effect was noted in women who started HRT more than 10 years after the menopause, with no difference in mortality or coronary heart disease compared to placebo or no treatment.

The additional key data on cardiovascular mortality reduction are compelling and as referred to in the literature review by NICE, 4 out of the 9 analyses identified suggested a lower risk of cardiovascular mortality.

The British Menopause Society believes that the effect of HRT on cardiovascular risk, both morbidity and mortality and the potential role in primary prevention in women under the age of 60 should be reviewed, taking into consideration the studies referred to above.

2. Venous thromboembolism:

The British Menopause Society suggests that the following reference should be included:


This study does not change the recommendation in the guideline that transdermal HRT has a neutral impact on VTE risk. However, it does add to the data and strengthens the level of evidence given the large study sample size. This neutral effect on VTE was noted with both low and high dose transdermal preparations. In addition, the study also demonstrated a differential effect with the type of

information to support discussion of the risks and benefits with patients.

The interplay between the risks and benefits of HRT on cardiovascular outcomes remains complex and with associated uncertainty. We have now decided to update the section of the guideline on risks and benefits of HRT.

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**Table 1: Stakeholder Consultation Comments Table for 2019 Surveillance of Menopause: Diagnosis and Management (2015)**

<table>
<thead>
<tr>
<th>British Menopause Society (BMS)</th>
<th>No</th>
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<tr>
<td><strong>3. Breast cancer:</strong>&lt;br&gt;We suggest including the following references:&lt;br&gt;Stute P, Wildt L, Neulen J. The impact of micronized progesterone on breast cancer risk: a systematic review. Climacteric. 2018 Apr;21(2):111-122.&lt;br&gt;Asi N, Mohammed K, Haydour Q, Gionfriddo MR, Vargas OL, Prokop LJ, Faubion SS, Murad MH. Progesterone vs. synthetic progestins and the risk of breast cancer: a systematic review and meta-analysis. Syst Rev. 2016 Jul 26;5(1):121.&lt;br&gt;These two recent systematic reviews / meta analyses could usefully add to the literature in an updated guideline as to the potential differential effects of less androgenic progestogens/progesterone on the risk of breast cancer with HRT.</td>
<td>The studies by Stute et al. (2018) and Stute et al. (2016) were not identified in our searches. However, the first abstract has no information on the methods of the systematic review and the second abstract does not report any analytic data, so these studies are ineligible for consideration in surveillance. The study by Asi et al. (2016) was not identified in our searches. We excluded systematic reviews from this surveillance because we expected that much of the data would be from studies that would have been available for consideration when the guideline was developed. The studies included in this systematic review date from 2007–13, therefore all the evidence was available for consideration in developing the guideline, and thus is ineligible for inclusion in surveillance.</td>
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<tr>
<td><strong>4. The effect of the type of progesterone within HRT on the risk of breast cancer / VTE / stroke and on the endometrium:</strong>&lt;br&gt;We suggest including the following references:&lt;br&gt;Stute P, Neulen J and Wildt L, et al. The impact of micronized progesterone on the endometrium: a systematic review. Climacteric 2016; 7137: 1–13.&lt;br&gt;Canonico M, Carcaillon L, Plu-Bureau G, et al. Postmenopausal hormone therapy and risk of stroke</td>
<td>The study by Canonico et al. (2016) was identified in our searches but was excluded from surveillance because it is a nested case-control study and this study design was excluded from the protocol for the evidence reviewed in developing the guideline. The study by Scarabin et al. (2018) was not identified in our searches. This study is described as a meta-analysis; however, the abstract has no information to indicate that this was produced using systematic review methods. Therefore, this study is not eligible for consideration in surveillance. During consultation on the decision not to update the guideline we became aware of the report by the Collaborative Group on Hormonal Factors in Breast Cancer (2019). This study is an individual patient data meta-analysis which analysed the data using a nested case-control design. This type of study was not eligible for</td>
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The guideline (NG23) made reference to the potential lower risk of VTE with micronised progesterone. There have been a number of meta-analyses published since that have reported on this.

In addition, a large observational series reported on the risk of stroke with different progestogens and progesterone and route of administration of oestrogen. There was no increased risk of stroke detected in transdermal oestradiol, natural progesterone and non-androgenic progestogen users. These could be a useful addition to the level of evidence in an updated guideline.

**Addendum** (sent in a separate email after the main comments above, but within the consultation period)

consideration when developing the guideline. However, we decided that because of the large dataset analysed, we should consider the impact of this study on the conclusions in the guideline. The MHRA has issued a Drug Safety Update based on this study, which we have also considered.

The results of this study were consistent with many of the findings from the guideline:

- data from observational studies indicate that oestrogen-only HRT use for up to 10 years is associated with a small increase in breast cancer
- data from randomised controlled trials indicate that oestrogen-only HRT use for up to 10 years is associated with lower or no risk of breast cancer
- data from observational studies indicate that combined HRT use for up to 10 years is associated with an increase in breast cancer
- data from randomised controlled trials indicate that oestrogen-only HRT use for up to 10 years is associated with an increased risk of breast cancer (but this risk is lower than that seen in observational studies)
- the risk of breast cancer increases with treatment duration
- the excess risk of breast cancer generally reduces with time since stopping treatment.

However, the new study suggested that risks of breast cancer after stopping HRT are higher than was previously estimated. The guideline currently reports that there would be fewer cases of breast cancer in women who had stopped HRT for more than 5 years than in those who had not taken HRT. The new data indicate that some excess risk remains for up to 20 years. Additionally, the impact of the route of estrogen administration and type of progestogen. Stroke 2016; 47: 1734–1741.

Stute P, Wildt L, Neulen J. The impact of micronized progesterone on breast cancer risk: a systematic review. Climacteric. 2018 Apr;21(2):111-122. [This reference has also been referred to in point 3 above].


Stute P, Wildt L, Neulen J. The impact of micronized progesterone on breast cancer risk: a systematic review. Climacteric. 2018 Apr;21(2):111-122. [This reference has also been referred to in point 3 above].

Scarabin PY. Progestogens and venous thromboembolism in menopausal women: an updated oral versus transdermal estrogen meta-analysis. Climacteric. 2018 Aug;21(4):341-345. [This reference has also been referred to in point 3 above].

The guideline (NG23) made reference to the potential lower risk of VTE with micronised progesterone. There have been a number of meta-analyses published since that have reported on this.

In addition, a large observational series reported on the risk of stroke with different progestogens and progesterone and route of administration of oestrogen. There was no increased risk of stroke detected in transdermal oestradiol, natural progesterone and non-androgenic progestogen users. These could be a useful addition to the level of evidence in an updated guideline.

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We believe this study should be referenced and reviewed in an updated guideline.

"Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence."


A meta-analysis published in the Lancet this week by the Collaborative Group on Hormonal Factors in Breast Cancer reported on the risk of breast cancer with HRT in relation to the type and timing of hormonal intake.

The review covered the period January 1992 to January 2018 and included information from 58 studies of which 24 were prospective. Prospective follow-up identified 108,647 postmenopausal women who developed breast cancer of which 55,575 (51%) had used HRT.

The report showed an increase in the risk of breast cancer with HRT intake. The meta-analysis sought information on breast cancer incidence but did not collect information on breast cancer mortality.

The risk of breast cancer was noted to be higher with combined estrogen / progestogen intake, but was also increased, although to a lesser extent, with estrogen only systemic HRT. The risk was reported to be higher with continuous combined HRT regimens compared to sequential regimens. The risk appeared to vary in relation to the type of progestogen used, with Dydrogesterone appearing to have a lower risk compared to other synthetic preparations. The review only included a small number of risk of breast cancer in past users increases with duration of HRT use. The guideline did not split the risk of past use by the duration of HRT use.

However, we had already identified other studies assessing the effects of HRT on breast cancer, with some inconsistent findings across studies. Therefore, we will update the section of the guideline on the long-term risks and benefits of HRT. While the update is in process, we will remove the risk table for breast cancer and cross-refer to the MHRA risk table until the update publishes.

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Appendix B: stakeholder consultation comments table for 2019 surveillance of Menopause: diagnosis and management (2015) 8 of 57
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In addition, this meta-analysis did not assess mortality associated with breast cancer and only reported on the incidence of breast cancer. It is important to highlight that previous large long-term follow (up to 13 years) data from the Women's Health Initiative (WHI) randomised controlled trials showed no significant difference in cancer deaths in the HRT arms of the study compared to placebo. In addition, no difference was noted in all-cause mortality in the HRT arms of the study compared to placebo.

Findings from this meta-analysis, including the risk of breast cancer in relation to the type of progestogen used, the type of progestogen regimen (continuous or cyclical) and the risk of breast cancer in women starting HRT before the age of 50 require further evaluation in adequately powered prospective studies.

