Menopause

Consultation on draft guideline - Stakeholder comments table

1 June 2015 – 13 July 2015

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
University Hospitals Southampton NHS Foundation Trust	Full	18 58	21 27	If FSH is to be measured in women > 45 years with an atypical presentation how will the results be interpreted? It has long been recognised that FSH levels may rise and then fall again into the reference range. Normal biochemical values can be seen in 30% of cycles early in the perimenopause and ovulatory cycles have been reported right up to the time of the menopause. This makes it difficult to define a threshold level. The data of Burger et al (1999) identifies a cut-off level of FSH of 107.9 IU/L as having a sensitivity of 85% and a specificity of 76% for postmenopausal status although this FSH level is inevitably rather high to be practically useful. Different reference ranges for gonadotrophins would be more appropriate in older women, where there is evidence showing significantly increased gonadotrophin levels (albeit with assays not currently in use in the UK) across the whole menstrual cycle in older women with normal cycles (Lee et al 1988) and confirmed in the late reproductive (stage 3) described in the STRAW classification (Harlow et al, 2012). References: Burger HC, Dudley EC, Hopper JL, Groome N, Guthrie JR, Green A, Dennerstein L JCEM 1999 84 4025-4030 Prospectively measured levels of serum FSH, oestradiol and dimeric inhibins during the menopausal transition in a population-based cohort of women; Lee SJ, Lenton EA, Sexton L, Coke, LD Human reproduction 1988 3 851-855 The effect of age on the	Thank you for your comment. The publications by Burger 1999, Lee 1988, and Harlow 2012 were excluded from the systematic review because they have a different study design from the one specified in the review protocol (see Appendix D). The diagnostic accuracy of FSH was assessed as part of the review question on diagnosis of menopause. The GDG did not set specific thresholds for diagnostic tests as part of the selection criteria of included studies nor did they find evidence for different thresholds of each test. The GDG agrees with the comment on fluctuation of FSH over short periods of time during the years leading up to the menopause and based also on the reviewed evidence which concluded that menopause in otherwise healthy women over 45 years old should be diagnosed without the use of laboratory tests. In addition, the GDG recommends that FSH should not be used as a diagnostic tool of menopause in women using combined oestrogen and progestogen contraception or high-dose progestogen.

				cyclical pattern of plasma LH, FSH, oestradiol and progesterone in women with regular menstrual cycles; Harlow SD, Gass M, Hall JE, Labo R, Make P, Rebar RW, Sherman S, Sluss PM, de Villiers TJ, Menopause The Journal of the North American Menopause Society, 2012 10 1-9 Executive summary of the Stages of Reproductive ageing workshop +10: addressing the unfinished agenda of staging reproductive aging.	
University Hospitals Southampton NHS Foundation Trust	Full	18 58	21 27	If samples are taken at mid-cycle measurement of LH may be necessary to identify this i.e. FSH levels above the upper reference limit to 45 IU/l.	Thank you for your comment. Although the GDG searched for diagnostic accuracy studies looking at a combination of tests or algorithms for diagnosis of menopause, no studies were found to consider the use of LH in combination with FSH for diagnosis of menopause.
University Hospitals Southampton NHS Foundation Trust	Full	18 57	21 27	There are several different manufacturers producing reagents for measurement of gonadotrophins that are in use across the UK and associated with these there is variability in bias. For the 5 most common methods the difference in bias between the highest and the lowest values is 17% (Cathy Sturgeon, UK-National External Quality Assessment Scheme, Edinburgh). Reference ranges should reflect assay bias.	Thank you for your comment. The GDG did not set specific thresholds of diagnostic tests as part of the selection criteria of included studies and we considered the evidence for different thresholds of each test. Reference to FSH values as presented in the included studies is given when the evidence was summarised. Although the recommendations do not refer to specific ranges or assay methods, we appreciate that there may be an assay bias on the interpretation of results and this is now reflected in the LETR section of the Chapter 5 of the full guideline.
Menopause UK	Full	Gen		We welcome the development of the guidelines as a significant achievement by all of the members of the guideline development group	Thank you for this comment.

	l	eral		as well as the wider team at NICE and the NCCWH. We applaud the care that has gone into their development. The guidelines demonstrate very clearly that menopause is a significant health issue, affecting many women's quality of life, employment, and long-term health, and – crucially – that effective help is possible. Overall we consider the guidelines to be very comprehensive. Our comments are focused towards maximizing the impact of the guidelines so that they: ▪ provide the clearest possible information for women and their carers; and ▪ lead to tangible improvements in the quality of women's health and care. In addition, we make detailed observations and suggestions on X clinical aspects of the guidelines, based on our insights into women's experiences in relation to: ▪ low mood and anxiety ▪ management of type two diabetes in menopause ▪ altered sexual function/testosterone ▪ transdermal v. oral HRT.	
Menopause UK	Ful	Gen	Gen	***The audience for these guidelines***	Thank you for your comment. A key aim of the guideline is to provide education for healthcare professionals and so it is essential that the important

	l	e r a l	er al	Utilising the **Stages of Change** approach, many healthcare professionals involved in the care of women seeking help for menopausal symptoms are likely to be in the **pre-contemplation stage**. In other words, they are unaware of the need to change (e.g. by improving their level of knowledge and reviewing the way they provide care). This fact has important implications for the way the guidelines are communicated to health professionals. It is an unfortunate reality that in many cases the end users of these guidelines at the time of publication will be health professionals who: ▪ are not up to date with current clinical advice or evidence relating to menopause ▪ will not recognize that they are not up to date ▪ will adhere strongly to outdated or wrong information. This is unsurprising given that menopause is often only covered in the most cursory manner in undergraduate medical or nursing training, if at all. Even during GP Registrar training, menopausal health post-reproductive health is not highlighted with any importance even though primary care practitioners will see the vast majority of menopausal women. The lack of formal clinical and academic education about menopause means that many health professionals will have formed their beliefs about menopause based on information from other sources. The	information is available in the recommendations and the care pathway, which will be supported by the implementation team at NICE. This comment has been forwarded to the NICE implementation support team to inform their support activities for this guideline. The GDG has worked to ensure the advice given is evidence-based and easy to follow. They agree about the importance of having a clear care pathway and have amended this in light of stakeholder feedback. Thank you for your offers of help.

				misinterpretation and misreporting of the Women's Health Initiative study and subsequent media coverage, plus deep-rooted social and cultural attitudes towards menopause, continue to influence the beliefs, behaviours and clinical practice of many health professionals. As a result, many health professionals, like the general public, tend to: ▪ overestimate the risks of HRT ▪ assume that the contraindications for HRT use are far more extensive than the guidelines state they are ▪ underestimate the impact of problematic menopausal symptoms on women's quality of life and ability to function ▪ fail to recognize menopause related health issues, or dismiss them as trivial ▪ assume that the alleviation of problematic menopausal symptoms does not merit the perceived risks of HRT. Working with a **Stages of Change** approach, the impact of the guidelines will be maximized when health professionals: ▪ are **concerned** about menopause as a condition which can seriously affect women's quality of life and long term health; ▪ **recognize** the symptoms of menopause and are able to take responsibility for confidently diagnosing it and managing it in women of all ages; and ▪ **believe** that it is possible to provide effective management and	

				treatment which will improve women's health and quality of life. There are a number of areas where the current draft could be improved to support implementation of key recommendations. In particular, we suggest work to: ▪ Clarification by the GDG and NICE of ***Fig. 1 The Care Pathway*** to remove anomalies and improve user-friendliness ▪ Provision by the GDG and NICE of additional summary material on key issues to provide 'at a glance' summary information, focusing on areas of clinical decision making where prescribers are likely to hold outdated beliefs (e.g. contraindications for HRT, impact and severity of menopause on health, recognition of menopausal symptoms and diagnosis) ▪ Provide additional material in the form of infographics to support women and healthcare professionals in understanding the risks and benefits of HRT and the impact and severity of menopause on health. Menopause UK would be happy to contribute to the implementation of the guidelines by developing the infographics referred to under the last bullet point above, and presenting them to NICE for endorsement. Assistance from NICE in the final stages, in the form of graphic design support once content has been agreed and finalised, would be appreciated.	
NHS	F	G	G	The Digital Assessment Service welcome the guidance and have no	Thank you for this comment.

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Choices	ull	eneral	eneral	comments as part of the consultation	
Royal College of Obstetricians and Gynaecologists	Full	General	General	This guideline is extremely comprehensive, well-written, clear and easy-to-read.	Thank you for this comment.
Royal College of Obstetricians and Gynaecologists	Full	General	General	The flowchart algorithm starts with woman aged 40ys. However, the recommendations all addresses the diagnosis in women aged 45 or more. Would be good to amend the chart accordingly or explain what happens between 40-45ys in the flowchart.	Thank you for your comment. The care algorithm starts with the age threshold of 40 years to clarify the distinction between menopause and POI which requires a different diagnostic and management pathway. However, we appreciate that this algorithm was not clear about the group of women between 40 to 45 years and this has now been amended.
Royal College of Obstetricians and Gynaecologists	Full	General	General	We wondered why, in section 10, there was no mention of: • The association between HRT and ovarian cancer *(Lancet 2015; 385: 1835-42)* • Colon cancer • The risks (or indeed protective effects) of different progestogen regimens on endometrial cancer	Thank you for your comment. These areas were not prioritised for inclusion following the NICE stakeholder workshop and public consultation of the scope.

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Royal College of Obstetricians and Gynaecologists	Full	General	General	The glossary is excellent	Thank you for this comment.
Royal College of Obstetricians and Gynaecologists	Full	General	General	Again an excellent explanation of terms and acronyms	Thank you for this comment.
Royal College of General Practitioners	Full	General	General	The draft guideline is generally very well done and most helpful however, in some ways contradicts Menopause Matters and other on-line advice sites.	Thank you for your comment. The GDG acknowledge how the process of developing guidelines may differ by organisation. It is expected that these organisations will update their information after the guideline is published. The NICE guidance is based on the best available clinical and cost effectiveness evidence. These recommendations were developed by topic-specific experts with clinical knowledge and experience of menopause.
Royal College of General Practitio	Full	Gener	General	There is no distinction made between different brands of HRT. Does the brand or dose make a difference? Patches are recommended but there is only one brand combined patch on the market – otherwise it is an oestrogen patch with oral progestogen monthly or three monthly. The College suggests more detail over prescribing and the implications of the study for prescribing	Thank you for your comment. It is beyond the scope of the guideline to review particular brands of medicines. However, the GDG consider the impact of different dosages of the same treatment upon the conclusions where data were available (please see NMA protocol

ners		al		would be helpful. For this reason the guidance is likely to be perceived as helpful but not enough.	in the Appendix K for more information).
Royal College of General Practitioners	Full	General	General	The guideline keeps making a recommendation of referring to a HCP with expertise in menopause, which is not precise enough. Does it mean a gynaecologist or the specialist Menopause clinic in London or the nurse practitioner who has been on a course or who is following this guideline? Local pathways will need to be made and commissioning implications follow.	Thank you for this comment. The expertise and remit of a menopause specialist is defined by the professional societies in this field and defining this is beyond the scope of this guideline development. The GDG accept that this may also differ according to local pathways.
London North West Healthcare NHS Trust	Full	General	General	General response to guidelines This guideline refers repeatedly to a recommendation to refer to specialists. Who will be the specialists? Will they be special clinics, or will they be GPs designated to care for menopausal women within a practice. What training will you need to be deemed a specialist?	Thank you for this comment. The expertise and remit of a menopause specialist is defined by the professional societies in this field and is beyond the scope of this guideline development.
London North West Healthcare NHS Trust	Full	General	general	in the scope it mentions Clonidine would be covered but I cannot find the evidence review for this licensed treatment or a recommendation?	Thank you for your comment. The GDG searched for the evidence on the effectiveness of clonidine's treatment to relieve short term menopause symptoms. A total of 10 studies related to clonidine were reviewed, however none of them met the inclusion criteria in the review protocol or reported data in a way that it could be used in the analysis (pair-wise or network meta-analysis). The exclusion reasons for these 10 studies were: - commentary and discussion papers (2 studies with no information on authorship), - 4 results couldn't be used in the analysis because either in graphs (Buijs 2009) or given by composite scores (Lindsay 1978; Salmi 1979; Gerdes 1982);

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					- not appropriate study population (Loprinzi 1994), - not appropriate study design and methodology (Edington 1980, Wren 1986), - non English paper (Schindler 1984). For further details of exclusion reasons please see Appendix G. However, the GDG discussed the use of clonidine for relief of menopausal symptoms and recommended that information should be given to women for the different options of pharmacological and non-pharmacological treatment of menopausal symptoms.
London North West Healthcare NHS Trust	Full	General	General	We welcome the inclusion of Premature ovarian insufficiency as a special group for recommendations, but consider that management should not be limited to adequate hormone replacement therapy. Recommendations are principally medical in origin and make little reference to adjunctive psychological support which we consider should routinely be offered along with HRT. Insufficient discussion of psychological sequalae of POI.	Thank you for your comment. The GDG agree that ensuring the psychological health of a women with premature ovarian insufficiency is equally as important as ensuring her physical health and have highlighted this in a recommendation for referral to health professionals with relevant experience who can facilitate management of all aspects of physical and psychosocial health related to their condition.
UK Clinical Pharmacy Association	Full	General	General	We welcome this guidance on menopause management, including its recognition and assessment of the evidence base for co-morbidities (diabetes, dementia, sarcopenia) with associated ageing that the population living longer will face. It provides for a framework to assist health professionals' management of women going through the menopause. This NICE guidance will help us to provide pharmaceutical advice and support to all health professionals via our UKCPA Women's Health Group of specialist pharmacists and for medicines optimisation when directly	Thank you for this comment.