We welcome this further data on the incidence of breast cancer which will help us counsel our patients and women in general better. This paper provides further data on the impact of estrogen and progestogen combined and estrogen that adds more detail to that we have already gathered from overall assessment of the literature and some new information which includes some on different types of progestogen that surprisingly were found not to vary as much as had been thought. Of particular interest though is the impact of estrogen and different regimens of combined HRT on obese women where the former is found to have little effect but the increase with the latter is greatest with continuous combined HRT. However, in practice this must be weighed against the rapidly rising

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The more recent one Islam et al. 2019, included 36 RCTs and 8480 participants. It showed that testosterone significantly increased sexual function and that transdermal administration had a neutral effect on lipid profile and on major risks. Following on from this systematic review and meta-analysis, a Global Consensus Position statement on the use of testosterone therapy for women is soon to be published which will guide prescribing. All of this would be useful information to include in an updated guideline. In addition, testosterone preparations used in clinical practice in the UK are used out of licence given the lack of licenced preparations. It would be useful to review the out of licence use of testosterone in an updated guideline.

The study by Anderson et al. (2017) was identified in the search but was excluded from surveillance because it focuses on women with breast cancer who received treatment with chemotherapy and goserelin. Therefore, we have logged this and will consider this study in the next surveillance of our guideline on early and locally advanced breast cancer.

The study by de Kat et al. (2019) was identified in the search but was excluded from surveillance because it did not report a standard measure of diagnostic accuracy, such as the area under the receiver-operating characteristic curve (AUC). However, on further consideration, because the reported data, the C-statistic, is equivalent to the AUC, we have now included this study. This study found that anti-Müllerian hormone measurements in premenopausal women had C-statistic values (equivalent to AUC) of 0.64 to 0.69. The authors concluded that this strategy 'does not improve prediction of menopause'.

6. Premature Ovarian Insufficiency (POI):
Diagnosis and prediction of POI with AMH:
The following studies provide a useful update on the potential role of AMH in diagnosis and prediction of POI:

The study by Anderson et al. (2017) was identified in the search but was excluded from surveillance because it focuses on women with breast cancer who received treatment with chemotherapy and goserelin. Therefore, we have logged this and will consider this study in the next surveillance of our guideline on early and locally advanced breast cancer.

The study by de Kat et al. (2019) was identified in the search but was excluded from surveillance because it did not report a standard measure of diagnostic accuracy, such as the area under the receiver-operating characteristic curve (AUC). However, on further consideration, because the reported data, the C-statistic, is equivalent to the AUC, we have now included this study. This study found that anti-Müllerian hormone measurements in premenopausal women had C-statistic values (equivalent to AUC) of 0.64 to 0.69. The authors concluded that this strategy 'does not improve prediction of menopause'.

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The evidence on the role of HRT versus the combined oral contraceptive pill in women with POI remains limited. However, we suggest including the below study which showed a more favourable effect of bone turnover with HRT compared to that with the combined contraceptive pill.


Therefore, this study is consistent with current recommendations that state:

- do not use anti-Müllerian hormone testing to diagnose perimenopause or menopause
- do not use anti-Müllerian hormone testing routinely to diagnose premature ovarian sufficiency.

The study by Lunding et al. (2015) was identified in our searches but was excluded from surveillance because it did not report any standard measures of diagnostic accuracy. Thus, it provides no information to determine whether anti-Müllerian hormone testing is useful for predicting premature ovarian sufficiency in women with Turner syndrome.

The study by Nyström et al. (2019) was identified in the search but was excluded from surveillance because it did not perform standard analyses expected of diagnostic accuracy studies. It reported on the difference in serum markers of ovarian function between women who had survived cancer in childhood and women who had not had cancer in childhood. Only a small proportion of participants in this study had premature ovarian sufficiency. Therefore, this study is not eligible for consideration in surveillance because it does not provide information to determine whether anti-Müllerian hormone testing is useful for detecting premature ovarian sufficiency in women with a history of childhood cancer.

The study by Plociennik et al. (2018) was not identified in our searches. However, this study compared the results of anti-Müllerian hormone testing across 4 types of assay. The abstract only reports the variation in measured anti-Müllerian hormone levels, not the relative accuracy of any assay. Therefore, this study is not eligible for consideration in this surveillance review because it does not...
not provide information to help determine whether specific assays may be more accurate for anti-Müllerian hormone testing.

The study by Cartwright et al. (2016) was identified in our searches, but was excluded because the sample size available for analysis (36 women across 3 groups) was lower than the minimum sample size of 100 set for this surveillance review. However, on reconsideration, this criterion should not have been applied to studies of premature ovarian sufficiency because the evidence base is substantially smaller for this population. We have re-checked the studies excluded on sample size and have not identified any other studies that meet the inclusion criteria of the protocol for the evidence review in the guideline. This study assessed the effects of HRT compared with the combined contraceptive pill and no treatment in women with spontaneous premature ovarian sufficiency. Results showed a significant increase in bone lumbar spine bone mineral density after 2 years with HRT compared with the combined contraceptive pill. Because the baseline bone mineral density of participants was not reported in the abstract, it is not possible to tell whether the small increase in bone mineral density is clinically important. Additionally, the abstract did not report analysis of each treatment compared with no treatment and did not report on effects on menopausal symptoms. Overall, this study contributes little to answering the question of whether HRT or the combined contraceptive is more effective in women with premature ovarian sufficiency. Therefore, no update is necessary.

British Menopause Society (BMS) | No | 7. Compounded bioidentical hormones:
There remains confusion on the topic of compounded bioidentical/body similar HRT versus non-compounded (regulated) products. This relates to the terminology used in the guideline ‘unregulated compounded bioidentical hormones’ is sufficiently similar to the wording used in the British Menopause Society’s consensus statement ‘compounded bioidentical hormone replacement therapy’.

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to describe these products as well as concerns related to the purity, safety, efficacy and regulatory aspects concerning compounded HRT products. The British Menopause Society has addressed these issues in a recent consensus statement, but we believe this topic would warrant an evaluation by NICE in an updated guideline. The guideline does not make any recommendations relevant to specific preparations of regulated bioidentical HRT, so we do not feel there is sufficient reason to add a definition of this concept. In the summary of evidence from surveillance, one study of regulated bioidentical hormones was identified, and the issue was raised by topic experts. We have made sure that we have used clear wording in this section.

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<th>British Menopause Society (BMS)</th>
<th>No</th>
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<td><strong>8. Depressive symptoms in the menopausal transition:</strong> We suggest including the following references: Gordon J.L., Rubinow D.R., Eisenlohr-Moul T.A. et al. (2018) Efficacy of transdermal estradiol and micronized progesterone in the prevention of depressive symptoms in the menopause transition: A randomized clinical trial. JAMA Psychiatry 75(2): 149-157. Gleason CE, Dowling NM, Wharton W, Manson JE, Miller VM, Atwood CS, Brinton EA, Cedars MI, Lobo RA, Merriam GR, Neal-Perry G, Santoro NF, Taylor HS, Black DM, Budoff MJ, Hodis HN, Naftolin F, Harman SM, Asthana S. Effects of Hormone Therapy on Cognition and Mood in Recently Postmenopausal Women: Findings from the Randomized, Controlled KEEPS-Cognitive and Affective Study. PLoS Med. 2015 Jun 2;12(6):e1001833; discussion e1001833. NICE have referred to the above studies on HRT improving symptoms of depression and indicated that they are consistent with the guideline (NG23) recommendations. However, the new information would be a useful addition. As you note, the studies by Gordon et al. (2018) and Gleason et al. (2015) are already included in the summary of evidence from surveillance and the findings of improved symptoms of depression with HRT use are consistent with evidence considered in developing the guideline, thus no update is necessary.</td>
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to the current data in an updated guideline in an area where there has been much controversy.

We have considered the additional studies on ospemifene and prasterone that you suggested. The study of ospemifene by Archer et al. (2019) is already included in the summary of evidence from surveillance.

The study of prasterone by Labrie et al. (2017) was identified in our searches but is not eligible for consideration in surveillance because there was no information to suggest that the 3 studies included in the pooled analysis had been identified using systematic reviewing methods. We included reports on the individual studies, so including this pooled analysis would have resulted in double-counting of the data resulting in the evidence base appearing larger than it is.

The study by Portman et al. (2015) was identified in our searches but is not eligible for consideration in surveillance because it did not report any statistical data in the abstract to inform the size or certainty of the reported effects.

The study by Bouchard et al. (2016) was not identified in our searches and is not eligible for consideration in surveillance because it is a single-group before and after study. This does not match the study designs specified in the protocol for the evidence review in the guideline (randomised controlled trials).

However, after considering stakeholder feedback we have decided to update the section of the guideline on urogenital atrophy, which will cover both of these drugs. We initially proposed not to update this section of the guideline because we thought that these treatments would not have a substantial impact on NHS resources. However, with the publication of a new study on the risks of breast cancer with HRT use (see above) we decided to update the section.


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<tr>
<th>British Menopause Society (BMS)</th>
<th>No</th>
<th>9. New products:</th>
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<td></td>
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<td>A. Ospemifene:</td>
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<td>We suggest including the following reference:</td>
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<td></td>
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<td>There has been accumulating evidence on this product reporting on its beneficial effects on sexual function, vaginal dryness and dyspareunia.</td>
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<td>Ospemifene was reviewed in the 2015 NICE guideline but no recommendations were made at the time given the limited evidence. A number of reports have now reported on Ospemifene and shown a beneficial effect.</td>
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<td>Ospemifene is licenced for the treatment of vulvovaginal atrophy in women with a history of breast cancer after endocrine therapies such as tamoxifen and aromatase inhibitors are completed. However, Ospemifene has not been formally studied in women with a prior history of breast cancer or in women receiving treatment of early or advanced breast cancer. This should be reviewed in an updated guideline.</td>
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<td></td>
<td>We have considered the additional studies on ospemifene and prasterone that you suggested. The study of ospemifene by Archer et al. (2019) is already included in the summary of evidence from surveillance.</td>
</tr>
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<td></td>
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<td>The study of prasterone by Labrie et al. (2017) was identified in our searches but is not eligible for consideration in surveillance because there was no information to suggest that the 3 studies included in the pooled analysis had been identified using systematic reviewing methods. We included reports on the individual studies, so including this pooled analysis would have resulted in double-counting of the data resulting in the evidence base appearing larger than it is.</td>
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<td></td>
<td></td>
<td>The study by Portman et al. (2015) was identified in our searches but is not eligible for consideration in surveillance because it did not report any statistical data in the abstract to inform the size or certainty of the reported effects.</td>
</tr>
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<td>The study by Bouchard et al. (2016) was not identified in our searches and is not eligible for consideration in surveillance because it is a single-group before and after study. This does not match the study designs specified in the protocol for the evidence review in the guideline (randomised controlled trials).</td>
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<td></td>
<td></td>
<td>However, after considering stakeholder feedback we have decided to update the section of the guideline on urogenital atrophy, which will cover both of these drugs. We initially proposed not to update this section of the guideline because we thought that these treatments would not have a substantial impact on NHS resources. However, with the publication of a new study on the risks of breast cancer with HRT use (see above) we decided to update the section.</td>
</tr>
</tbody>
</table>
B. Prasterone:
We suggest including the following references:

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One of these studies above, reported efficacy and safety data up to 52 weeks. These data warrant inclusion and evaluation. In addition, this is now a licensed new class of drug for treating menopausal symptoms and this would warrant reviewing in an updated guideline.

<table>
<thead>
<tr>
<th>British Menopause Society (BMS)</th>
<th>No</th>
</tr>
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<tbody>
<tr>
<td><strong>C. Oestradiol and progesterone capsules (Bijuva TX-001HR), 0.003% oestradiol vaginal cream and oestradiol vaginal inserts:</strong></td>
<td></td>
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<tr>
<td>There are a number of published studies on these new preparations which NICE have referenced. There are now licensed in the US. While these are not yet available in Europe, they are likely to be marketed in the UK in due course. The BMS is of the view, that these should be reviewed in an updated guideline.</td>
<td></td>
</tr>
<tr>
<td>As you have noted, the summary of evidence from surveillance included studies of a variety of preparations of hormone treatments including oral, transdermal and intravaginally administered products (see the section on hormone replacement therapy in the summary of evidence from surveillance). The evidence generally showed hormonal treatments to be effective compared with placebo, but analyses comparing different hormone treatments showed no clear difference in effects. Therefore, the evidence is consistent with recommendations on offering HRT and intravaginal oestrogen and does not indicate a need to assess the relative effectiveness of different preparations. An update in this area is not considered necessary at this time.</td>
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</table>

**D. Oxybutynin:**

We suggest including the following reference:


This RCT (referenced in the NICE document) included 148 women showed significant reduction in vasomotor symptoms. The findings suggest that this product, which is available for use out of licence in the UK, would be a useful

As you noted, we included the study of oxybutynin by Simon et al. (2016). However, we concluded that larger studies are necessary to clarify the role of this treatment in menopause. We will consider this area again at the next surveillance review of the guideline.
addition to the limited choice of non-hormonal options for managing vasomotor symptoms in women with breast cancer.

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<th>British Menopause Society (BMS)</th>
<th>No</th>
<th>E. Laser treatment for genitourinary syndrome of menopause:</th>
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<tr>
<td></td>
<td></td>
<td>We suggest including the following references:</td>
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<tr>
<td></td>
<td></td>
<td>The published data on laser use for treatment of genitourinary syndrome of menopause have mainly consisted of uncontrolled case series. While this remains an area that requires further evaluation, it would be beneficial to have this reviewed in an updated guideline.</td>
</tr>
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</table>

The study by Pitsouni et al. (2017) was not identified in our searches. It is a systematic review of laser therapy in postmenopausal women. However, there was no information in the abstract to determine whether the included studies were randomised controlled trials, which would be necessary for evaluation of a new intervention in the guideline. Therefore, this study is not eligible for consideration in surveillance.

The study by Cruz et al. (2018) was identified in searches but was excluded from the surveillance review because it did not meet the minimum sample size of 100 participants set for this surveillance. This study included only 45 participants spread across 3 groups. Therefore, larger studies are needed to assess the safety and effectiveness of laser therapy in women with urogenital atrophy. An update in this area is not necessary at this time.

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<tr>
<th>British Menopause Society (BMS)</th>
<th>No</th>
<th>F. NK antagonist data:</th>
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<tr>
<td></td>
<td></td>
<td>The development of these new products is probably too early to warrant a new recommendation, but could certainly be included in the research recommendations section of an updated guideline.</td>
</tr>
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</table>

We did not identify any studies of this class of drugs in women with menopausal symptoms, and because no references have been provided, we cannot consider this class of drugs in surveillance. An update in this area is not necessary at this time, but we will consider any forthcoming evidence in this area at the next surveillance review.
<table>
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<tr>
<th>Comment</th>
<th>No</th>
<th><strong>G. Cognitive Behavioural Therapy (CBT) and Complementary and Alternative Medicines (CAM):</strong> The new data on CBT and CAM research, while not conclusive, would be a useful addition to the body of evidence in an updated guideline.</th>
<th>We identified several studies focusing on physical and psychological treatments including cognitive behavioural therapy, alternative and complementary medicines, Chinese medicine, and acupuncture. As you have noted, the evidence is not conclusive. An update in these areas is not considered necessary at this time.</th>
</tr>
</thead>
<tbody>
<tr>
<td>British Menopause Society (BMS)</td>
<td>No</td>
<td><strong>H. 10. Inconsistencies between the guideline (NG23) and the clinical knowledge summary (CKS) produced by NICE:</strong> CKS refers to the need for regular attempts to discontinue HRT treatment for vasomotor symptom control and for regular attempts (at least annually) to stop topical (vaginal) oestrogen. The NG23 guideline on the other hand refers to 'long term treatment' with topical vaginal oestrogens. The BMS feels these recommendations should be reviewed and updated.</td>
<td>The clinical knowledge summary has included additional information from the summary of product characteristics for intravaginal oestrogen. NICE guidelines do not generally include extensive prescribing instructions (see writing the guideline in Developing guidelines: the manual), but we expect prescribers to follow the summary of product characteristics. However, the guideline’s recommendation for annual review of each treatment for short-term menopausal symptoms includes intravaginal HRT. The annual review may involve an attempt to stop treatment. Clinical knowledge summaries are not NICE guidance, although they often use NICE guidance as a major source for their content. They provide primary care practitioners with a readily accessible summary of the current evidence base and practical guidance on best practice for common or significant primary care presentations. They may draw on resources covering areas that were not in the scope of a NICE guideline and may omit information that is more relevant to secondary care.</td>
</tr>
<tr>
<td>British Menopause Society (BMS)</td>
<td>No</td>
<td>The guidelines need more emphasis on the importance of exercise in peri &amp; post menopausal women.</td>
<td>Thank you for your comment. We identified new evidence on physical activity interventions. However, evidence suggested no effect of an exercise intervention on symptoms of menopause. Studies of pedometer monitored walking indicated benefits; however, there was no indication that new recommendations on walking are needed for this specific</td>
</tr>
<tr>
<td>Pelvic, Obstetric and Gynaecological Physiotherapy</td>
<td>No</td>
<td>The guidelines need more emphasis on the importance of exercise in peri &amp; post menopausal women.</td>
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| Royal College of Nursing | No | Some of our members do not agree with this proposal as the guideline is 4 years old and does not include data on differences in HRT types and breast cancer risk, VTE risk. Our members also feel that The Guideline Group made recommendations which do not appear to have been implemented. We feel there should be some discussion around why this is the case and what might need to change as it has not been reviewed in 4 years. The guideline should be reviewed in light of current practice. There also needs to be an update on the use of testosterone as there is only one line in the guideline and this is hard for women to get as off licence. |