				supporting patients.	
Primary Care Women's Health Forum	Full	General	General	This guideline is extensive and answers many questions that women ask their primary healthcare provider and provides excellent evidence to support women during the menopause. The PCWHF members are very supportive of this document	Thank you for this comment.
Primary Care Women's Health Forum	Full	General	General	No comment about contraception use and menopause – other than use of COC for women with POI as an alternative to HRT	Thank you for your comment. Although provision of contraception during menopause was not within the guideline scope, the GDG recognises the importance of addressing contraception needs for women who are in the perimenopausal and postmenopausal period and have added a recommendation.
Primary Care Women's Health Forum	Full	General	General	It would be helpful to have a flow chart of recommendation of HRT prescribing for primary care clinicians who do not have an interest or to signpost to other resources – Map of Medicine, Menopause matters	Thank you for your comment. The purpose of the care algorithm is to provide a summary of the basic steps of care for women presenting with menopausal symptoms. This algorithm has been amended after public consultation to improve clarity. Because this guideline systematically evaluates evidence using the methodology outlined in the NICE guideline manual 2014 which may lead to reaching different conclusions compared with other guidance, it does not typically signpost to other resources.
British Menopause Society	Full	Gene	Gener	Overall I think this is an excellent document and it provides a high level of detail to assist those designing and delivering specialist or general menopause care. Overall the recommendations are sound, practical and on the most part, deliverable. With modest refinement this guideline will	Thank you for this comment.

		ral	al	undoubtedly become the definitive guideline that will have reach beyond that of the UK	
British Menopause Society	Full	General	General	For the 'description of included studies' tables such as those in section 7.4 and further on in the document might it not be useful for them to have a column for the GRADE rating of the quality of the evidence? That would help readers when they come to read the sections on evidence statements	Thank you for your comment. The quality of evidence is assessed on outcome and not on study level following the GRADE approach. Detailed description of quality assessment per individual study is given at Evidence Tables (Appendix H). Please refer to GRADE tables (Appendix I) for detailed description of downgrading the quality of evidence and refer to evidence statements in the full guideline for a summary of the evidence quality.
British Menopause Society	Full	General	General	The evidence statements would be much easier to read were they to state which paper is being quoted as being of 'low quality' for example. This would aid those who wish to read more into the evidence behind your conclusions and possibly to challenge at a later date	Thank you for your comment. The evidence statements are based on the outcomes as presented in the GRADE tables (Appendix I). The GRADE tool is used to evaluate various quality domains of the evidence, including the certainty around the effect size for outcomes pooled across studies rather than at the individual study level. The overall quality statement reflects the confidence in the results and the implications for decision making. Please see section 3.3.5 in the full guideline for further information on formulation of evidence statements. Please note also that referencing studies in evidence statement does not follow the standard methods described in the NICE Manual.
British Menopause Society	Full	Gene	Gener	I accept the enormity of my suggestion but I do find it amazing that only short term measures were considered in the overall economic evaluations. The answer we all want to see is whether long term HRT actually makes sense from an economic standpoint when you take into account benefits such as	Thank you for your comment. A decision was made from the outset to restrict the economic evaluation to short term treatment (up to 5 years). Studies have not been undertaken that have evaluated the different

		r a l	al	symptom control, osteoporosis, CVD etc against the costs of risks and that of HRT itself. I do see the lack of this as a big disappointment and a potential major flaw and criticism of the document.	classes of treatment for menopausal symptoms and their long term risks; only models comparing HRT versus no HRT. It was the GDG's view that an updated model evaluating the long-term health economic model comparing HRT with no HRT would be of little value in a clinical decision-making scenario which takes into account the specific risks of the individual woman. The GDG didn't find a benefit for CVD and its inclusion in the model would therefore have added additional complexity for limited added value. The decrease in the number of fractures in our age group is small and so again the impact on the cost-effectiveness was likely to be negligible. Furthermore, the group acknowledged how the remit was to inform women on the risks and benefits of HRT rather than recommending them to take something for disease prevention.
British Menopause Society	F u l l	G e n e r a l	G e n er al	I consider myself to be a senior clinician with a reasonable ability to read and understand scientific information. The economic arguments are however extremely difficult to understand and I think a 'real world' version of appendix L is required. Some summarising will be required but I think this will be a good investment towards the readability of the document.	Thank you for this comment. It is acknowledged that Appendix L uses technical language, although the "economic evidence" in 7.6 is intended to summarise Appendix L and revisions have been made to this section to try and improve the readability for a non-technical audience.
British Menopause	F u l	g e n	g e n	Why are there no references to the meta-analyses of RCTs showing significantly reduced CHD in those initiating HRT aged <60 years or <10 years postmenopause? (Salpeter SR, Walsh JME, Greyber E, Salpeter EE.	Thank you for this comment. The systematic review on HRT use and cardiovascular diseases was led by the evidence that met the inclusion criteria set out in

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Society	l	e r a l	er al	Coronary heart disease events associated with hormone therapy in younger and older women. J Gen Intern Med 2006; 21: 363-66 / Boardman et al. Cochrane Database Syst Rev 2015; DOI: 10.1002/14651858.CD002229.pub4)	the relevant systematic review protocols (Appendix D). We have checked carefully the evidence suggested in your comment and these were not included for the following reasons: • Salpeter et all 2006 was a meta-analysis but not a systematic review and no clear inclusion criteria were reported to allow the way the evidence was collected. In addition, most of the studies reported CHD as an adverse event and not as primary outcome. • Boardman et al 2015 Cochrane review was published after our cut off time point for the latest searches of evidence before the guideline going out for the stakeholders consultation. However, we now considered carefully this review and this doesn't fit with our review protocol due to differences in the inclusion criteria for population characteristics and outcomes. The analysis for both reviews pooled all HRT types whereas the GDG considered different types of HRT separately (for example, results from trials reporting the effect of oestrogen plus progestogen intervention and the effect of oestrogen alone on CHD effect). In addition, the GDG considered results separately for trials that haven't provided subgroups by different type of HRT. Although these references were not included in our

					evidence base for this review question, we considered all their individual studies for inclusion. All the individual studies from both references that matched our review protocol were already part of our evidence base (PEPI 1995; WHI 2002; WHI 2004, DOPS 2012).
British Menopause Society	Full	General	General	General response to guidelines This guideline refers repeatedly to a recommendation to refer to specialists. Who will be the specialists? Will they be special clinics, or will they be GPs designated to care for menopausal women within a practice. What training will you need to be deemed a specialist? Covered in other part of BMS response	Thank you for your comment. The expertise and remit of a menopause specialist is defined by the professional societies in this field and is beyond the scope of this guideline development. This comment has been forwarded to the NICE implementation support team to inform their support activities for this guideline.
British Menopause Society	full	general	general	in the scope it mentions Clonidine would be covered but I cannot find the evidence review for this licensed treatment or a recommendation?	Thank you for your comment. The GDG searched for evidence on the effectiveness of treatment with clonidine to relieve short term menopause symptoms. Studies on clonidine were excluded due to either incomplete outcome reporting (data were reported only in medians and ranges, data reported without measures of uncertainty (standard deviation or confident interval) or the relevant outcome data being reported as part of a composite score. However, the GDG discussed the use of clonidine for the relief of menopausal symptoms and recommended that

					information should be given to women about the different options of pharmacological and non-pharmacological treatment of menopausal symptoms.
British Menopause Society	Full	General	General	I found this document to be very comprehensive and inclusive	Thank you for this comment.
British Menopause Society	Full	General	General	'Menopause' is a mis-nomer where Dr's/Patients are often talking at cross-purposes. I could not find any reference in the document explaining this.	Thank you for your comment. The guideline uses the definition of menopause which is outlined in the glossary.
Pharma Care Europe	Full	General	General	There are numerous examples in the Guideline whereby Isoflavones (whether red clover-based or soy-based) are grouped together with Black Cohosh, other herbal preparations and biomedical hormones as a single entity. Firstly, we do not feel this is acceptable as each of these separate non-hormonal treatments will have its own method of action as well as its own set of limitations. Secondly, we are concerned that healthcare professionals will treat these separate non-hormonal treatment options as one broad category rather than look at each of them individually for their own merits.	Thank you for your comment. Although these treatments are often grouped under the heading of non-pharmacological or herbal treatments to collect them into different sections of the guideline, they have been analysed separately where possible. Different types of isoflavones (e.g. red clover, genestein, soy) have been grouped together as these are considered to have a similar mechanism of action. However, other non-pharmacological treatments such as black cohosh and valerian root have been reported separately and are not pooled. There were some instances where study authors did not specify accurately which type of Chinese herbal medicine was used, and in these

					cases we have grouped these unknown treatments under "Chinese herbal medicine".
Cornwall Menopause Referral Service	FULL	General	General	We still do not understand why black cohosh comes out so favourably on cost effectiveness..	Thank you for this comment. The relative cost-effectiveness of black cohosh, is driven largely by the results of the network meta-analysis which we consider to be the best available evidence on the relative treatment effects of the different treatment alternatives in terms of the impact on frequency of hot flushes. Figure 71 in Appendix K shows that black cohosh has the 2nd lowest mean ratio for the relief of vasomotor symptoms for women with a uterus and that this is a statistically significant result. Table 9 of Appendix K, shows that in the network meta-analysis, black cohosh has the 2nd highest probability of being the most effective treatment and the probabilistic sensitivity analysis for the economic modelling, which gives the probability of black cohosh being the most cost-effective treatment, will reflect this. However, at lower symptom severity black cohosh has a higher probability of being cost-effective because of its lower cost relative to non-oral oestrogen plus progestogen and lower risk of breast cancer and VTE. However, as symptom severity increases (clinical effectiveness becomes a more important driver of cost-effectiveness) the probability of black cohosh being the most cost-effective treatment declines - see Figure 93 of Appendix L. The discussion of results in the LETR has been amended to make this clearer.

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Derbyshire Community Sexual Health Service	full	general	general	Advise Check all occurrences of 'VSM' ? should it be 'VMS'	Thank you for your comment, this has been amended.
NCRI - Breast CSG Working Group on Symptom Management	FULL	GENERAL	GENERAL	The section Review and Refer should include women who prefer not to use HRT as well as women who have contraindications. Could this be rephrased?	Thank you for your comment. A recommendation was added at the beginning of the information section about the different options on pharmacological and non-pharmacological treatment of menopausal symptoms.
National Osteoporosis Society	Full	General	General	We welcome the guideline which recognises the increased risk of osteoporosis in postmenopausal women. Although the guideline does not cover treatment of chronic diseases such as osteoporosis, exploration of the long-term health risks and benefits of HRT are helpful. We believe that the guideline will aid health professionals in discussions with patients considering use of HRT to tackle menopausal symptoms.	Thank you for this comment.
National Osteoporosis Society	Full	General	General	Although outside the scope of the guideline, it may be helpful to note that the National Osteoporosis Society has produced a position statement on use of HRT for the treatment and prevention of osteoporosis. This is available online at: https://www.nos.org.uk/health-professionals/resources/our-statements. Our position statement states that HRT has a role to play in the treatment of osteoporosis in postmenopausal women under the age of 60.	Thank you for your comment. The GDG have noted this reference to existing NICE guidance on osteoporosis: assessing the risk of fragility fracture.