Thank you for your comment. We included studies matching the protocol for the evidence review in the guideline covering the risk of both breast cancer and venous thromboembolism. Although the guideline looks at oestrogen-only and combined HRT separately, it does not cover differences between different types of oestrogen or different types of progesterone. Overall, there was no strong evidence to suggest lower risk with any particular type of oestrogen or progesterone over another. We have discussed the results of the recent study by the Collaborative Group on Hormonal Factors in Breast Cancer (2019) above and note that we will be updating this section of the guideline. Unfortunately, without details about specific recommendations that you have seen low uptake of, we are unable to determine whether an update would improve implementation. We have not identified any additional information or evidence to allow us to explore this issue further. Please see our response to another comment about testosterone above. |

population. NICE already has a guideline on walking and cycling that applies to all ages. The guideline on menopause also recommends ‘Give information to menopausal women and their family members or carers (as appropriate) that includes... lifestyle changes and interventions that could help general health and wellbeing’. We recognise the important of physical activity for women of all ages. NICE has a range of guidelines that aim to improve physical activity levels. These are brought together in NICE’s interactive flowchart on physical activity. |
The previous NICE NG23 guideline (2015) did not make any conclusion on when ospemifene should be used for the treatment of Vulvo-Vaginal Atrophy (VVA). At the time, not all evidence was available to review this technology plus there was no price and it was not launched in the United Kingdom (UK).

Since then, a substantial amount of new data (safety and efficacy) from randomised control trials (RCT) that included over 2,500 patients was published. In addition, to the new RCT data, 3-year results from the Post-Authorisation Safety study (PASS) long-term safety data were also published.

Furthermore, with the £39.50 price for the 28-tablet ospemifene pack, a cost-effectiveness analysis was performed and has been accepted for publication (Dymond et al November 2019, Perard et al October 2019). The Scottish Medicine Consortium (SMC) appraised ospemifene and is positively recommending its use (full licensed indication) by the NHS from September 9th, 2019.

In regard to ospemifene, the surveillance review proposal gave 2 reasons why the guideline should not be up-dated:
1. “the new evidence did not report on adverse events associated with ospemifene.”
2. “It was not possible to tell from the abstracts whether the effects were clinically meaningful, or durable.”

Regarding point 1, we feel the new evidence presented below demonstrates thorough reporting on adverse events associated with ospemifene:

Thank you for your comment.

We have checked the references that you provided against our inclusion criteria for this surveillance review.

We have checked the full text reports of Archer et al. (2019) and Constantine et al. (2015) and have updated the summary of evidence to include information on adverse event rates.

The other studies are not eligible for consideration in this surveillance. The reasons are detailed below.

The study by Bruyniks et al. (2018) did not appear to be either a systematic review or a randomised controlled trial. It is unclear whether the participants would have been analysed in published reports from randomised controlled trials.

The study by Cai et al. (2019) is a conference abstract and this type of evidence is not eligible for consideration in surveillance.

The study by Cui et al. (2014) is a systematic review that was published before the guideline published and was available for consideration during guideline development. Therefore, it is outside of the period covered by our searches and is not eligible for consideration in this surveillance review.

The study by de Villiers et al. (2019) is not clearly either a systematic review or a randomised controlled trial, and had no statistical data in the abstract to inform the size or certainty of the reported effect.

The study by Goldstein et al. (2019) appears to be an additional analysis of the participants covered by the report by Archer et al. (2019) that is included in the summary of evidence. The outcomes reported in this secondary analysis are surrogate outcomes that do not match those considered in the guideline, which focused on...
The peer-reviewed Archer et al 2019 publication titled "the Efficacy and safety of ospemifene in postmenopausal women with moderate-to-severe vaginal dryness: a phase 3, randomized, double-blind, placebo-controlled, multicenter trial" reports:

§ in the abstract on serious adverse events including no treatment-related serious AEs.

§ in table 3 of the full manuscript treatment emergent adverse events such as hot flushes, upper respiratory infection, urinary tract infection, bronchitis, nasopharyngitis etc are reported.

An additional two secondary publications reporting additional efficacy and safety data associated to ospemifene from the primary Archer et al 2019 publication are available (de Villiers et al 2019; Goldstein et al 2019).

We would also like to draw your attention to the 2-year and 3-year data from the Post-Authorisation Safety Study published by Bruyniks et al 2018 and Cai et al 2019, respectively. These publications report on the safety of ospemifene in the real-world clinical practice with long term follow up.

Furthermore, another reference reporting on safety appears to be omitted from the literature review associated to NG23 guideline: Simon et al 2014. This publication reports on safety up to a 52-weeks of use.


patient-oriented outcomes, such as dryness or dyspareunia. Therefore, this report is not eligible for consideration in surveillance.

The report by Perard et al. (2019) is a conference abstract and as such it is not eligible for consideration in surveillance. Additionally, no online resource for this reference could be found.

The report by Simon et al. (2018) is a pooled analysis from several studies but the abstract does not describe systematic review methodology. Additionally, several of the included studies were captured in the evidence reviewed when the guideline was developed, and we would wish to avoid double-counting of data. Therefore, this report is not eligible for consideration in surveillance.

The report by Simon et al. (2014) was excluded from the evidence review for the guideline because it was a secondary publication of data already included in the guideline. Therefore, this report is not eligible for consideration in surveillance.

Although much of the suggested evidence was not eligible for inclusion in surveillance, we have decided to update the section of the guideline on urogenital atrophy, which will cover ospemifene. As part of the update, the developers will review the literature in this area, which could include the cited references. We initially proposed not to update this section of the guideline because we thought that these treatments would not have a substantial impact on NHS resources. However, with the publication of a new study on the risks of breast cancer with HRT use (see above) we decided to update the section of the guideline on the long-term risks and benefits of HRT. While the update is in process, we will remove the risk table for breast cancer and cross-refer to the MHRA risk table until the update publishes.

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menopausal women with VVA, such as, dyspareunia and vaginal dryness.
Shionogi trust that the evidence presented above would help NICE to update the guideline NG23 section “managing urinogenital atrophy” (MUA).

References:


Cai B, Nordstrom B, Yoshida Y et al. Incidence of venous thromboembolism (VTE) among postmenopausal women prescribed ospemifene, selective oestrogen receptor modulators (SERM), or untreated vulvar and vaginal atrophy Maturitas 2019; June;124: 162


Cui Y, et al. The efficacy and safety of ospemifene in treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy: a systematic review and meta-

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<th>Name</th>
<th>Response</th>
<th>Comment</th>
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<tr>
<td>Target Ovarian Cancer</td>
<td>No</td>
<td>Long term risks should be updated to include ovarian cancer. A robust analysis of existing data from 52 studies, involving over 20,000 women from North America, Europe and Australia found taking hormone replacement therapy (HRT) increases a woman’s risk of developing ovarian cancer by 43 per cent, compared to a woman who has never taken HRT. (Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. (2015). The Lancet). Although this is a small risk it is something that women should be made aware of the same way the guideline currently does for breast cancer. Thank you for your comment. The study by the Collaborative Group on Epidemiological Studies of Ovarian Cancer (2015) is already included in the summary of evidence from surveillance. The increased risk of ovarian cancer with HRT use is already recognised in the SPCs of HRT products. We expect prescribers to follow NICE guidance in conjunction with the SPC for any treatments. We recognise the importance of shared decision-making between healthcare professionals and patients. The guideline aims to provide information to support discussion of the risks and benefits with patients. NICE is also developing a guideline on shared decision-making, which is expected to publish in April 2021. The interplay between the risks and benefits of HRT remains complex and with associated uncertainty for many outcomes. However, we have decided to update the section of the guideline on risks and benefits of HRT, because of new evidence on risks of breast cancer (see above).</td>
</tr>
<tr>
<td>The Royal College of Obstetricians and Gynaecologists</td>
<td>No</td>
<td>The RCOG does not agree with the proposal not to update the guideline. The RCOG believes that the current guideline, whilst extremely useful for women and practitioners, requires updating as important areas of the management of the menopause have seen either new data or the health landscape of the management of the menopause has changed. The RCOG has contributed to the detailed response as part of this consultation process by the relevant specialist society, the British Menopause Society (BMS) and as such fully endorse the comments made by the BMS. Thank you for your comment. Guidelines are recommended for update when we identify evidence indicating that recommendations need to change. We do not recommend updates to add newly published studies to the evidence reviews. Therefore, the evidence identified in this surveillance review has been considered in terms of whether results suggest an impact on current recommendations. We note the RCOG endorses the comments made by the BMS. Please see the full response to the comments made by the British Menopause Society above.</td>
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The management of many of the health issues that affect women in their post reproductive years should be a major part of the NHS's strategy to improve the health of women and the RCOG feels that an updated menopause guideline will be vital to underpin this. We also believe that much more emphasis should be placed on the recognition that entering the menopause is a key milestone and that, if identified appropriately, it can be used as a vital opportunity to educate all women in some of the important disease prevention strategies that should be employed. A key example is education around lifestyle choices women make and how they impact on women's health.

Women are still unaware of some of the major health benefits and disease prevention opportunities from the use of hormone replacement therapy. New data have been published in the 4 years since the guideline has been published. These affect key areas such as cardiovascular mortality and morbidity, venous thromboembolic disease and the treatment of premature ovarian insufficiency. The RCOG believes that with this new data an opportunity exists for NICE to perform an economic evaluation of HRT use as a tool in the prevention of disease when given to the right woman at the right time.

The Guideline alludes to the potential benefits of HRT in the context of chronic disease prevention. The Guideline refers to osteoporosis and CVD prevention in women commencing it at the time of the menopause. New data

The guideline already recommends giving women information and advice including lifestyle changes and interventions that could help general health and wellbeing. The guideline also provides information on both the long-term risks and benefits of HRT so that clinicians can discuss these fully with patients when considering treatments for symptoms of menopause.

The interplay between the risks and benefits of HRT remains complex and with associated uncertainty for many outcomes. We have decided to update the section of the guideline on risks and benefits of HRT because of new evidence on risks of breast cancer (see above).

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supporting further the role in CVD prevention have been published in the last 3 years.

| King's College Hospital NHS Foundation Trust | No | We do not agree with the proposal not to update the guideline. The Menopause service at King's College Hospital believes there are sufficient new data on cardiovascular mortality, VTE, testosterone and POI diagnosis and prediction to justify an update of the guideline. There is also an urgent need to clarify the differences and regulatory issues concerning compounded HRT products. In addition, there have been a number of new products that have been approved for managing menopausal symptoms that warrants review in an updated guideline. The literature review of the evidence provided by NICE has captured most of the evidence related to this topic since the publication of the guideline in 2015. However, we do feel that a number of key references have not been included and these have been referred to in the appropriate sections below. We believe that the new data published since 2015 would justify an update of the NICE guideline. We have included below our comments on the main areas that we believe would benefit from an update: |

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| Appendix B: stakeholder consultation comments table for 2019 surveillance of Menopause: diagnosis and management (2015) 29 of 57 | Thank you for your comment. Please see the full response to the comments made by the British Menopause Society above, which raised the same issues. |
cardiovascular and all-cause mortality. Menopause. 2015 Sep;22(9):976-83.

In addition, while the below reference had been included in the original guideline in 2015, the the level of evidence it included and the Cochrane conclusion from the analysis on cardiovascular benefits should be re-considered in an updated guideline.


The Cochrane review concluded that women who started HRT within 10 years of their menopause had lower mortality (RR: 0.70; 95% CI: 0.52–0.95) and coronary heart disease, including death from cardiovascular causes and non-fatal myocardial infarction (RR: 0.52; 95% CI: 0.29–0.96) compared to placebo or no treatment. On the other hand, a neutral effect was noted in women who started HRT more than 10 years after the menopause, with no difference in mortality or coronary heart disease compared to placebo or no treatment.

The additional key data on cardiovascular mortality reduction are compelling and as referred to in the

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<td>literature review by NICE, 4 out of the 9 analyses identified suggested a lower risk of cardiovascular mortality. We believe that the effect of HRT on cardiovascular risk, both morbidity and mortality and the potential role in primary prevention in women under the age of 60 should be reviewed, taking into consideration the studies referred to above.</td>
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<td>2. Venous thromboembolism: We feel that the following reference should be included: Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. BMJ. 2019 Jan 9:364: k4810. This study does not change the recommendation in the guideline that transdermal HRT has a neutral impact on VTE risk. However, it does add to the data and strengthens the level of evidence given the large study sample size. This neutral effect on VTE was noted with both low and high dose transdermal preparations. In addition, the study also demonstrated a differential effect with the type of progestogen used, with dydrogesterone appearing to have a lower risk compared to other progestogens.</td>
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<td>3. Breast cancer: We suggest including the following references:</td>
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Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence

Collaborative Group on Hormonal Factors in Breast Cancer, Lancet 2019


These recent systematic reviews / meta analyses could usefully add to the literature in an updated guideline as to the potential differential effects of less androgenic progestogens/progesterone on the risk of breast cancer with HRT.

4. The effect of the type of progesterone within HRT on the risk of breast cancer / VTE / stroke and on the endometrium:

We suggest including the following references:


Postmenopausal hormone therapy and risk of stroke

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Stute P, Wildt L, Neulen J. The impact of micronized progesterone on breast cancer risk: a systematic review. Climacteric. 2018 Apr;21(2):111-122. [This reference has also been referred to in point 3 above].
The guideline (NG23) made reference to the potential lower risk of VTE with micronised progesterone. There have been a number of meta-analyses published since that have reported on this.
In addition, a large observational series reported on the risk of stroke with different progestogens and progesterone and route of administration of oestrogen. There was no increased risk of stroke detected in transdermal oestradiol, natural progesterone and non-androgenic progestogen users. These could be a useful addition to the level of evidence in an updated guideline.
We believe this study should be referenced and reviewed in an updated guideline.

“Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence.”
A meta-analysis published in the Lancet this week by the Collaborative Group on Hormonal Factors in Breast Cancer reported on the risk of breast cancer with HRT in relation to the type and timing of hormonal intake.

The review covered the period January 1992 to January 2018 and included information from 58 studies of which 24 were prospective. Prospective follow-up identified 108,647 postmenopausal women who developed breast cancer of which 55,575 (51%) had used HRT.

The report showed an increase in the risk of breast cancer with HRT intake. The meta-analysis sought information on breast cancer incidence but did not collect information on breast cancer mortality.

The risk of breast cancer was noted to be higher with combined estrogen / progestogen intake, but was also increased, although to a lesser extent, with estrogen only systemic HRT. The risk was reported to be higher with continuous combined HRT regimens compared to sequential regimens. The risk appeared to vary in relation to the type of progestogen used, with Dydrogesterone appearing to have a lower risk compared to other synthetic preparations. The review only included a small number of women on micronised progesterone and as a result it would be difficult to draw meaningful conclusions from this report on the risk of breast cancer with micronised progesterone.

The meta-analysis reported that the risk of breast cancer remained elevated for more than 10 years after discontinuing HRT and this appeared dependant on the duration of HRT use.
The meta-analysis also suggested that starting HRT between the age of 40 and 50 was also associated with an increased risk of breast cancer compared with postmenopausal women younger than 50 years not using HRT. This, however, was not compared to age-matched premenopausal women which would have provided a clinically more meaningful comparator. In addition, the number of women in this sub-group was relatively small and it is not possible to determine from the presented data what proportion of women in this group discontinued HRT before the age of 50. These findings need to be further evaluated in an adequately powered prospective study. Furthermore, this also needs to be taken in the context of the significant bone protective effects and cardiovascular benefits that HRT offers to younger postmenopausal women.

There are a number of limitations that need to be taken into consideration when interpreting the findings from this meta-analysis including the heterogeneity of the data and the differences in study protocols given the various observational studies included.

In addition, this meta-analysis did not assess mortality associated with breast cancer and only reported on the incidence of breast cancer. It is important to highlight that previous large long-term follow (up to 13 years) data from the Women's Health Initiative (WHI) randomised controlled trials showed no significant difference in cancer deaths in the HRT arms of the study compared to placebo. In addition, no difference was noted in all-cause

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mortality in the HRT arms of the study compared to placebo.

Findings from this meta-analysis, including the risk of breast cancer in relation to the type of progestogen used, the type of progestogen regimen (continuous or cyclical) and the risk of breast cancer in women starting HRT before the age of 50 require further evaluation in adequately powered prospective studies.

We welcome this further data on the incidence of breast cancer which will help us counsel our patients and women in general better. This paper provides further data on the impact of estrogen and progestogen combined and estrogen that adds more detail to that we have already gathered from overall assessment of the literature and some new information which includes some on different types of progestogen that surprisingly were found not to vary as much as had been thought. Of particular interest though is the impact of estrogen and different regimens of combined HRT on obese women where the former is found to have little effect but the increase with the latter is greatest with continuous combined HRT. However, in practice this must be weighed against the rapidly rising incidence of endometrial cancer which is significantly decreased by the continuous combined preparations.

The overall findings from this study should also be considered in comparison to the risk of breast cancer with other lifestyle factors such as alcohol intake and obesity which have been shown to be associated with a higher risk compared to that with HRT. This should also be taken in the context of the overall benefits obtained from using...
HRT including symptom control and improving quality of life as well as considering the bone and cardiovascular benefits associated with HRT use.

5. Testosterone:

We suggest including the following references:


The benefits of testosterone treatment for women with diminished sexual wellbeing were referred to in the guideline (NG23). The two meta-analyses above were carried out since the guideline was published.