		l		HRT is recommended in those with early menopause until the normal age of menopause (around 50 years), but is not considered suitable in women over 60.	
The Daisy Network	Full	General	General	It is very welcome that POI – a life altering condition and an umbrella term that includes iatrogenic and spontaneous aetiologies - has been recognised as different from typical age menopause, and that therefore management may also differ (eg Hormone Therapy for the typical aged woman is based on risk-benefit ratio & is largely a matter of individual choice; Hormone Replacement Therapy for POI is recommended to *replace* premature loss of estrogens). However, we believe that several areas surrounding the care of women with POI have not been sufficiently covered within the new guidelines.	Thank you for your comment. The GDG acknowledge the importance of different areas care of women with POI that were not covered within this guidance. However, the scope of this guideline was large and topics had to be prioritised for inclusion. The GDG agree that POI needs specialist attention, and have added a recommendation about referring women with POI to health professionals with relevant experience, who can facilitate management of all aspects of physical and psychosocial health related to their condition.
Shionogi Limited	Full	General	General	The recent Marketing Authorisation for 60 mg ospemifene (Senshio) gives this product the licensed indication: the treatment of moderate to severe symptomatic vulvar and vaginal atrophy (VVA) in post-menopausal women who are not candidates for local vaginal oestrogen therapy. Based on the scope for these guidelines, recommendations will normally fall within licensed indications. There are no other products licensed for this specific indication and a comparison with products that are explicitly excluded from the indication (i.e. local vaginal oestrogens) would appear inappropriate and may lead to off-label prescribing. We therefore respectfully ask the GDG to consider ospemifene specifically for this group of women for whom no other prescription treatment is available. Based on the principles of the NICE equality policy, women who are not candidates for local vaginal oestrogen treatment would create a potential equality issue if a treatment like Senshio is available for this population but is excluded from the recommendations.	Thank you for your comment. The GDG is now aware of ospemifene's licence status and the evidence was discussed again.
Shionog	F	G	G	We are concerned that the quality of the data from the ospemifene trials is	Thank you for your comment. 1. The evidence was

i Limited	u l l	e n e r a l	e n er al	repeatedly been referred to as low. We consider the level of evidence high, based on the Cochrane GRADE approach to assess the levels of quality in a body of evidence. We see no reason to downgrade the level of evidence which is traditionally 'high' for randomized trials: 1. There were no limitations in the design and implementation of the trials. These were all double-blind, placebo controlled. Blinding was accomplished by supplying both dose levels of ospemifene and placebo as tablets identical in appearance. There was no large loss to follow-up (study completion was 95.6% in Rutanen 2003, 89.9% in Portman 2013, 87.6% in Portman 2014, 83% in Bachmann 2010, 81.9% in Goldstein 2014 and 77.8% in Simon 2013 respectively) and none of the trials were stopped early. 2. The evidence presented is collected in the relevant trial population. Apart from the study reported by Rutanen (2003), all subjects had to have physical signs of vulvovaginal atrophy, as determined by a proportion of superficial cells <5% in the vaginal smear and a vaginal pH <5. The evidence is collected directly against placebo as comparator. However, the subjects in the study reported by Rutanen 2003 were postmenopausal and the mean percentage of superficial cells at baseline was below 5%. The study contributed 79 subjects to the total of 1968 women reviewed (4%) and therefore has little impact on the overall result. 3. Since all 5 studies show similar results for efficacy and safety for 60 mg ospemifene the results do not display any degree of unexplained heterogeneity or inconsistency. 4. The ospemifene studies are some of the largest double blind, randomised, placebo controlled clinical trials in the indication vulvar and vaginal atrophy ever conducted. The phase 2 study reported by Rutanen (2003) was slightly smaller, but had the highest level of completers (95.6%). In addition, since the results are consistent with the other three studies, here can be	quality assessed using the GRADE approach (for full details please section 3.3.3.1, 3.3.3.2, 3.3.3.4, 3.3.3.5 in Methods Chapter of the full guideline). The GRADE approach assesses the evidence at the outcome as opposed to study level. The main reasons for downgrading the included studies was the lack of information on allocation concealment which is an important criterion for assessing the domain of risk of bias in GRADE approach. 2. The GDG agree that the evidence presented refers to the population of interest; post-menopausal women reporting symptoms of vaginal/urogenital atrophy. All included evidence was considered applicable to our population of interest. 3. In terms of the heterogeneity observed in the pooled analysis of results, this assessment followed standard approach of assessing inconsistency based on GRADE approach using both the results on chi-squared p< 0.1 and I-squared inconsistency statistic of >50% (for full details please see section 3.3.3.4 in Methods Chapter of the full guideline). 4. Imprecision on results was assessed following the GRADE approach and concerns whether the uncertainty (95% confidence interval) around the estimate of effect (risk ratio) means that it is not clear whether there is a clinically significant difference between the intervention and control arms. Therefore, imprecision in guideline development is not related to whether the point estimate is accurate or correct but it is concerned with the uncertainty around the point estimate for decision making. This uncertainty is

				little doubt about the precision of the results. 5. Publication bias is suspected when a large number of small trials demonstrate benefit. In this case, the 5 trials represent nearly 2000 patients. The data provided in the 6 publications, covering the five studies under review, are confirmed by the data available from the Senshio Public Assessment Report of the EMA (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002780/WC500182777.pdf) as well as in the US FDA Medical Reviewer's report of 60 mg ospemifene (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203505Orig1s000MedR.pdf). This also confirms the absence of any publication bias for this outcome.	reflected in the width of the confidence interval by looking at the 3 zones (clinically important benefit, clinically important harm or no clinically important benefit or harm) as defined by the Minimally Important Differences (MIDs). The GDG used the default MIDs to assess these three zones as defined by the GRADE approach (please see section 3.3.3.6 in Methods Chapter of the full guideline).
Royal College of Nursing	Full	General	General	Our members also point out that although the scope of the guideline mentions that Clonidine would be covered there does not seem to be the evidence review for this licensed treatment or a recommendation?	Thank you for this comment. The developers searched for evidence on the effectiveness of Clonidine, but did not find any study that matched the review protocol. Please refer to the protocol in Appendix D and to the exclusion lists in Appendix G for more information.
The Yes Yes Company Ltd	Full	General	General	Our comments on the Draft Guideline for the Diagnosis and Management of Menopause in relation to Urogenital Atrophy are based on the three and a half years of research that we carried out from 2003 – 2006 on the formulation of vaginal moisturisers and lubricants, considering safety and side effects. My background is in Pharmacovigilance and I was aware of the potential irritancy to the mucosa of the ingredients in many commercial lubricants and vaginal moisturisers. Since 2006 we have received numerous communications from women telling us that many products for Urogenital Atrophy have caused irritation. We set out to formulate products that would be free from endocrine disruptors and mucosal irritants and one that would not upset the delicate vaginal environment. We are concerned for all women	Thank you for your comment. The GDG acknowledges this concern but did not review the evidence for the various formulations of moisturisers and lubricants used for urogenital atrophy. However, adverse events and withdrawal due to adverse events were among the outcomes selected for this review and presented when available.

				suffering from Urogenital Atrophy and want to ensure that Health Professionals have the information that allows them to recommend safe and non irritating vaginal moisturisers and lubricants either on prescription or OTC.	
The Yes Yes Company Ltd	Full	General	General	We believe that all references in the Draft Guideline to moisturisers and lubricants which can be bought over the counter should give guidance to Health Professionals and patients about the importance of selecting correctly pH balanced products and those which have been specifically developed to be suitable for use on mucosal tissue. pH values greater than pH4.5 should also be avoided. There is new evidence available on the osmotic values of moisturisers and lubricants many of which are hyper-osmotic with the potential for epithelial cell damage thus causing irritation. Some products which are also currently available on prescription fall into this category. Use and procurement of additional lubricants for male and female condoms: WHO/UNFPA/FHI360. Advisory Note. http://apps.who.int/iris/bitstream/10665/76580/1/WHO_RHR_12.33_eng.pdf Article in C&EN on the safely of Personal Lubricants http://cen.acs.org/articles/90/i50/Studies-Raise-Questions-Safety-Personal.html Summary of results from Lab Pharmaceutical Technology, University of Ghent, Belgium for pH and Osmolality of NHS Prescription and OTC Moisturisers and Lubricants. June 2015 https://www.yesyesyes.org/pdf/pH-Osmo-Test-June-2015.pdf As a result of this evidence, and to reduce potential complications/side-effects requiring further treatment, we propose that no products with pH values greater than pH 4.5 or osmolality values greater than 1200 mOsm/kg	Thank you for your comment. The GDG acknowledges this concern but did not review the evidence for the various formulations of moisturisers and lubricants used for urogenital atrophy. However, adverse events and withdrawal due to adverse events were among the outcomes selected for this review and presented when available.

				should be prescribed or recommended.	
British Psychological Society	FULL	General	general	There is an underlying premise in this document that menopause should be accompanied by symptoms; this is not supported in the literature. Informing women that they will experience a range of symptoms might influence their expectations and hence their attributions of symptoms, such as mood, to the menopause, when other factors, for example, psychosocial factors are stronger predictors. Even in the case of vasomotor symptoms (VSM), general health, socioeconomic status and anxiety/stress (before the menopause) are key influences on how troublesome VMSs are perceived. Moreover, if 20-25% of women with VMS find them troublesome and seek medical help, then 75-80% do not. An overly biomedical perspective may be unhelpful in reinforcing negative attitudes to menopausal and mid-aged women in general.	Thank you for your comment. The guideline focuses on women with menopausal symptoms, although reference is made to some aspects of chronic disease prevention which is relevant to all women around the age of menopause. However, as stated in the introduction of the full guideline, not all women will experience a range of menopausal symptoms and not all of those women with symptoms will seek for medical treatment. However, this guidance aims to provide advice for both women and health care professionals regarding the menopause and the way symptom relief can be achieved.
British Psychological Society	FULL	General	General	The document is permeated by a lack of equipoise between hormonal and psychological intervention. Current evidence on psychological input for managing hot flushes is not included and this needs to be rectified and the studies represented. Given the equivocal information on risk of HRT the principle should be firstly do no harm. Medication should not be the first line of intervention for hot flushes or any menopausal difficulties if psychological interventions to manage responses are effective and acceptable.	Thank you for your comment. The GDG recognise the importance of providing women with information about all of the available options including hormonal, non-hormonal and psychological treatments for women with menopausal symptoms and have made this explicit when amending the recommendations. The order of recommendations is not meant to imply a hierarchy of treatment options, rather it reflects the order of chapters in the full guideline following a standard care pathway in the identification, diagnosis and management of menopause. The GDG agree that women with preferences or medical reasons for non-hormonal treatments must be included and have reiterated that information about these treatment

					options be offered. The review protocol on short term symptoms looked for the evidence on psychological treatments such as CBT to relief of menopausal symptoms (vasomotor symptoms, low mood, anxiety, sexual dysfunction). However, not all studies on the psychological treatments provide data in line with the protocol for all outcomes (for example, studies on CBT contributed to the outcomes of low mood and depression whereas relaxation contributed to both vasomotor symptoms and low mood). The evidence that met the protocol requirements is presented in Section 8 of the full guideline.
British Psychological Society	FULL	General	General	The Society also has concerns regarding the guideline's emphasis of HRT as a primary or first option treatment approach. Ongoing concerns around the long term use of HRT (*Jama,* 2002), although now considered less significant, have resulted in a general reduction in its use (Menon et al, 2007). Therefore, to reaffirm, "Medication should not be the first line of intervention for hot flushes or any menopausal difficulties if psychological interventions to manage responses are effective and acceptable".	Thank you for your comment. The order of recommendations is not meant to imply a hierarchy of treatment, rather it reflects the order of chapters in the full guideline following a standard care pathway in the identification, diagnosis and management of menopause. The GDG agree that women with preferences or medical reasons for non-hormonal treatments must be considered and have reiterated that information about these treatment options be offered. The review protocol on short term symptoms included psychological treatment options such as CBT to relieve menopausal symptoms (vasomotor symptoms, low mood, anxiety, and sexual dysfunction). However, not all studies on the psychological treatments provided data in line with the protocol for all outcomes (for example studies on CBT contributed to the outcomes of low mood and depression whereas relaxation contributed to both

					vasomotor symptoms and low mood).The evidence that met the protocol requirements is presented in Section 8 of the full guideline. The clinical and cost effectiveness analysis on the most effective treatment of reducing the frequency of vasomotor symptoms for women in menopause is presented in section 8 of the full guideline concluded that, based on available evidence, HRT is the most suitable treatment. The GDG agree that women with preferences or medical reasons for non-hormonal treatments must be considered and have recommended that they should be informed about all of the available treatment options for relief of menopausal symptoms including hormonal, non-hormonal and psychological treatments before they will be offered the choice of HRT.
British Psychological Society	FULL	General	General	Due to noted health risks of taking HRT, current guidelines imply a recommendation of using HRT for a shorter duration of time compared to the actual duration that many women report symptoms (e.g. median duration of hot flushes as being 7.4 years with maximum duration 11.4 years (Avis et al, 2015). Therefore, suggested care for VMS that occur after stopping HRT, or longer term treatment options should be provided (e.g. the effects of CBT are maintained when measured at 6 month follow up, i.e. after treatment stops, which is not the case for HRT) (Gentry-Maharaj et al, 2015).	Thank you for your comment. The GDG acknowledge this point and have added a recommendation on the provision of information regarding all the available treatment options for the relief of menopausal symptoms including hormonal, non-hormonal and psychological treatments. In addition the GDG added a recommendation to consider referring to a healthcare professional with an expertise in menopause those women who are identified in the review appointment with ongoing symptoms, contraindications to HRT or if there is uncertainty about the most suitable treatment options for their menopausal symptoms.
British Psychol	FU	Ge	Ge	A biospsychosocial approach should be the basis of the guidance rather than	Thank you for your comment. The GDG agree with your argument and this is captured in the introduction

ogical Society	LL	neral	neral	an overly biomedical approach given that the menopause is a highly variable process influenced very much by psychosocial and cultural factors, beliefs, attitudes, past and current environmental factors, and socioeconomic factors (Archer et al, 2011). "A bio-psycho-social multi-disciplinary approach consistent with recent NHS developments around helping patient's take charge of their care when dealing with longer term health symptoms (e.g. Department of Health, 2009, www.nice.org.uk) is very much needed."	of the guideline. The GDG also acknowledges the importance of psychosocial factors in the management of menopause and a recommendation was added on provision of information to women regarding all the available treatment options for the relief of menopausal symptoms including hormonal, non-hormonal and psychological treatments before the offer of a specific treatment.
University Hospitals Southampton NHS Foundation Trust	Full	12	General	Guidance on which days to test for the perimenopause for women who are still menstruating is included for the premature menopause (measure FSH on day 3–5 of the cycle) in the CKS but not the full guidelines and not for women >45 years . This guidance would be beneficial; again there was significant variability in the advice being given by UK NHS laboratories with 6 different regimens employed.	Thank you for your comment. The GDG agree that interpretation of FSH in the perimenopause depends on the phase of the cycle when measurements were taken. FSH measurement is only recommended in women aged under 40 and 40-45 with cycle disturbance (oligo-amenorrhoea). The recommendation and linking evidence to recommendation section of the guideline have been amended to reflect this.
Novo Nordisk	Full	General	General	Novo Nordisk appreciates the extensive work and efforts involved in the NICE clinical guideline review process and are thankful for this opportunity. We request that the below information is kindly considered to help in updating the NICE Menopause guidelines as it is important that they accurately reflect the licensed status of existing medicines.	Thank you for your comment. The GDG considered the evidence for each treatment in light of its licensed indication and it is expected that they are prescribed in accordance with the Summary of Product Characteristics. Where a treatment is prescribed off-label, this this been noted.
Royal College of Pathologists	Full	General	General	Units of measurement for biochemistry tests quoted vary throughout the document. These need to be standardised to one unit of measurement to allow them to be understood and compared. Different units are used for the same test.	Thank you for your comment. The GDG have standardised the units for biochemistry tests based on the on the recommendations from UK Pathology Harmony.

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Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

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Royal College of Pathologists	Full	General	General	Units of measurement for biochemistry tests and terminology for test names should be standardised to SI units in use in NHS laboratories in the UK and quoted in previous NICE guidelines and recommended by UK Pathology Harmony. Correct test names and units as follows: FSH IU/L ; oestradiol pmol/L ; AMH pmol/L ; Inhibin B ng/L ; cholesterol mmol/L ; HbA_{1c} mmol/mol ; 25 hydroxy vitamin D nmol/L ; 1,25 dihydroxy vitamin D pmol/L; deoxypiridine nmol/L. Note units used for ALP and oesteocalcin correct. Also applies to use of BMI unit of kg/m^2	Thank you for your comment. We have standardised the units for biochemistry tests based on the on the recommendations from UK Pathology Harmony.
Royal College of Pathologists	Full	General	General	Cut-offs are quoted for biochemical tests for inclusion in studies, for likelihood ratios etc. A comment should be added that results vary between methods used (see UKNEQAS for information) so results may not be directly comparable between studies.	Thank you for your comment. A comment has been added to the full guideline as suggested.
Royal College of Pathologists	FULL	General	General	All changes to biochemistry test names, units and concentrations listed above need to be made to Appendix H	Thank you for your comment. We have standardised the units for biochemistry tests based on the on the recommendations from UK Pathology Harmony.
Royal College of	Full	Gen	4	It refers to this document's purpose as providing advice to women – will there be a patient information leaflet produced in parallel as the length of this guideline will put people off reading it?	Thank you for your comment. An information for patients' document is produced by NICE to support the implementation of the guideline. This document

Obstetricians and Gynaecologists	l	eral			presents the recommendations using language suitable for a lay audience.
University Hospitals Southampton NHS Foundation Trust	Full	11	2	Within the field of Clinical Biochemistry the limitations of hormone measurements have long been recognised with the consequent waste of precious NHS resources (Proceedings of the Annals of Clinical Biochemistry, 1999, 2012, 2013). As a speciality we act as an important interface between secondary care and GPs. We therefore welcome the advice you give, in particular to general practitioners, about testing for the perimenopause and menopause. Earlier this year a National audit was undertaken by AA on behalf of the Association of Clinical Biochemists (ACB). This was circulated to all NHS Clinical Biochemistry departments providing FSH and LH measurements, to establish current practice for biochemical testing and conformity with existing standards. The findings of this audit were presented at the ACB national meeting in June 2015. As part of this work AA established that for UHSNFT, serving a population of 1 million, approximately 23% of women age 45-54 years were tested for the menopause over a 10-year period, excluding repeat testing of patients and requests for legitimate causes (e.g. post chemotherapy)(Lee and Armston, 2014). The actual number of requests made was just over 2000 per annum, at a cost of £22,000 to the NHS. If this practice is replicated nationally this means 1.3 million women aged 45-54 years are tested in a 10 year period, at a cost to the NHS of £14 million. Reference Lee S and Armston A, Proceedings of the Annals of Clinical Biochemistry 2014	Thank you for this comment.
Mylan EPD (BGP Product	Full	11	5	Mylan suggest to expand this statement to include an increase in the number of women consulting a GP, and more new referrals to secondary care	Thank you for this comment. We have reworded the statement.

s Ltd)					
Primary Care Women's Health Forum	Full	11	33	We are particularly concerned that the following statement 'Premature ovarian insufficiency (POI) and early perimenopause (menopause between the ages of 40 and 45 years) are associated with an increased risk of mortality, and with serious morbidity including cardiovascular disease (CVD), neurological disease, psychiatric disorders and osteoporosis.' is inconsistent with the draft management pathway which makes consistent reference to the management of POI only (menopause under 40), but not early menopause. In so doing, throughout the guidance, there is a lack of guidance re managing women with menopause between 40 and 45.	Thank you for your comment. The GDG acknowledge your concern and have amended the care pathway so that the age group of 40 to 45 years has been removed, which ensures that women in this age group are clearly captured. The recommendations for the treatment of menopause symptoms apply to women in this age group.
Sheffield Teaching Hospitals NHS Foundation Trust	Full	11	41	Although this is a summary it would be helpful to Ref- Scottish study- what was the age range of these women- pre or post menopausal?	Thank you for your comment, this reference has now been included. The age range of the women in this study was 45-54 years.
British Menopause Society	Full	12	9	Whilst the MWS may have had a major impact on prescribing it was hardly a "landmark" study being that it was an observational study with all the flaws and limitations of that type of study	Thank you for your comment. This study was described as 'landmark' not on methodological grounds but because it was influential in the UK. The text in the full guideline has been reworded to describe this study as influential.
British Menopause Society	full	12	9	I would have thought it was HERS and WHI not the million women study that changed practice. MWS was not highly regarded.	Thank you for your comment. This study was described as 'landmark' not on methodological grounds but because it was influential in the UK. The text in the full guideline has been reworded to describe

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					this study as influential.
Poole Hospital NHS Trust	Full	12	9	Whilst the MWS may have had a major impact on prescribing it was hardly a "landmark" study being that it was an observational study with all the flaws and limitations of that type of study	Thank you for your comment. This study was described as 'landmark' not on methodological grounds but because it was influential in the UK. The text in the full guideline has been reworded to describe this study as influential.
UK Clinical Pharmacy Association	Full	12	27 28	We support the statement that women should be invited to a health and lifestyle consultation at age 50	Thank you for this comment.
British Menopause Society	full	12	32	Should be www.menopausematters.co.uk not …org.uk	Thank you for this comment. The text has been amended.
British Menopause Society	Full	12	43	There is plenty of consensus on the risks/benefits of HRT eg. Endocrine Society Consensus Statement plus International, European, North American and British Menopause Society consensus documents	Thank you for your comment. This text was referring to a lack of consensus in the scientific literature on HRT. The documents referred to in this comment are guidance based on expert opinion. The guideline text has been amended to clearly reflect the intended meaning.
Poole Hospital NHS Trust	Full	12	43	There is plenty of consensus on the risks/benefits of HRT eg. Endocrine Society Consensus Statement plus International, European, North American and British Menopause Society consensus documents	Thank you for your comment. This text was referring to a lack of consensus in the scientific literature on HRT. The documents referred to in this comment are based on expert opinion. The guideline text has been amended to clearly reflect the intended meaning.
UK	F	1	4	It would be useful to provide the interpretation of risk benefit for HRT and	Thank you for your comment. The GDG would also

Clinical Pharmacy Association	ull	2	7	CVD in age bands, eg 50-60, 60-70, 70+ as for eg. Drug Safety Update 2007	have preferred to present the risk data in terms of 10 year age bands, but the data did not allow for this.
British Menopause Society	Full	12	47	This statement is misleading - WHI initially reported an increased incidence of cardiovascular events with HRT but when the same data were subsequently analysed and published by age it was found that women under 60 had a lower risk whilst women over 70 had a higher risk. It is not a question of the results now being interpreted differently, it is just further analysis of the original data from the authors themselves.	Thank you for your comment. The statement has been amended to improve clarity.
Poole Hospital NHS Trust	Full	12	47	This statement is misleading - WHI initially reported an increased incidence of cardiovascular events with HRT but when the same data were subsequently analysed and published by age it was found that women under 60 had a lower risk whilst women over 70 had a higher risk. It is not a question of the results now being interpreted differently, it is just further analysis of the original data from the authors themselves.	Thank you for your comment. The statement has been amended to improve clarity.
Mylan EPD (BGP Products Ltd)	Full	136799	1 223 284447	Mylan welcome the NICE Clinical Guideline on Menopause and welcome NICE views that women need to know the available HRT treatment options, their benefits and risks. With this in mind Mylan is concerned that the Guidance is limited with respect to highlighting the different forms of progestogen in HRT preparations as these differ markedly with respect to their risk profiles. Not all HRT preparations are the same, for example dydrogesterone, compared to other progestogens has no oestrogenic, androgenic or glucocorticoid side effects (as per selective receptor binding activity below). Also studies have shown marked differences amongst HRT preparations in their associated risk of breast cancer and VTE.	Thank you for your comment. The GDG considered this at the time of protocol development and prioritised the evaluation of the various routes of administration (e.g. oral versus transdermal) over the different preparations of oestrogen or progesterone in HRT. This is acknowledged as a limitation of the review, and a possible topic for future research. The review of HRT for the treatment of short term symptoms, as well as the reviews on the long term benefits and risk of HRT, did not evaluate treatments by dose. The NMA protocol was specified that results from studies with different dosages of the same

Progestogen	Progestogenic	Estrogenic	Androgenic	Anti-androgenic	Glucocorticoid	Anti-mineralocorticoid
Progesterone	+	–	–	±	+	+
Dydrogesterone	+	–	–	±	–	±
Drospirenone	+	–	–	+	–	+
MPA	+	–	±	–	+	–
Norethisterone	+	+	+	–	–	–

+ Effective; ± Weakly effective; – Not effective

Table reproduced from Maturitas, 46 (S1), Schindler AE, Campagnoli C, Druckman R, Huber J, Pasqualini JR, Schweppe KW, Thijssen JHH. Classification and pharmacology of progestins. 7–16. Copyright (2003), with permission from Elsevier.

Mylan is concerned that this lack of explanation may result in women being ill-informed of the difference amongst HRT preparations.

treatment should be pooled and investigated in a sensitivity analysis if the results were associated with high levels of heterogeneity. For example, to investigate differences in results between oral and non-oral oestrogen plus progestogen versus placebo, a sensitivity analysis was conducted to investigate if a study using a low dose of oral oestrogen plus progestogen may have skewed the pooled effect for this treatment. However, neither the point estimate nor the confidence interval appeared to be sensitive to this assumption.
Between treatment comparison of different dosages was not part of the focus of the review questions for the relief of menopausal symptoms, therefore, the GDG are not able to make recommendation on this aspect of treatment.
The guideline development group have noted the evidence submitted in this comment and will pass it to the NICE surveillance team for consideration.

				Dose of oestrogen Both The 2013 British Menopause Society & Women's Health Concern recommendations on hormone replacement therapy(1) and the Updated 2013 International Menopause Society recommendations on menopausal hormone therapy and preventive strategies for midlife health (2) highlight the need to treat women with menopausal symptoms with the lowest effective dose. This is of particular importance when prescribing HRT for the first time in women over the age of 60. Although higher doses may be needed in women suffering severe menopausal symptoms, regimens containing ultra low doses such 0.5mg oestradiol have shown to provide clinical significant reduction in vasomotor symptoms in under 12 weeks. (4,5) and low doses (e.g 0.3 mg of conjugated equine oestrogen/ 1mg oestradiol) are sufficient enough to also prevent osteoporotic fractures. Low/ ultra low dose oestrogen and progestogen are also associated with less endometrial stimulation with high rates of amenorrhea. (3) Dose of oestrogen is also important when factoring risks such as thromboembolism and breast cancer. Ref: 1. Panay N et al. The 2013 British Menopause Society & Women's Health Concern recommendations on hormone replacement therapy Menopause International 2013; 19: 59-68 2. De Villiers TJ et al. The Updated 2013 International Menopause Society recommendations on menopausal hormone therapy and preventive strategies for midlife health Climacteric 2013;16:316–337 3. Gambacciani M, Genazzani AR. Hormone replacement therapy: the benefits in tailoring the regimen and dose. 195–201	