The more recent one Islam et al. 2019, included 36 RCTs and 8480 participants. It showed that testosterone significantly increased sexual function and that transdermal administration had a neutral effect on lipid profile and on major risks. Following on from this systematic review and meta-analysis, a Global Consensus Position statement on the use of testosterone therapy for women is soon to be published which will guide prescribing. All of this would be useful information to include in an updated guideline.
In addition, testosterone preparations used in clinical practice in the UK are used out of licence given the lack of licenced preparations. It would be useful to review the out of licence use of testosterone in an updated guideline.

6. **Premature Ovarian Insufficiency (POI):**

7. **Diagnosis and prediction of POI with AMH:**

The following studies provide a useful update on the potential role of AMH in diagnosis and prediction of POI:


Nyström A, Mörse H, Nordlöf H, Wiebe K, Artman M, Øra I, Giwercman A, Henic E, Elfving M. Anti-müllerian hormone compared with other ovarian markers after

**Appendix B: stakeholder consultation comments table for 2019 surveillance of Menopause: diagnosis and management (2015)**

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The evidence on the role of HRT versus the combined oral contraceptive pill in women with POI remains limited. However, we suggest including the below study which showed a more favourable effect of bone turnover with HRT compared to that with the combined contraceptive pill.


8. Compounded bioidentical hormones:

There remains confusion on the topic of compounded bioidentical/body similar HRT versus non-compounded (regulated) products. This relates to the terminology used to describe these products as well as concerns related to the purity, safety, efficacy and regulatory aspects concerning compounded HRT products. We believe this topic warrants an urgent evaluation by NICE in an updated guideline.

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9. New products:

A. Ospemifene:
We suggest including the following reference:

There has been accumulating evidence on this product reporting on its beneficial effects on sexual function, vaginal dryness and dyspareunia.

Ospemifene was reviewed in the 2015 NICE guideline but no recommendations were made at the time given the limited evidence. A number of reports have now reported on Ospemifene and shown a beneficial effect.

Ospemifene is licenced for the treatment of vulvovaginal atrophy in women with a history of breast cancer after endocrine therapies such as tamoxifen and aromatase inhibitors are completed. However, Ospemifene has not been formally studied in women with a prior history of breast cancer or in women receiving treatment of early or advanced breast cancer. This should be reviewed in an updated guideline.

B. Prasterone:
We suggest including the following references:
Labrie F, Archer DF, Martel C, Vaillancourt M, Montesino M. Combined data of intravaginal prasterone against...
One of these studies above, reported efficacy and safety data up to 52 weeks. These data warrant inclusion and evaluation. In addition, this is now a licensed new class of drug for treating menopausal symptoms and this would warrant reviewing in an updated guideline.

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### C. Laser treatment for genitourinary syndrome of menopause:

We suggest including the following references:


The published data on laser use for treatment of genitourinary syndrome of menopause have mainly consisted of uncontrolled case series. While this remains an area that requires further evaluation, it would be beneficial to have this reviewed in an updated guideline.

### 10. Inconsistencies between the guideline (NG23) and the clinical knowledge summary (CKS) produced by NICE:

CKS refers to the need for regular attempts to discontinue HRT treatment for vasomotor symptom control and for regular attempts (at least annually) to stop topical (vaginal) oestrogen. The NG23 guideline on the other hand refers to 'long term treatment' with topical vaginal oestrogens. We feel these recommendations should be reviewed and updated.

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The Eve Appeal  
Yes  
We agree with reasons not to update guidelines on the additional pharma now available.
Our nurse specialist information service Ask Eve regularly guides women to these guidelines when we receive queries on HRT prescribing.
We are delighted to see post cancer patients have a section in the guidelines.
people undergoing bilateral salpingophtrectomy with a mutated BRCA gene also benefit from the guidelines.

Thank you for your comment.
We have decided to update the section of the guideline on risks and benefits of HRT because of new evidence on risks of breast cancer (see above).
We appreciate that you find the guideline useful for people at high risk of hormonal cancer. The guideline also directs readers to the guideline on familial breast cancer, which provides additional recommendations relevant to this population.

2. Do you have any comments on areas excluded from the scope of the guideline?

<table>
<thead>
<tr>
<th>Stakeholder</th>
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<th>Comments</th>
<th>NICE response</th>
</tr>
</thead>
</table>
| Besins Healthcare UK Ltd             | Yes              | 1. An estriol based intravaginal preparation (0.03 mg estriol pessary - Imvaggis) has received marketing authorisation for the indication of managing vaginal atrophy in postmenopausal women due to oestrogen deficiency. The drug will be marketed in the UK in 2019. The 3 month duration efficacy clinical trial for the 0.03 mg estriol pessary (Griesser 2012) was reviewed in the NG23 2015 and was shown to be effective in managing vaginal symptoms. This drug is not new and has been marketed in the German market and other European countries under the Oekolp brand name for more than 25 years and hence possesses vast post-marketing efficacy and safety data. | Thank you for your comment.
We identified several studies of intravaginal preparations of oestrogen that support the current recommendation to offer vaginal oestrogen to women with urogenital atrophy.
Although the guideline does not contain recommendations about specific products, we identified several studies looking at different HRT products. The evidence indicated that all were effective when compared with placebo, but evidence on comparative effectiveness that could indicate superiority of specific products was inconsistent. |

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The drug is priced at £13.38 for 24 pessaries. This drug is relatively cheaper compared to the intravaginal tablet (Vagifem) and would provide clinicians with other options for managing urogenital atrophy. The inclusion of the cost for Imvaggis in Tables 14 and 15 would be beneficial for clinicians to decide on the different options available in UK to manage vaginal symptoms due to menopause.

2. Differentiate gels within transdermals for the management on short-term symptoms, safety profile (VTE risks, Stroke etc.) and long-term (CVD, Diabetes, Osteoporosis).

3. Differentiation of natural micronized progesterone vs synthetic progestogens on safety profile (Breast Cancer, VTE risks etc.)

4. Inclusion of pathway/flowchart on available HRT (Systemic and Local) to manage menopausal symptoms.

However, we have decided to update the sections of the guideline on urogenital atrophy and risks and benefits of HRT to consider the new treatments ospemifene and prasterone.

We initially proposed not to update this section of the guideline because we thought that these treatments would not have a substantial impact on NHS resources. However, with the publication of a new study on the risks of breast cancer with HRT use (see above) we decided to update the section of the guideline on the long-term risks and benefits of HRT. Changes in the benefits and risk profiling of HRT may lead to changes in acceptability of HRT to women and therefore increase the prominence of other interventions for treatment of menopausal symptoms, and therefore the update should also consider intravaginal treatments for urogenital atrophy.

<table>
<thead>
<tr>
<th>British Acupuncture Council</th>
<th>No</th>
<th>Not answered</th>
<th>Thank you for your response</th>
</tr>
</thead>
<tbody>
<tr>
<td>British Menopause Society (BMS)</td>
<td>Yes</td>
<td>The British Menopause Society does have comments on the areas excluded from the scope of the guideline. Areas excluded from the scope of the guideline (NG23): A. Health implications of early menopause 40-45 years of age. B. Use of HRT for reasons other than menopausal symptoms. e.g. Osteoporosis prevention and treatment. C. Use of HRT in women beyond 60 / 65 years of age.</td>
<td>Thank you for your comment. We did broad searches for new evidence related to the menopause, without restrictions on the sub-populations that you have suggested. However, we did not identify new evidence to address any of the issues raised in your response. If we become aware of significant new evidence, we will consider its impact on the guideline as soon as possible. Although the new evidence did not indicate that an update was necessary for HRT’s effects on osteoporosis or use after breast</td>
</tr>
</tbody>
</table>
D. HRT use after breast cancer and in women with familial breast cancer.

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| Royal College of Nursing | Yes | covered in other guidelines, does it need more emphasis in the menopause guidelines? Many studies have shown that lower muscle function is associated with greater mortality and morbidity. Higher grip strength was associated with a range of health outcomes and improved prediction of an office based risk score. [https://www.bmj.com/content/361/bmj.k1651](https://www.bmj.com/content/361/bmj.k1651) Celis Morales et al 2018, studied women 40-60 years old. A recent systematic review by Travers et al (2018) in British Journal of General Practice looked to find the most effective ways to prevent frailty in later life. Bone health and exercise In terms of exercising all that is mentioned in the guidelines as far as I can see Loss of muscle mass and strength 1.5.16 Explain to women that: there is limited evidence suggesting that HRT may improve muscle mass and strength muscle mass and strength is maintained through, and is important for, activities of daily living. bone health are the Royal Osteoporosis guidelines to be considered? Bone health and exercise We identified several studies indicating that HRT improved bone mineral density and reduces fragility fractures. This is consistent with current recommendations in the menopause guideline around discussing bone health, the risk of osteoporosis, and the benefits of HRT. NICE has a guideline on assessing the risk of fragility fracture. This guideline will be updated, and topic experts suggested a need to include recommendations on non-drug interventions. Although the new evidence did not indicate that an update was necessary for HRT’s effects on osteoporosis or use after breast cancer or in women with familial breast cancer, we decided to update the section of the guideline on risks and benefits of HRT because of new evidence on risks of breast cancer (see above). The study by [Celis-Morales et al. (2018)](https://www.bmj.com/content/361/bmj.k1651) is a non-comparative observational study and as such is not eligible for inclusion in surveillance because it does not meet the criteria for evidence included in the evidence review for the guideline. Additionally, this included both men and women and the abstract had no indication that separate analyses for postmenopausal women were conducted. Therefore, no update in this area is necessary. | Thank you for your comment. We did broad searches for new evidence related to the menopause, without restrictions on the population. In selecting evidence for surveillance, we were open to including evidence on the |

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b) Care of women with BRCA mutations, including use of HRT after RR BSO
c) Management of women with symptoms beyond age 60 – continuation of HRT, long term benefits and risks of continuing or stopping HRT
effectiveness and safety of HRT in people with or at risk of cancers. However, no eligible evidence was identified.
We did not identify any eligible information that could inform the use of HRT in women older than 60 years.
However, we have decided to update the section of the guideline on risks and benefits of HRT because of new evidence on risks of breast cancer (see above).