				4. Notelovitz M, Lenihan JP, Mcdermott M, Kerber IJ, Nanavati N, Arce JC. Initial 17β-oestradiol Dose for Treating Vasomotor Symptoms. Obstet Gynecol 2000;95:726–31 5. Stevenson JC et al. Oral ultra-low dose continuous combined hormone replacement therapy with 0.5mg 17β-ooestradiol and 2.5mg dydrogesterone for the treatment of vasomotor symptoms: Results from a double-blind, controlled study. Maturitas 67 (2010) 227–232 Different progestogens Different classes of progestogen are available, such as retroprogesterone (e.g. dydrogesterone [D]), 17α-hydroxyprogesterone derivatives (e.g. MPA), 19-nortestosterone derivatives (e.g. norethisterone), and spironolactone derivatives (e.g. drospirenone). Besides the progestogenic effect, which is in common to all, the various progestogens exhibit a range of different biological effects and this should be taken into account when prescribing HRT (6) Micronized progesterone or dydrogesterone used with oestradiol may be associated with a better risk profile for breast cancer than synthetic progestogens. A large European observational study (7) suggested that micronized progesterone or dydrogesterone used in association with oral or percutaneous estradiol may be associated with a better risk profile for breast cancer than synthetic progestogens. A registry study from Finland (8) also reported no increase in risk with dydrogesterone after at least 5 years of use compared to synthetic progestogens which were	

				associated with a small increase in risk 6. Schindler AE, Campagnoli C, Druckman R, Huber J, Pasqualini JR, Schweppe KW, Thijssen JHH. Classification and pharmacology of progestins. 7–16 De Villiers TJ et al. Climacteric 2013;16:316–337 7. Fournier A et al. Unequal risks for breast cancer associated with 9 different hormone replacement therapies: Results from the E3N cohort study, Breast Cancer 10 Research and Treatment, Breast Cancer Res Treat 2008;107:103–11 8. Lyytinen H et al. Obst Gyn 2009;113:65–73	
UK Clinical Pharmacy Association	Full	14 15 123 127 129	34 35 89 313 2	Please clarify whether women at risk of thrombosis require a referral to haematology when the evidence base suggests that the VTE risk with standard dose transdermal HRT is no higher than baseline risk. Please clarify / state whether the use of progesterone vs progestogen / type of progestogen is important for prescribing with thrombosis risk.	Thank you for your comment. The GDG recommend that referral to a haematologist should be considered when a woman's individual risk is believed to be high (for example, those with a strong family history of VTE or a hereditary thrombophilia). This is discussed in the linking evidence to recommendation section of the guideline (see section 10.1.8). The data used in the analysis of this chapter related to route of administration rather than type of progestogen.
Primary	F	1	G	The flow chart is useful but there are recommendations to refer women to	Thank you for your comment. The GDG recognise

Care Women's Health Forum	Full	7	General	specialist services. In many areas there are no specialist services. In the main document the wording is more appropriate – healthcare professional with expertise in menopause management.	that referral pathways may vary depending on local service configurations. However, where specialist services are stated in a recommendation this is because of the complexity of the management under consideration. In other places the recommendations allow for care to be delivered by the most suitable healthcare professional with expertise in the care of women with menopause. The GDG discussed the definition of a healthcare professional with expertise in menopause management, and considered this was within the remit of specialist societies who provide training and assessment for health professionals. This comment has been forwarded to the NICE implementation team to inform their support activities for this guideline.
British Menopause Society	Full	17	General	On the left side of the diagram, "diagnosis of menopause" about a third down there is a diamond 'start treatment' and I think the 'no' box should be on the left, effectively on the way to information provision etc	Thank you for your comment, the layout of the diagram has been adjusted to improve clarity.
British Menopause Society	Full	17	General	On the right side of the diagram underneath diagnosis of POI perhaps an interim box with 'Enter on national register' or similar	Thank you for your comment. This is a research recommendation and therefore does not appear in the flowchart.
British Menopause Society	Full	17	General	Good algorithm which is clinically useful but why if menopause diagnosed (left side) and suitable for treatment is option just left at "start treatment" Yes/No? If no then should reason be explored or referral to specialist service particularly if under 45.This bit of pathway leaves women under 45 quite vulnerable to just being left without any treatment. I would suggest a 3rd	Thank you for your comment. The care algorithm has been amended to reflect referral to a specialist service if the woman is unsuitable for treatment.

				option - unclear - with line to refer to specialist service.	
British Menopause Society	Full	17	General	? other investigations ? thyroid function - yes or no?	Thank you for your comment. Thyroid function measurement as a single test was not included in the review protocol of diagnosis of menopause. The GDG did not consider that a thyroid function investigation would be an independent diagnostic test for menopause for women who don't experience any menopausal symptoms.
Poole Hospital NHS Trust	Full	17	general	Good algorithm which is clinically useful but why if menopause diagnosed (left side) and suitable for treatment is option just left at "start treatment" Yes/No? If no then should reason be explored or referral to specialist service particularly if under 45.This bit of pathway leaves women under 45 quite vulnerable to just being left without any treatment. I would suggest a 3rd option - unclear - with line to refer to specialist service.	Thank you for your comment. The care algorithm has been amended to reflect referral to a specialist service if the woman is unsuitable for treatment.
Primary Care Women's Health Forum	Full	17	general	We are concerned that, as per comment 1, there appears to be a cut-off at age 40, rather than 45, for specific consideration of investigation and management of menopause, which may lead to many women with early menopause (between 40 and 45) being 'missed', and denied treatment. If, as per the introduction. morbidity and mortality are increased with early, as well as premature menopause (POI), we would suggest that the differentiating cut-off age be 45, rather than 40.	Thank you for your comment. The care algorithm starts with the age threshold of 40 years to clarify the distinction between menopause and POI which requires a different diagnostic and management pathway. However, the GDG appreciate that the algorithm was not clear about the group of women between 40 to 45 years and this has been amended.
Mylan EPD (BGP Products Ltd)	Full	17	General	Mylan recommend to define treatment failure in order for the care pathway to be successfully implemented and to consider dose titration. Also although the Care pathway includes alternatives. Mylan suggests that once the alternatives are prescribed a further follow up is performed to assess resolution of menopausal symptoms. Mylan suggest that the Care Pathway is expanded to aid physicians in HRT treatment type and choice for women with or without a uterus	Thank you for your comment. This level of detail is not considered appropriate for the care algorithm, particularly as it may vary according to the individual. The evidence for dosing titration was not considered as part of the guideline and therefore it cannot be added to the algorithm.
Clinical	F	1	G	This is a very helpful algorithm.	Thank you for your comment. There may be times

Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	ull	7	eneral	Will GPs interpret 'diagnosis of menopause' in top left easily? Suggest change/add 'symptoms suggestive of menopause'	when a woman presents with atypical symptoms of menopause so this has not been amended.
Menopause UK	Full	18 21 22 23	General	***Menopausal symptoms/contraindications to HRT*** Many health care professionals will be likely to over-estimate the risks of HRT, and assume that the contraindications for HRT use are far more extensive than the guidelines state they are. It would be helpful to add some tables with summary information to maximize the visibility and user friendliness of the recommendations and guidelines. Using a **Stages of Change** approach, this will help practitioners to: ▪ **recognize** the symptoms of menopause and take responsibility for confidently diagnosing it and managing it in women of all ages; and ▪ **believe** that it is possible to provide effective management and treatment which will improve women's health and quality of life.	Thank you for your comment. The guideline assumes that prescribers will use a medicine's summary of product characteristics to support decisions made together with individual patients. This comment has been forwarded to the NICE implementation support team to inform their support activities for this guideline.

				The following tables are intended to be illustrative only and provide draft suggestions for further consideration and refinement. For example: **Contraindications to HRT** Undiagnosed vaginal bleeding Suspected or active breast or endometrial cancer Active or recent VTE or myocardial infarction Active liver disease with deranged LFTS Previous low-grade endometrial stromal sarcoma Pregnancy Porphyria cutanea tarda **The following are NOT absolute contraindications to HRT** Family history of breast cancer (suggest GDG qualifies this with reference to personal risk profile eg genotype and family incidence and link to NICE guidelines on breast cancer)	

				Previous endometrial disease. There is no evidence that HRT is contraindicated after successful treatment of endometrial carcinoma. Low-grade endometrial stromal sarcoma (very rare), however, IS hormone-dependent and is considered an absolute contraindication to HRT. Previous resolved VTE or myocardial infarction. (GDG to consider how to summarise: previous VTE – depends on whether provoked or unprovoked and if unprovoked would need a discussion with haematology) Previous resolved liver disease Age (there is no evidence to support the cessation of HRT in women above the age of 60 or any other arbitrary age who find it beneficial in alleviating problematic menopausal symptoms and for whom benefits of HRT outweigh the risks) Migraine with aura *NB: A suitably qualified practitioner should be able to advise on effective therapy in the presence of the above conditions*	
Royal College of General Practitio	Full	18	General	The use of follicle stimulating hormone (FSH) alone for menopause diagnosis in under 45s is interesting and challenging to implement. If normal, does it mean that no hormone replacement therapy (HRT) can be given? Vasomotor symptoms often seem to precede periods stopping.	Thank you for your comment. This recommendation relates to diagnosis, and does not exclude the clinical decision to treat a symptomatic patient. The GDG noted the lack of precision of FSH measurement which can fluctuate in the perimenopause.

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British Menopause Society	Full	18	General	FSH - 2 OCCASIONS Why 4-6 weeks? why not at least 4 weeks.	Thank you for your comment. The selection of time interval (4 to 6 weeks) was based on Committee's expert opinion following standard clinical practice in order to best capture any fluctuations of FSH in a period around menstrual cycle, and as such has not been amended.
British Menopause Society	Full	18	General	and/or irregular periods - ? Mirena IUS	Thank you for your comment. The guideline is not designed to cover all treatment eventualities and the decisions about which treatment to prescribe will require a degree of clinical judgement depending on an individual's circumstances.
British Menopause Society	Full	18	General	Info to menopausal women - where/what info sheets- needs a standard uptodate location for info	Thank you for your comment. An information for patients' document is produced by NICE to support the implementation of the guideline. This document presents the recommendations using language suitable for a lay audience.
Besins Healthcare	Full	18 104 12	36 42	We agree with your conclusion that "There is strong evidence that transdermal oestradiol plus progestogen greatly reduces the frequency of hot flushes in women with a uterus". We also agree with the findings and analysis of the GDG about the risk of VTE with HRT and that there is a clear differentiation between transdermal oestrogen and oral oestrogen, in that oral HRT increases the risk of VTE and this can occur immediately after starting HRT treatment and there is no significantly increased risk of VTE in women using transdermal preparations compared to non-users We also agree with the health economic analysis in women with and without	Thank you for your comment. The incidence of VTE is very low and the evidence for the superiority of transdermal preparations over oral specifically was determined only in women at risk of developing VTE. For vasomotor symptoms the results from the network meta-analysis found a large degree of uncertainty for the efficacy of oral oestrogen plus progestogen, rather than showing conclusively that they were ineffective. Therefore the GDG believe that it was important that the treatment choices available to patients were not restricted because of this finding.

		390		a uterus that transdermal preparations are the most cost-effective within the scope of the model. It is therefore not clear given there was “no strong evidence of efficacy of oral oestrogens plus progestogen” why the overall recommendation of the draft guideline does not distinguish between the oral and transdermal preparations. Therefore our main comment, based on the evidence described in the draft guideline, is that the overall recommendation should propose transdermal oestrogens as preferred therapies in patients presenting with the vasomotor symptoms of menopause, in particular patient at risk of VTE. We agree with the statement on page 20 about that the risk of VTE is greater with oral than transdermal preparations however this important consideration for vasomotor complications should form part of the main recommendation (section 11 page 19) to the management of vasomotor symptoms rather than in section 37 or page 20 where it could be overlooked. Given the historical safety concern prescribers and patients have about the use of HRT treatments arising from incorrect interpretation of data, to ensure broad implementation of these guidelines the recommendation must be clear and weighted to supporting the evidence base. The evidence base is more supportive of the use of transdermal than oral preparations in the management of vasomotor symptoms. The RCT trial known as KEEPS underlines the evidence suggesting a difference between oral and transdermal HRT in menopausal women <65 years old. (KEEPS trial : http://www.ncbi.nlm.nih.gov/pubmed/25069991)	KEEPS trial was not included in our evidence base as the study’s outcomes (annual change in carotid artery intima-media thickness, changes in markers of CVD risk) did not match our review protocol.

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Consultation on draft guideline - Stakeholder comments table

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Royal College of Obstetricians and Gynaecologists	Full	18	1	- What are CBH. (Compounded Bioidentical hormones are plant-derived hormones that are chemically similar or structurally identical to those produced by the body.) May be this needs insertion into text	Thank you for your comment, this has been added to the glossary.
Royal College of Obstetricians and Gynaecologists	Full	18	1	If transdermal HRT risk for VTE is no higher than background, why is transdermal HRT not the first line recommendation for everyone? Also page 129 line 42	Thank you for your comment. The incidence of VTE is very low and the evidence for the superiority of transdermal preparations over oral specifically was determined only in women at risk of developing VTE. The recommendations about treatments for short-term symptoms (hormonal, non-hormonal and non-pharmacological) take into account the risk and benefits in the short term whereas the recommendations on benefits and risk of HRT (such as VTE, CVD and breast cancer) aim to provide information to women about the different risks and benefits of HRT in long term. The evidence showed that transdermal HRT doesn't increase the risk of VTE above the baseline population risk whereas oral preparations of HRT may be associated with a higher risk of VTE compared with transdermal preparations. Therefore the GDG believe that it was important that the treatment choices available to patients were not restricted because of this finding.
British	F	1	1	I think this whole section would be readable if it were divided in to sections	Thank you for your comment. The order of the

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Menopause Society	full	8	3	such as 'diagnosis, information, iatrogenic menopause, symptom control' etc	recommendation is designed to follow the chapters of the full guideline.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	18	5	Add 'In women not using hormonal contraception'?	Thank you for your comment. The recommendation has been amended as suggested.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	18	7	Specify for contraception to avoid confusion – see point above	Thank you for your comment. The recommendation has been amended for clarity using a different example.
Royal College of	Full	18	10	Section 10 - Excellent recommendations about giving information to women. Could there be an earlier recommendation about treating women with sympathy and taking their concerns seriously?	Thank you for your comment. The GDG agree that all care relating to the menopause should take account of each woman's individual circumstances and they

Obstetricians and Gynaecologists	l				stress the importance of maintaining a respectful and empathetic approach. This should underpin all recommendations and, as such, a recommendation has been added at the beginning of the guideline which cross-refers to the NICE guideline on Patient Experience.
Royal College of Obstetricians and Gynaecologists	Full	18	17	Section 17 - The recommendation about the provision of CBT for women suffering from low mood will provide a challenge for the NHS as this is being extensively recommended now for many conditions	Thank you for your comment. This has been forwarded to the NICE implementation support team to inform their support activities for this guideline.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	18	19	There is a small study which suggests that menopause can be diagnosed reliably in women using Depo-Provera (Beksinska2011 SAfMedJ) that is frequently quoted and useful in clinical practice.	Thank you for your comment. Whilst the Beksinska study suggests differences in FSH may be informative for determining menopausal status, it does not assess the use of FSH as a diagnostic marker for perimenopause or menopause. Because of this, the study does not meet the inclusion criteria of the review.
British Menopause Society	full	18	21	If we don't feel that FSH is helpful, then also not helpful in women with atypical symptoms. In this situation, more appropriate would be other tests, eg TSH, rather than FSH	Thank you for your comment. Following stakeholder feedback, this recommendation has been amended and the investigation of women presenting with atypical symptoms using FSH has been removed. As

					the use of TSH was not reviewed as part of this guideline, the GDG are unable to make a comment on its use.
University Hospitals Southampton NHS Foundation Trust	FULL	18	21	If a women presents to a practitioner with atypical signs of the menopause how much difference will measuring an FSH make?	Thank you for your comment. Following stakeholder feedback, this recommendation has been amended and the investigation of women presenting with atypical symptoms using FSH has been removed.
University Hospitals Southampton NHS Foundation Trust	Full	18 13	21	It is unclear from the draft guidelines as to what the definition of atypical symptoms is, although the CKS includes more comprehensive coverage of this topic in the section on differential diagnosis. Accepting that some conditions do not require confirmation by further testing, it would be useful to include those investigations where testing is necessary. In the absence of such specific recommendations, the default will be for clinicians to consider all symptoms of women over 45 as being atypical and potentially leading to misdiagnosis.	Thank you for your comment. The guideline specifies typical symptoms (for example, vasomotor symptoms, irregular or absent periods), but cannot provide a list of all possible atypical symptoms. Following feedback from stakeholders on the difficulty of interpretation in practice, the recommendation has been amended so that the use of FSH in this population of women has been removed.
Primary Care Women's Health Forum	Full	18	22	We are concerned about the value of doing FSH levels in women between 40 and 45 with menopausal symptoms, including a change in menstrual cycle, since normal FSH levels may be misleading and lead to an incorrect assumption that the patient is not peri-menopausal and, again, a missed opportunity to offer appropriate treatment for symptoms e.g. vasomotor symptoms. There is no provision in the pathway to guide management after checking FSH levels in these ladies.	Thank you for your comment. This recommendation relates to diagnosis, and does not exclude the clinical decision to treat a symptomatic patient. The GDG noted the lack of precision of FSH measurement which can fluctuate in the perimenopause.

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Bayer PLC	Full	18	25	During the consultation on the draft scope for this clinical guide, we provided feedback regarding our concerns that *'contraception during the menopause'* was listed as a clinical issue that would not be covered by the guideline. Following the scope consultation, we noted that similar comments were also made other stakeholders including the British Menopause Society (BMS), the Faculty of Sexual & Reproductive Healthcare (FSRH) and the Royal College of Nursing (RCN). The developer's response to the stakeholder feedback[1] suggested *that 'information on contraception at the menopause'* would form part of a new clinical question on information provision for women. Full developer's response:[1] *"Given the finite resources and time available to develop a guideline, a full review of contraception for women in the menopause was not considered to be a priority for the guideline. However, the topic of 'Information on contraception at the menopause' will form part of a new clinical question on information provision for these women. Whilst a separate evidence will not be done for contraception, this topic will be considered within the systematic review for advice that women should be given during the menopause"* also that *"It has been agreed that the GDG will address providing information about contraception to women going through the menopause as a new topic in the scope."*[1] However, looking through the draft guidelines and the review questions, it does not seem that this agreement was followed through into the development of the guideline. This is despite the fact that in the full clinical guideline, it is reported that *'fertility issues'* was identified in the included studies as a topic that was *"found helpful by women or would have been helpful if they had received it"* (Table 10, p62 of full guideline). We would like to reiterate that effective contraception is an important issue for	Thank you for your comment. Although provision of contraception during menopause was not within the guideline scope, the GDG recognises the importance of addressing contraception needs for women who are in the perimenopausal and postmenopausal period and have added a recommendation based on expert opinion.

				this group of women. The most recently published ONS statistics reveal that in 2013, 28.3% of conceptions in women aged 40 and over resulted in a legal abortion; this is higher than the proportions in women aged 30-34 and 35-39 at 13.2 and 16.3 respectively.[2] As we previously acknowledged, we appreciate that this area is sufficient to warrant a guideline in its own right, and therefore it cannot be fully addressed in this guideline, however, we are concerned that its complete omission may lead to important issues which are integral to the holistic management of peri-menopausal and menopausal women being overlooked. For example, hormone replacement therapy (HRT) does not consistently suppress ovulation,[3] and therefore it is advised that it should not be relied upon as a contraceptive.[4] This is an important point for a guideline covering the use of treatments for symptomatic relief of the menopause. As a minimum, we suggest that a recommendation or cross reference should be included to ensure that the contraceptive needs of peri-menopausal women are considered and discussed in line with recommendations from nationally recognised guidelines such as those from the NICE accredited provider the Faculty of Sexual & Reproductive Healthcare, Clinical Guidance on Contraception for Women Aged Over 40 Years (July 2010).[4] Suggested adaption to recommendation 6. 6. Give information to menopausal women and their family members or carers (as appropriate) that includes: • an explanation of the stages of menopause • common symptoms (see recommendation 8) and diagnosis • lifestyle changes and interventions that could help general health and wellbeing	

				• the benefits and risks of treatments for menopausal symptoms. • the recommendations regarding effective contraception for women who wish to avoid pregnancy from nationally recognised guidelines such as those from the NICE accredited provider the Faculty of Sexual & Reproductive Healthcare, Clinical Guidance on Contraception for Women Aged Over 40 Years (July 2010).[4] (1) National Institute for Health and Care Excellence. Menopause Scope Consultation Table. 24 May - 21 June 2013. 12 Aug. 2013. Available from: http://www.nice.org.uk/guidance/GID-CGWAVE0639/documents/menopause-stakeholder-consultation-comments-table2. (Last accessed: 8/7/2015). (2) Office for National Statistics (ONS). Conceptions in England and Wales, 2013 - Conceptions leading to abortion. 24 Feb. 2015. Available from: http://www.ons.gov.uk/ons/rel/vsob1/conception-statistics--england-and-wales/2013/stb-conceptions-in-england-and-wales-2013.html#tab-Conceptions-Leading-to-Abortion . (Last accessed: 8/7/2014). (3) Gebbie AE, Glasier A, Sweeting V. Incidence of ovulation in perimenopausal women before and during hormone replacement therapy. Contraception 1995 Oct;52(4):221-2. (4) Faculty of Sexual & Reproductive Healthcare (FSRH) Clinical Effectiveness Unit. Clinical Guidance - Contraception for Women Aged Over 40 Years. July 2010. Available from: http://www.fsrh.org/pdfs/ContraceptionOver40July10.pdf. (Last accessed: 8/7/2015).	
Royal College of Obstetri	Full	18	26 2	We welcome the recommendation that all women have a health check at the age of 50	Thank you for this comment.

cians and Gynaecologists			9		
Royal College of Obstetricians and Gynaecologists	Full	18	27	Statements 19 and 20 could be combined. If HRT contraindicated consider referral to HCP with expertise in HRT for advice on vaginal oestrogen and dosage. Also for page 114 line 26-30	Thank you for your comment. A separate recommendation has been added about the referral of women who have contraindications to treatment.
University College London Hospitals NHS Foundation Trust	Full	18	33	Whilst agreeing with the principle of discussing with women what to expect, this recommendation needs some qualification as only some women will experience to a greater or lesser extent some of these symptoms. Previous experience with NICE guidelines has shown that recommendations are often taken literally (and sometimes out of context) and this particular recommendation could have a negative effect on women both before and during perimenopause	Thank you for your comment. The GDG acknowledge the concern raised, and stress that while the list was not intended to be prescriptive of all women, the giving of such information should be tailored to the requirements of the individual woman. A recommendation about following the principles set out in the NICE guideline on patient experience has been added in support of this approach.
British Menopause Society	full	18	37	Was disturbed sleep included, perhaps not enough evidence	Thank you for your comment. Disturbed sleep was not included in this recommendation as it difficult to evaluate, and likely arises as the result of vasomotor symptoms.
British Menopause Society	Full	18	40	This should be 'offer premenopausal women……'	Thank you for your comment. The GDG have not amended the recommendation as they believe that it already implies coverage of premenopausal women.

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British Menopause Society	Full	19	General	Define 'healthcare professional with 'expertise' in Menopause' raised elsewhere	Thank you for this comment. Defining the specific competencies and remit of a healthcare professional with expertise in menopause falls under the remit of the professional societies in this field is beyond the scope of this guideline. The GDG accept that this may currently differ according to local pathways.
British Menopause Society	Full	19	General	Testosterone supplementaion - what/how/dose?	Thank you for your comment. Testosterone (as a class) supplementation was evaluated only for the outcome of sexual function in women with the menopause. There are currently no preparations licensed for this indication. The GDG have made a note in the linking evidence to recommendation section of the guideline of which doses and preparations were used in the included studies.
University College London Hospitals NHS Foundation Trust	Full	19	3	Reference to stages of menopause at odds with conclusion of Section 5 that there is no clinical usefulness to identifying stages of menopause. The implication of this recommendation as written is that there is a usefulness or pattern to the stages. Suggest re-phrasing this recommendation to "Adapt a woman's treatment as her symptoms change".	Thank you for your comment. The recommendation has been amended as suggested.
Primary Care Women's Health Forum	Full	19	5	We are concerned that the wording of this recommendation ('Offer hormone replacement therapy (HRT) for vasomotor symptoms after discussing the short-term (up to 5 years) and longer-term benefits and risks') may be misleading in the care of women with early or premature menopause, in whom there should be no differentiation between short and long-term treatment until such treatment is continued beyond the average age of menopause. Suggest add comment, at this point, that HRT in women with	Thank you for your comment. The treatment recommendations in this section of the guideline are not intended for the management of women with premature ovarian syndrome. However, the longer-term risk associated with HRT treatment are presented by treatment duration in Section 11 of the full guideline.

				early or premature menopause (POI) should ideally be continued to the average age of menopause and then reviewed. This recommendation currently does not appear until page 24 and if not fully appreciated by patients and prescribers may result in HRT being stopped too early. Alternatively, could add rider to original comment e.g. ('up to 5 years over age 50 / average age of menopause').	
Bayer PLC	Full	19	5	Recommendation 11 states *"Offer hormone replacement therapy (HRT) for vasomotor symptoms after discussing the short-term (up to 5 years) and longer-term benefits and risks. Offer a choice of oral or transdermal preparations as follows:* • *oestrogen and progestogen to women with a uterus* • *oestrogen alone to women without a uterus."* It should be made clear that the Levonorgestrel-releasing intrauterine system (IUS) (containing 52mg levonogestrel, releasing 20 micrograms/24 hours) is licensed for protection from endometrial hyperplasia during oestrogen replacement therapy for 4 years,[5] and therefore the choice for the progesterone component of HRT extends beyond oral or transdermal preparations. (5) Bayer plc. Mirena® 20 micrograms/24 hours intrauterine delivery system - Summary of Product Characteristics (SPC). 1 July 2015. Available from: http://www.medicines.org.uk/emc/medicine/1829. (Last accessed: 8/7/2015).	Thank you for your comment. The GDG looked for the evidence on the efficacy of levonorgestrel-releasing intrauterine systems but none of the studies that identified by the search matched the review protocol. Please refer to Appendix G for further details on the exclusion reasons of these studies. In the absence of such data, the GDG are unable to make a comment about the effectiveness of this HRT route.
Pharma Care Europe	Full	19	13	We believe that the recommendation "*Explain to women that although there is some evidence that isoflavones or black cohosh may relieve vasomotor symptoms, their safety is unknown and different preparations may vary*" is too broad. It is important that healthcare professionals understand that there are specific branded isoflavone preparations available such as Promensil with a good safety record, including clinical study-based safety evidence, that also	Thank you for your comment. The protocol for the review of isoflavones did not separate the evidence by preparation, and therefore the GDG cannot comment about difference in safety and efficacy associated with these different preparations. In Section 7.8.2 of the guideline they discuss this limitation of the review.