<table>
<thead>
<tr>
<th>Company</th>
<th>Response</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Shionogi Limited</td>
<td>Yes</td>
<td>The area excluded from the scope &quot;Managing Urogenital Atrophy&quot; (MUA) is not justified considering the available evidence associated to ospemifene in terms of safety and efficacy. (The evidence is outlined in reply to the previous question) In addition, we are reporting that the SMC is positively recommending the use of ospemifene within its full licensed indication for use in the NHS. This recommendation should provide a further information to update ospemifene in this guideline NG23. In not updating this section of the guideline (MUA), NICE could create inequality amongst post-menopausal women suffering from VVA in England compared to those in Scotland. Thank you for your comment. However, we have decided to update the sections of the guideline on urogenital atrophy and risks and benefits of HRT to consider the new treatment ospemifene. We initially proposed not to update this section of the guideline because we thought that ospemifene would not have a substantial impact on NHS resources. However, with the publication of a new study on the risks of breast cancer with HRT use (see above) we decided to update the section of the guideline on the long-term risks and benefits of HRT. Changes in the benefits and risk profiling of HRT may lead to changes in acceptability of HRT to women and therefore increase the prominence of other interventions for treatment of menopausal symptoms, and therefore the update should also consider intravaginal treatments for urogenital atrophy.</td>
</tr>
<tr>
<td>Target Ovarian Cancer</td>
<td>No</td>
<td>Not answered</td>
</tr>
</tbody>
</table>
The Royal College of Obstetricians and Gynaecologists  
Yes  
The RCOG believes that over the past 5 years there have been some significant developments that require clarification through an updated guideline:

- Regulatory concerns about the use of alternative, compounded hormone products marketed by the independent sector.
- The risk profile of HRT use as clarified in NG23 helped women and prescribers with their choices however new data about timing of HRT use, routes of administration and types of progesterone have emerged that could influence decision making and prescribing.
- Following a recent shortage of HRT products and the concerns of women around the UK it is clear that a guideline should highlight the benefits of some of the new drugs that target different menopausal symptoms such as ospemifene, prasterone and oxybutynin.
- Research and development of new drugs or treatment modalities should be championed by an updated guideline. The effect of menopausal cognitive decline should be a key research topic, investigating links with cognitive decline and dementia, and any effects of hormone therapy.
- AMH and prediction of menopause. We were surprised that this was not mentioned as the FDA has recently certified the use of AMH in diagnosis of menopause. The diagnosis is currently retrospective, based on age and menstrual rhythm. This is inappropriate for many women, particularly those who are young. The data on which the FDA based its decision comes from the Swan study – the

Thank you for your comment.

**Compounded hormone products**

The guideline has the following recommendation:

‘Explain to women that the efficacy and safety of unregulated compounded bioidentical hormones are unknown.’

Because these preparations are privately obtained and are legal, an update to the guideline is unlikely to resolve this issue.

**Specific HRT products**

Although the guideline does not contain recommendations about specific products, we identified several studies looking at different HRT products. The evidence indicated that all were effective when compared with placebo, but evidence on comparative effectiveness that could indicate superiority of specific products was inconsistent.

Overall, evidence did not indicate a need to update the guideline at this time.

**Ospemifene and prasterone**

After considering stakeholder feedback we have decided to update the section of the guideline on urogenital atrophy, which will cover the new treatments ospemifene and prasterone. We initially proposed not to update this section of the guideline because we thought that these treatments would not have a substantial impact on NHS resources. However, with the publication of a new study on the risks of breast cancer with HRT use (see above) we decided to update the section of the guideline on the long-term risks and benefits of HRT.

Changes in the benefits and risk profiling of HRT may lead to changes in acceptability of HRT to women and therefore increase

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lead author is Ninette Santaro. It is currently unpublished although should be by the time of any update.

The RCOG also fully supports the exclusions highlighted by the BMS:

1. Health implications of early menopause 40-45 years of age (please see references below).
2. Use of HRT for reasons other than menopausal symptoms, e.g. osteoporosis prevention and treatment.
3. Use of HRT in women beyond 60/65 years of age.
4. HRT use after breast cancer.

the prominence of other interventions for treatment of menopausal symptoms, and therefore the update should also consider intravaginal treatments for urogenital atrophy.

HRT shortage

Thank you for highlighting a shortage of HRT products. We are aware of a news item published by the British Menopause Society that details which products are in short supply and which are widely available. Prescribers may find such information useful during this period. This is reportedly a temporary issue rather than permanent withdrawal of particular products. Furthermore, the guideline does not contain recommendations about specific products so an update to the guideline is unlikely to resolve this issue.

Research and development

NICE supports research and development to increase the understanding of the mechanisms of disease as well as treatments. Research recommendations developed during guideline development can help to influence research priorities. However, the main purpose of a guideline is to inform practice based on existing evidence. We have now suggested updating the sections of the guideline on long term risks and benefits of HRT and managing urogenital atrophy. The guideline committee may develop new research recommendations as part of this process.

Anti-Müllerian hormone testing

We did not identify any new evidence on Anti-Müllerian hormone testing that could inform an update in this area. In response to stakeholder comments (see above) we have now included one study on anti-Mullerian hormone testing. This study found that anti-Mullerian hormone measurements in premenopausal women
had C-statistic values (equivalent to AUC) of 0.64 to 0.69. The authors concluded that this strategy ‘does not improve prediction of menopause’.

Therefore, this study is consistent with current recommendations that state:

- do not use anti-Müllerian hormone testing to diagnose perimenopause or menopause
- do not use anti-Müllerian hormone testing routinely to diagnose premature ovarian sufficiency.

The Study of Women’s Health Across the Nation (SWAN) is a longitudinal observational study that has published a large volume of studies. We will check for publication of the results reporting on anti-Müllerian hormone testing and menopause prediction and evaluate the impact on the guideline.

**Other exclusions**

We did not identify new evidence to address any of the issues raised in your response. If we become aware of significant new evidence, we will consider its impact on the guideline as soon as possible. However, we have decided to update the section of the guideline on risks and benefits of HRT because of new evidence on risks of breast cancer (see above). Although the new evidence did not indicate that an update was necessary for HRT’s effects on osteoporosis or use after breast cancer or in women with familial breast cancer.

| King’s College Hospital NHS Foundation Trust | Yes | We do have comments on the areas excluded from the scope of the guideline. | Thank you for your comment. Please see the full response to the comments made by the British Menopause Society above, which raised the same issues. |
11. **Areas excluded from the scope of the guideline (NG23):**

- Health implications of early menopause 40-45 years of age.
- The role of HRT in the prevention and treatment of osteoporosis.
- HRT use after breast cancer and in women with familial breast cancer.