				contain high quality standardised levels of the active ingredients. According to J. Johnston (Climacteric Journal 2011;14 (Suppl 2):8–12. Johnston J, Managing the menopause: practical choices faced in primary care), "*I suggest recommending a small number of well-researched natural products, which contain standardized ingredients, are supported by data, are safe and are supported with patient information. Being specific in recommendations ensures that you know that women are taking products that meet these criteria. This is the one situation where you should not be afraid to recommend products by brand because this keeps you safe, from a medicolegal perspective, as well as keeping your patients safe*". It is important that healthcare professionals are able to give women a choice. For some women HRT will be the best and only option; however, for women who choose to manage symptoms naturally and/or cannot take HRT for specific medical reasons it is vitality important healthcare professionals know what the best alternative options are (e.g. Promensil). It is also worth noting that Black Cohosh has been linked with potential liver toxicity; Red Clover isoflavones such as those used in Promensil have not. PharmaCare has an on-going involvement and partnership with the British Menopause Society as well as key individual healthcare professionals to keep them up-to-date with developments and clinical research.	
Clinical Effectiveness Unit of Faculty of Sexual	Full	19	19 21	This is slightly confusing as people may wonder how this relates to women considering SSRI to help vasomotor symptoms – overall use of SSRI for VMSx was not that clear	Thank you for your comment. The review of evidence for the use of SSRIs is discussed in section 7.8.2 of the full guideline. While SSRIs were not found to be effective in relieving vasomotor symptoms, and significantly worse in terms of high discontinuation rates compared to the other treatments, the GDG did not rule out their use given the limitations of the

& Reproductive Healthcare					evidence review and need for patient choice.
Primary Care Women's Health Forum	Full	19	23	Testosterone replacement. Although there is a qualifying statement about no licensed indication this may be difficult to implement without recommendation of dose/monitoring requirement etc	Thank you for your comment. Testosterone (as a class) supplementation was evaluated only for the outcome of sexual function in women with the menopause. There are currently no preparations licensed for this indication. The GDG have made a note in the linking evidence to recommendation section of the guideline of which doses and preparations were used in the included studies.
University College London Hospitals NHS Foundation Trust	Full	19	23	This is a very controversial recommendation as the evidence on which it is based is highly debateable and of poor quality. In particular, the available studies have only used healthy, mainly Caucasian, heterosexual women in sexually active relationships and the data may not be applicable to all women.	Thank you for your comment. The GDG considered the quality of the evidence and the generalisability of results given that the majority of women had surgically-induced menopause. However, the GDG also used clinical experience and decided that testosterone, although unlicensed for this indication in women, should only be offered as an option of improving low sexual desire for women in menopause when HRT is not effective. The GDG's rationale is described in the linking evidence to recommendation section in Chapter 7 of the full guideline.
Clinical Effectiveness Unit of Faculty	Full	19	23	GPs will find this recommendation difficult – is there scope to consider women who have had surgical oophorectomy separately? Many formularies will not support this use and there is a paucity of data related to normal women with intact ovaries.	Thank you for your comment. The GDG acknowledge that the data underpinning this recommendation is limited, which they have reflected in the wording of the recommendation and discussed in section 7.8.2 of the guideline.

of Sexual & Reproductive Healthcare					
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	19	27 28	Need to clarify that this refers to treatment of local vaginal symptoms and not for systemic symptoms.	Thank you for your comment. The recommendation has been amended for clarity.
UK Clinical Pharmacy Association	Full	19 114	25 26 232	Please provide clarification for dose for 'low dose' vaginal oestrogen?	Thank you for your comment. The GDG considered this comment and agreed that the term "low-dose" was not universally agreed and often defined by the manufacturer. Therefore, this term has been removed from the recommendation. A preparation that is designed to treat local as opposed to systemic symptoms should be used.

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British Menopause Society	Full	20	General	remove 'than for transdermal' as implies there is a risk of VTE with transdermal which is then contradicted next line.	Thank you for your comment. The wording of the recommendation has been amended for clarity following stakeholder consultation.
UK Clinical Pharmacy Association	Full	20/04/15	56 68 11	There is a statement highlighting the drug interaction between Tamoxifen and St John's Wort. We suggest that the guidance document also highlight the possible drug interaction between Tamoxifen and SSRIs that are potent CYP450 drug inducers - see BNF A1: Interactions. Noting that the use of SSRIs may be on evidence base for vasomotor symptom control or for licensed indication for clinical depression. NB: London N W Healthcare Trust has developed prescribing guidance for breast cancer and menopause, which we would be happy to share on request. Contact: Joan Pitkin / N Tanna via jyoti.rao@nhs.net	Thank you for your comment. The GDG agree that it is important to highlight the possible drug interaction between SSRIs with tamoxifen and have revised the following recommendation so that this is highlighted ('Offer menopausal women with, or at high risk of, breast cancer: • information on all available treatment options • information that the SSRIs paroxetine and fluoxetine should not be offered to women with breast cancer who are taking tamoxifen • referral to a healthcare professional with expertise in menopause').
Sheffield Teaching Hospitals NHS Foundat	FULL	20	15	In Sheffield we are lucky to have NHS acupuncture service . However access to CBT, hypnosis is very difficult and often not NHS funded. Using the private sector is a lottery and it is not possible to endorse or recommend practitioners.Even to access the acupuncture from a dedicated menopause clinic IU have to complete a justification form for commissioners. Patients are limited to 6 sessions of treatment.	Thank you for your comment. The issue of service configuration is related to the implementation of guideline and this has been forwarded to the NICE implementation support team to inform their support activities for this guideline.

ion Trust					
British Psychological Society	FULL	20	15 18	We believe that the guidelines suggest a useful pathway of treatment for health professionals to follow. However, currently the document suggests non-medical options (such as CBT, acupuncture, lifestyle changes, etc.) should only be considered after the patient has undergone a trial of HRT. Clarity is needed here to ensure this is not the pathway being advocated, given the above comments. We know that some women who do seek help have a clear preference for non-hormonal approaches. Also, HRT is not recommended for breast cancer patient who experience more severe and intense HFNS (Mom et al, 2006) than naturally menopausal women. Appropriate consideration and incorporation of these treatment options should be adequately accounted for in the guidelines. Namely, the option of psychological treatment approaches rather than just HRT or after HRT has been tried or denied first. Patients should be made aware of all safe and effective options available to them.	Thank you for your comment. The order of recommendations in the guideline is not meant to imply a hierarchy of treatment options, rather it reflects the order of chapters in the full guideline. The GDG recognise how not all women will wish to take hormonal treatments and therefore the availability of non-hormonal and non-pharmaceutical options is an important consideration. This is reflected in the recommendations which requires that information on all available treatment options be offered to women in menopause and their families.
Primary Care Women's Health Forum	Full	20	39	We are concerned that the statement 'the risk of venous thromboembolism (VTE) associated with HRT is greater for oral than transdermal preparations' may be misleading and is inconsistent with the next statement. In isolation, this statement suggests that there IS an increased risk of VTE associated with transdermal oestrogens, but not as high as with oral oestrogens. Suggest reword the statement on line 39 to 'there is an increased risk of venous thromboembolism (VTE) associated with oral HRT'	Thank you for your comment. The GDG discussed the concerns about the potential for confusion resulting from the wording of this recommendation. They have amended the recommendation in light of these comments, ensuring that it appropriately reflects the evidence base.
British Menopause	Ful	20	40	the risk of venous thromboembolism (VTE) associated with HRT is dose dependent	Thank you for your comment. The focus of this review question was on assessing the effects of HRT administered for menopausal symptoms on the risk of

Society	I				developing venous thromboembolism. The dose dependent effect of HRT on VTE was not considered as part of this review question.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	20	41 42	Suggest reword for clarity 'is no greater than in women not taking HRT' rather than baseline risk	Thank you for your comment. Baseline population risk is used throughout the document and therefore the GDG feel that it is more consistent to keep the original working in this instance.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	21 22 23	General	Category of 'Women on any HRT' - for greater clarity would suggest that you add '(oestrogen only and combined HRT)' as this was not immediately obvious that it was a composite of the two categories above. The baseline risks need greater prominence in the tables as they are rather hidden away in the headings.	Thank you for your comment. The information about women in this category (of women on any HRT) is derived from studies in which type of HRT is not clearly specified. However a footnote has been added to the table for clarity.
British Menopa	Fu	21	1	Overall the tables are helpful but I find the words in brackets 'from 7 fewer to 3 fewer' as grammatically challenging when presented multiple times in each	Thank you for your comment. The wording in the tables has been amended in conjunction with the

use Society	ll	23	4	table. Using -7 and +4 with perhaps an explanatory note for all of the tables as to what '+7' or '-4' mean. This will make it quicker for readers to interpret the tables contents	NICE editor to ensure clarity.
British Menopause Society	Full	21	8	does not increase cardiovascular disease risk and reduces the risk of coronary heart disease when started in women aged under 60 years	Thank you for your comment, however the wording of this recommendation was crafted to carefully reflect the available evidence and therefore the GDG do not believe that it should be changed in this instance.
British Menopause Society	Full	21	9 43	reduces the risk of dying from cardiovascular disease when started in women aged under 60 years Explain to women that taking oral (but not transdermal) oestrogen is associated with a small increase in the risk of stroke, but this risk is dose dependent. Also explain that the baseline risk of stroke in women 21 aged under 60 years is very low (see table 2).	Thank you for your comment. The review protocol did not include the evaluation of different HRT dosages on the outcome of cardiovascular disease. This is noted in the section 10.2.8.5 in the full guideline. The aim of this recommendations is to offer advice on the risk of cardiovascular disease for women taking different routes of administration of oestrogen.
British Menopause Society	full	21	10	Agree with other's statements about studies showing reduced risk from using HRT	Thank you for your comment.
Sheffield Teaching Hospitals NHS Foundation Trust	FULL	22	1	Table of stroke risk- could you clarify if the oestrogen only is td or oral – it is confusing as this suggests a small raised risk and the text suggests no increased risk .	Thank you for your comment. The GDG considered evidence on different HRT administration routes where available. The majority of the evidence was for on oral administration of HRT. This information has now been added for clarity as a note to the risk tables . The GDG also considered evidence from both RCTs and observational studies and this was reflected in our recommendation. Evidence from RCTs and cohort studies are slightly inconsistent as some observational studies showed increased risk of stroke associated

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					with HRT use, while RCTs largely showed no significant difference. The recommendation was made in consideration of the whole body of evidence.
British Menopause Society	Full	22	5	Explain to women that taking HRT (either orally or transdermally) may be associated with a reduced risk of developing type 2 diabetes.	Thank you for your comment. The randomized evidence from a study of almost 10,000 women found no difference in the risk of developing type 2 diabetes between those women who had taken HRT and those who didn't. Although the evidence from cohort studies identified that there may be a reduced risk of developing type 2 diabetes for women taking HRT, the GDG did not feel confident that this evidence is translated in clinical practice given the limitations of observational evidence to ensure comparability of the intervention and control groups under investigation.
British Menopause Society	Full	22	14	The wording around 'baseline risk' is very confusing and unclear. It would be better to state that most breast cancers (~90% diagnosed annually) are diagnosed in women who are at population (i.e. average risk for their age). Only about 10% of cancers diagnosed annually are diagnosed in women who have an elevated baseline risk (due to a family history)	Thank you for your comment. The full description is given as "baseline population risk in the UK population" in the tables, which the GDG believe to be accurate. However, the recommendation has been clarified so that it now discusses how each individual women's level of risk depends on her underlying risk factors.
British Menopause Society	Full	22	16	HRT with oestrogen alone is associated with a possible decrease in the risk of breast cancer	Thank you for your comment. The GDG did not find evidence to suggest oestrogen alone is associated with a decreased in the risk of breast cancer and refer you to Table 3 in the list of recommendations (full guideline) for risk estimates. Specifically, the evidence suggest a trend toward a reduction in risk, although this is not statistically significant, nor consistently demonstrated in all data.

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British Menopause Society	Full	22	16	It would be more accurate (based on available clinical evidence) to state that risk is not increased with use less than 5 years in duration and this applies to both unopposed conjugated equine oestrogens and oestradiol valerate. There is no dosage effect and there is no difference in risk according to age group or time from menopause	Thank you for your comment. The recommendations in this section were based on the evidence reviewed which included RCTs and cohort studies. The GDG did not conclude that the conclusion on the risk of breast cancer for women taking oestrogen alone would be different based on the duration of treatment and they did not evaluate the effect of dose so cannot make a comment about this.
British Menopause Society	Full	22	18	HRT with oestrogen and progestogen can be associated with an increase in the risk of breast cancer depending on the type of progestogen	Thank you for your comment. The systematic review of data for risk of breast cancer associated with HRT was not sub-grouped according to type of progesterone, as agreed by the GDG at the time of developing the protocol. In the absence of such data, the GDG are unable to make a statement about any perceived differences between the preparations.
British Menopause Society	Full	22	18	It would be more accurate (based on clinic evidence) to state that the risk of increased diagnosis is duration dependent, beginning to emerge after at least 3 years exposure. It would also be valid to state that risk of diagnosis is unaffected by route of administration but may differ according to the class of progestin prescribed. There is no dosage effect or difference in risk according to time from menopause	Thank you for your comment. The impact of duration on treatment is discussed in section 10.5.8.2 of the guideline. No data were found for differences in the route of administration and the protocol did not differentiate data by type of progesterone. In the absence of such data, the GDG are unable to make a statement about either points.
Mylan EPD (BGP Products Ltd)	Full	22	18 19	HRT with oestrogen and progestogen can be associated with an increase in the risk of 18 breast cancer – Whilst Mylan agree with this statement consideration should be given to adding a line to say that not all HRT preparations containing Oestrogen and progestogen carry the same risk (see table provide in our comments number1), thereby affording women an informed choice of treatment.	Thank you for your comment. The systematic review of data for risk of breast cancer associated with HRT did not differentiate by type of preparations (for example, different types of progesterone), as agreed by the GDG at the time of developing the protocol. In the absence of such data, the GDG are unable to make a statement about any perceived differences.