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<tr>
<th>Stakeholder</th>
<th>Overall response</th>
<th>Comments</th>
<th>NICE response</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Eve Appeal</td>
<td>Yes</td>
<td>We imagine the next iteration may change as we are moving to an era where research is looking at conservation of ovaries for the younger woman with just removal of Fallopian tubes, see the PROMISE programme led by Dr Ranjit Manchanda at St Barts.</td>
<td>Thank you for your comment. We did not identify any eligible evidence on this issue; therefore, an update is not necessary at this time.</td>
</tr>
<tr>
<td>British Menopause Society (BMS)</td>
<td>Yes</td>
<td>The British Menopause Society does have comments on equality issues.</td>
<td>Thank you for your comment. We appreciate these points being raised, but unfortunately, we did not identify any new evidence supporting these views that could inform an update to this surveillance review. We would consider a</td>
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</tbody>
</table>

### 3. Do you have any comments on equality issues?

<table>
<thead>
<tr>
<th>Stakeholder</th>
<th>Overall response</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Besins Healthcare UK Ltd</td>
<td>No</td>
<td>Not answered</td>
</tr>
<tr>
<td>British Acupuncture Council</td>
<td>No</td>
<td>Not answered</td>
</tr>
<tr>
<td>British Menopause Society (BMS)</td>
<td>Yes</td>
<td>The British Menopause Society does have comments on equality issues.</td>
</tr>
</tbody>
</table>

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## Appendix B: Stakeholder Consultation Comments Table for 2019 Surveillance of Menopause: Diagnosis and Management (2015)

<table>
<thead>
<tr>
<th>Stakeholder Comments</th>
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</thead>
<tbody>
<tr>
<td><strong>Equality issues that need to be considered in an updated guideline:</strong></td>
</tr>
<tr>
<td>A. A recent DoH taskforce acknowledged inequalities of HRT prescribing with no uniformity across England and Wales. CCG formulary issues should be addressed by NICE in an updated guideline. This would promote evidence based good prescribing practice and limit the current practical issues associated with post-code variations.</td>
</tr>
<tr>
<td>B. Women who experience early menopause (40-45) are not fully addressed in the original guideline and their care can be sub-optimal. Symptom management is discussed, but there is little reference to the potential impact of an early menopause on bone and cardiovascular risk in this group.</td>
</tr>
<tr>
<td>C. Recent evidence shows that women with HIV have problems accessing menopause care. This needs to be addressed in an updated guideline.</td>
</tr>
<tr>
<td>D. In addition, the original guideline makes no reference to women with learning disabilities who have problems accessing menopause care. This needs to be addressed in an updated guideline.</td>
</tr>
<tr>
<td>E. Transgender issues and HRT should be addressed in an updated guideline, as per the guidance from the recent position statement from the Royal College of General Practitioners. <a href="https://www.rcgp.org.uk/policy/rcgp-policy-areas/transgender-care.aspx">https://www.rcgp.org.uk/policy/rcgp-policy-areas/transgender-care.aspx</a></td>
</tr>
</tbody>
</table>

We will look for evidence in these areas again in the next surveillance review.

However, in the absence of any measures of reduced access to or uptake of services for the groups listed in your comment it is difficult to ascertain how an updated guideline would help.

We have been unable to find publicly available information on the Department of Health and Social Care taskforce by web-searching and a separate search on the gov.uk website.

We did not identify new evidence that quantifies the effects of early menopause.

We did not identify any information that could inform an update to the guideline for women with HIV. We expect services to follow recommendations on individualised care. The guideline contains the following recommendation:

> 'Adopt an individualised approach at all stages of diagnosis, investigation and management of menopause. Follow recommendations in the NICE guideline on [patient experience in adult NHS services.](https://www.nice.org.uk/guidance/CG167)'

NICE also has a guideline on [care and support of people growing older with learning disabilities](https://www.nice.org.uk/guidance/NG34), which has the following recommendation:

> 'Discuss with people the changes that may occur with age. Ask them about and monitor them for symptoms of common age-related conditions or changes in any existing conditions, including menopausal symptoms…'

We did not identify any information that would support an update of the guideline to address the use of HRT in transgender people. It is unclear whether the comment is referring to specific hormonal...
Pelvic, Obstetric and Gynaecological Physiotherapy

No

Not answered

Thank you for your response.

Royal College of Nursing

Yes

The guideline group needs to address inequality issues across CCGs and Trusts. Inequalities in accessing advice and specialist care where needed and inequalities in formulary updates and availability. Women with HIV are missing out on good menopause care, despite complex needs – this needs addressing

Thank you for your comment. We did not identify any information that could inform an update to the guideline for women with HIV. We expect services to follow recommendations on individualised care. The guideline contains the following recommendation:

'Adopt an individualised approach at all stages of diagnosis, investigation and management of menopause. Follow recommendations in the NICE guideline on patient experience in adult NHS services.'

Shionogi Limited

Yes

We believe that the NICE guideline aims to promote best practice and reduce clinical variation across the United Kingdom. The proposal to not review ospemifene would lead to further variation in the United Kingdom with women in Scotland able to access ospemifene following the positive SMC guidance to use ospemifene with in its full licensed indication.

We hope NICE will consider updating this guideline section (Managing Urogenital Atrophy) with ospemifene clinical efficacy, safety and cost-effectiveness analysis to

Thank you for your comment. However, we have decided to update the sections of the guideline on urogenital atrophy and risks and benefits of HRT to consider the new treatments ospemifene and prasterone. We initially proposed not to update this section of the guideline because we thought that these treatments would not have a substantial impact on NHS resources. However, with the publication of a new study on the risks of breast cancer with HRT use (see above) we decided that the section on risks and benefits

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<table>
<thead>
<tr>
<th>Target Ovarian Cancer</th>
<th>No</th>
<th>Not answered</th>
<th>Thank you for your response.</th>
</tr>
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<tbody>
<tr>
<td>The Royal College of Obstetricians and Gynaecologists</td>
<td>Yes</td>
<td>The RCOG feels that an updated guideline should be as accessible as possible – offering prescribers and professionals the opportunity to devise and deliver relevant information for all patients. Where possible, population differences in the experiences of the menopause and its management should be highlighted. The needs of the transgender population should be considered in an updated guideline. The RCOG also endorses the BMS position on national inequalities of the prescription and CCG availability of HRT, highlighting of the needs of women with an early menopause and women with HIV going through the menopause. References added for interest: This is not a comprehensive list - there are more references related to the impact of HRT on CVD risk in women of different ages. NICE should also be aware of data regarding the impact of stopping HRT on the incidence of cardiac events. Prev Med Rep. 2019 Jul 14;15:100955. doi: 10.1016/j.pmedr.2019.100955. eCollection 2019 Sep.</td>
<td>Thank you for your comment. Please see the response to the comment by the British Medical Society, which raised similar issues. We identified a range of studies of HRT reporting on cardiovascular outcomes. Overall, the new evidence was generally consistent with the guideline's conclusions about cardiovascular risks associated with HRT use. The study by Malek et al. (2019) is cohort study that performed analyses by comparing mortality in women with early menopause (defined as younger than 45 years) with that of women who had menopause at 45 years or older. It did not report any direct comparisons of mortality in HRT users compared with no-HRT use. Therefore, the results do not provide information that could be used to develop further advice on the use of HRT in women with early menopause. The study by Anderson et al. (2017) was identified in the search but was excluded from surveillance because it focuses on women with breast cancer who received treatment with chemotherapy and goserelin. The study by Xue et al. (2019) measured anti-Müllerian hormone in women with hormone-receptor-positive breast cancer before chemotherapy to predict amenorrhoea after treatment. The study by Malisic et al. (2018) measured anti-Müllerian hormone in women with early menopause.</td>
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Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

The association of age at menopause and all-cause and cause-specific mortality by race, postmenopausal hormone use, and smoking status.
Malek AM1, Vladutiu CJ2, Meyer ML3, Cushman M4,5, Newman R6, Lisabeth LD7,8, Kleindorfer D9, Lakkur S10, Howard VJ11.
The utility of anti-Müllerian hormone in the diagnosis and prediction of loss of ovarian function following chemotherapy for early breast cancer.
Anderson RA1, Mansi J2, Coleman RE3, Adamson DJA4, Leonard RC5.
Pretreatment anti-Müllerian hormone-based nomogram predicts menstruation status after chemotherapy for premenopausal women with hormone receptor-positive early breast cancer.
Xue C1, Wei W1, Sun P1, Zheng W2, Diao X1, Xu F1, Huang J1, An X1, Xia W1, Hong R1, Jiang K1, Huang R1, Yuan Z1, Wang S1, Li A2, Zou R2, Shi Y3.
The utility of anti-Müllerian hormone in the diagnosis and prediction of loss of ovarian function following chemotherapy for early breast cancer.

Müllerian hormone in women after different treatments for breast cancer. Therefore, these studies will be considered in the next surveillance of NICE’s guideline on early and locally advanced breast cancer.
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| Anderson RA1, Mansi J2, Coleman RE3, Adamson DJA4, Leonard RCF5 | | We do have comments on equality issues.  
**12. Equality issues that need to be considered in an updated guideline:**  
A recent DoH taskforce acknowledged inequalities of HRT prescribing with no uniformity across England and Wales. CCG formulary issues should be addressed by NICE in an updated guideline. This would promote evidence based good prescribing practice and limit the current practical issues resulting from this.  
Women who experience early menopause (40-45) are not fully addressed in the original guideline and their care can be less than optimal. Symptom management is discussed, but there is little reference to the potential impact of an early menopause on bone and cardiovascular risk in this group.  
Recent evidence shows that women with HIV have problems accessing menopause care. This needs to be addressed in an updated guideline. |
| Malisic E1, Susnjar S2, Milovanovic J3, Todorovic-Rakovic N3, Kesic V4. | | Thank you for your comment. Please see the full response to the comments made by the British Menopause Society above, which raised the same issues. |
| King’s College Hospital NHS Foundation Trust | Yes | |

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<th>Thank you for your response.</th>
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