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Royal College of General Practitioners	Full	23	9 11	After 5 years of stopping HRT (table 4), does it mean that the risk of fragility fracture can be more with those who have taken HRT? If the risk is from 19 fewer to 27 more?	Thank you for your comment. The GDG examined the effect of timing of HRT stopping on the risk of osteoporosis and the observational evidence showed that the risk of any type of fracture, non-vertebral, hip and osteoporotic fracture was not significantly different between previous HRT users discontinued HRT less than 5 years ago compared to no HRT users. The confidence interval suggests that the true estimate of effect is likely to fall within the range of 19 fewer to 27 more fractures.
British Menopause Society	Full	24	General	? LH and Oestradiol for <40 as in flow chart - make the same.	Thank you for your comment. The flowchart has been amended to reflect the recommendations in the POI section.
British Psychological Society	FULL	24	17	Research recommendations should include more alternative and psychological interventions, as well as non-medical factors and their impact on menopausal symptoms, including perceived intensity, bothersomeness, or interference for the above reasons. This should be addressed and included in the document.	Thank you for your comment. The GDG reviewed the evidence on alternative and psychological interventions using the set of outcomes outlined in the review protocol (see Appendix D.4 for the protocol and section 7.8 of the full guideline for a discussion on the evidence), and acknowledge the importance of ensuring that a woman with menopausal symptoms has access to non-hormonal treatment options. The outcomes of perceived intensity, bothersomeness, and interference were not prioritised for inclusion in the review protocol, and therefore the GDG are unable to comment on the currently evidence base for these.
Clinical	F	2	1	AMH routine testing is rarely available on the NHS for this indication and this	Thank you for your comment. The GDG

Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	full	4	4	recommendation is difficult to interpret. This is not a very helpful recommendation and will be challenging to implement in practice. It rather conflicts with recommendation number 57.	recommended that testing for AMH should not be routinely used to diagnose premature ovarian insufficiency. This feedback has been forwarded to the NICE implementation support team to inform their support activities for this guideline. Further, recommendation 57 has been amended following stakeholder consultation and now states that if a diagnosis of premature ovarian insufficiency if uncertain then a woman should be referred to a specialist healthcare professional with expertise in menopause or reproductive medicine.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	24	16	Change 'combined oral contraceptive' to 'combined hormonal' as the standard terms as it includes contraceptive rings and patches	Thank you for your comment. This has been amended as suggested.
British Menopause Society	Full	24	19	Clarify the advice given in that there is no evidence starting HRT in women at a younger age who have had a premature menopause increases the risk of breast cancer diagnosis. Years of HRT exposure should be counted from the age of 50 (the average age of the menopause).	Thank you for your comment. The guideline did not consider evidence for risk of breast cancer specifically in this age group of women. However, a recommendation has been included that states that the underlying baseline population risk increases with age and is considered to be very low in this group of women. Because of these differences in underlying

					risk, it is not possible to extrapolate the evidence from women in the higher age group.
University College London Hospitals NHS Foundation Trust	Full	24	20	This recommendation implies that there is no difference between using HRT or the COCP in women with POI, when in fact the limited available data would suggest that the benefits of HRT are greater than those of the COCP and that the risks of the latter are higher than the risks of the former. This recommendation should be reworded to reflect that the 2 options are not equal. However, the COCP does have a place in the management of POI, eg for women requiring contraception or in whom compliance is better with the COCP (often for social/psychological reasons)	Thank you for your comment. There were insufficient data comparing HRT with COCP in this population for the GDG to make a definite recommendation and therefore both are available as treatment options. It has been highlighted as an area for further research.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	24	23 25	As above	Thank you for your comment.
University College London Hospitals NHS	Full	24	25	Bone protection in women with POI is probably better with HRT than the COCP	Thank you for your comment. The recommendation reflects the best available evidence, although it is acknowledged that the quality of the evidence is very low.

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Foundation Trust					
British Menopause Society	Full	24	33	As all randomised trials of HRT (including tibolone) in breast cancer survivors have been stopped due to the first unfavourable interim analysis of the HABITS trial (and subsequently the LIBERATE trial) it is highly unlikely further trials of HRT will ever take place. There is a need however for RCTs of alternatives in symptomatic patients for the management of iatrogenic vasomotor symptoms	Thank you for your comment. The research recommendation has been amended to cover alternatives to systemic HRT treatment.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	24	35	Suggest add 'VTE and stroke' as it is the same issue.	Thank you for your comment. The GDG did not include stroke because the event rate in this population of women is so low that such a study is unlikely to be funded.
British Menopause Society	Full	24	36	Better to promote RCTs of progesterone or micronised progesterone (based on evidence from observational studies) and breast cancer diagnosis as preliminary data suggests less effect on risk of diagnosis compared with synthetic progestins	Thank you for your comment. This is already addressed by a research recommendation (What is the difference in the risk of breast cancer in menopausal women on HRT with either progesterone, progestogen or selective oestrogen receptor modulators?).
Sheffiel	F	2	3	Replace LNG secreting system with LNG releasing system – this is an error	Thank you for your comment. This has been

d Teaching Hospitals NHS Foundation Trust	UL L	4	8	throughout the document and in the abbreviations , specify dose of LNG (52mg)a nd mirena to avoid confusion with Jaydess – (contraceptive only)and levosert – 52 mg LNG but not licensed for endometrial protection	amended as requested.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	24	38	Correct term is 'levonorgestrel-releasing' not secreting	Thank you for your comment. This has been amended.
UK Clinical Pharmacy Association	Full	27 104	32 21	Under hormonal pharmaceutical treatments, the category 'oestrogen combined with natural progesterone' is missing. Note that evidence base considers natural progesterone, for eg. pg 96, line 1 Should the guidance state: oestrogen and progestogen / progesterone in women with uterus?	Thank you for your comment. This section of the guideline is a replication of the final scope that was agreed following public consultation. The scope does not explicitly exclude oestrogen combined with natural progesterone, which was subsequently prioritised for inclusion by the GDG at the time of protocol development.
Shionogi	Fu	31	NA	Section 7.11: The name 'ospemifene' has been misspelled as 'ospemefine'. Please correct.	Thank you for your comment, this has been amended.

Limited	ll				
Novo Nordisk	Full	3110710710810910911013	7.1133031322734382 1	Ospemifene inconsistent spelling Novo Nordisk recommends amending the spelling of ospemifene so that it is consistent throughout the whole document and consistent with the Summary of Product Characteristics.	Thank you for your comment, this has been amended.
Royal College	Fu	47	17	Should the median age of women having a natural menopause be used instead of mean age. The mean age of 51 years will be lower than the	Thank you for your comment. This text has been amended.

of Pathologists	ll			median due to women with POI and therefore less reflective of the age distribution of women having a natural menopause.	
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	49	13	Suggest change to 'women aged 21 to 55 years'	Thank you for your comment, this has been amended.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	49	32	'along with their duration'	Thank you for your comment. We have amended this sentence.
British	f	5	G	Figures 3 to 8 not very useful at all.	Thank you for your comment. Stakeholder feedback

Menopause Society	ull	053	eneral		indicates that these figures are useful for some readers and therefore they remain in the guideline. The quality of the figures has been improved to assist with readability.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	050 51	General	Graphs are useful but would benefit from being enlarge for greater clarity	Thank you for your comment. The quality of the figures has been improved to assist with readability.
Royal College of Pathologists	Full	51	6	FSH mIU/ml should be IU/L ; AMH <0.5ng/ml convert to 3.57 pmol/L ; Estradiol <34.5pg/ml should be Oestradiol < 126.6 pmol/L	Thank you for your comment. The units for biochemistry tests have been standardised based on the on the recommendations from UK Pathology Harmony.
Royal College of Pathologists	Full	52	2	As for comment 5; Inhibin B should be <0.4 ng/L	Thank you for your comment. The units for biochemistry tests have been standardised based on the on the recommendations from UK Pathology Harmony.
NCRI - Breast	FU	53	GE	Economic evidence: As a breast cancer patient suffering from severe menopausal symptoms, I know how they have affected my ability to work. I	Thank you for this comment. The GDG recognise how vasomotor symptoms can have a debilitating effect on

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CSG Working Group on Symptom Management	LL		NERAL	am a highly trained PhD scientist and I have been unable to work due to the effects of my hot flushes. Our Working Party conducted a survey of women with breast cancer and it was quite shocking how often we were told about women having to leave or down-size their job because of ho flushes and lack of sleep.	women. As such, the economic model assigns a substantial loss to health related quality of life arising from hot flushes.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	53	111 113	This sentence is not clear and would benefit from being rephrased – as well as what?	Thank you for your comment. This sentence has been rephrased.
Clinical Effectiveness Unit of Faculty of Sexual & Reprod	Full	53	114	'less or equal than 45 or 50 years' – this is not clear	Thank you for your comment. This sentence has been rephrased.

uctive Healthcare					
University College London Hospitals NHS Foundation Trust	Full	53	17	Use UK “flushes” not US “flashes” for consistency	Thank you for your comment. The terminology "flashes" has been changed to "flushes" wherever it appears in the guideline.
Royal College of Pathologists	Full	54	24	FSH mIU/ml should be IU/L	Thank you for your comment. The units for biochemistry tests have been standardised based on the on the recommendations from UK Pathology Harmony.
Royal College of Pathologists	Full	54	25	FSH mIU/ml should be IU/L	Thank you for your comment. The units for biochemistry tests have been standardised based on the on the recommendations from UK Pathology Harmony.
University College London Hospitals NHS	Full	54	26	Why quote AMH in ng/ml rather than in SI units of pmol/l? Please quote SI equivalent (as done in line 28 for ooestradiol). Most UK labs/clinicians use pmol/l for AMH	Thank you for your comment. The units for biochemistry tests have been standardised based on the on the recommendations from UK Pathology Harmony.

Foundation Trust					
Royal College of Pathologists	Full	54	26	AMH <0.5ng/ml convert to 3.57 pmol/L	Thank you for your comment. The units for biochemistry tests have been standardised based on the on the recommendations from UK Pathology Harmony.
Royal College of Pathologists	Full	54	27	AMH >0.5ng/ml convert to 3.57 pmol/L	Thank you for your comment. The units for biochemistry tests have been standardised based on the on the recommendations from UK Pathology Harmony.
Royal College of Pathologists	Full	54	28	Error in oestradiol conversion 126.6 pmol/L not pmol/mL	Thank you for your comment. The units for biochemistry tests have been standardised based on the on the recommendations from UK Pathology Harmony.
Royal College of Pathologists	Full	54	29	oestradiol >34.5pg/ml should be oestradiol > 126.6 pmol/L	Thank you for your comment. The units for biochemistry tests have been standardised based on the on the recommendations from UK Pathology Harmony.
Royal College of Pathologists	Full	54	34	inhibin B should be <0.4 ng/L	Thank you for your comment. The units for biochemistry tests have been standardised based on the on the recommendations from UK Pathology Harmony.
Royal	F	5	3	inhibin B should be >0.4 ng/L	Thank you for your comment. The units for

College of Pathologists	Full	4	5		biochemistry tests have been standardised based on the on the recommendations from UK Pathology Harmony.
Royal College of Pathologists	Full	55	7	cm3 should be cm^3	Thank you for your comment, this has been amended.
Royal College of Pathologists	Full	55	42	FSH mIU/ml should be IU/L	Thank you for your comment. The units for biochemistry tests have been standardised based on the on the recommendations from UK Pathology Harmony.
Royal College of Pathologists	Full	55	43	FSH mIU/ml should be IU/L	Thank you for your comment. The units for biochemistry tests have been standardised based on the on the recommendations from UK Pathology Harmony.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive	Full	57	22 23	As above, measuring hormone levels in women using hormonal contraception comes up a lot in clinical practice – most clinicians do rely on these results, including in women using Depo-Provera (Beksinska 2011 SAfJ Med). It can still be a useful positive diagnostic test.	Thank you for your comment. The GDG point out that the hormone levels may be confounded by hormonal contraception and this is discussed in the linking evidence to recommendation section 5.8 of the guideline.

Healthcare					
London North West Healthcare NHS Trust	Full	58	3	Agree wholeheartedly, but so many GPs measure FSH, LH, oestradiol regardless of age symptoms and amenorrhoea. How to change that behaviour?	Thank you for your comment. This has been forwarded to the NICE implementation support team to inform their support activities for this guideline.
British Menopause Society	Full	58	3	Agree wholeheartedly, but so many GPs measure FSH, LH, oestradiol regardless of age symptoms and amenorrhoea.	Thank you for your comment. This has been forwarded to the NICE implementation support team to inform their support activities for this guideline.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	58	49	We feel that checking FSH levels in women using almost all methods of hormonal contraception can give valid results. The sections here about women using hormonal contraception do suggest limitation of these tests which in practice can be useful and valid.	Thank you for your comment. The GDG point out that the hormone levels may be confounded by hormonal contraception and this is discussed in the linking evidence to recommendation section 5.8 of the guideline.
British Menopa	Fu	58	4.8.	The clinical usefulness of diagnosis is also covered well in the guidelines from the faculty of sexual and reproductive health entitled “Contraception for	Thank you for your comment. A recommendation has been added to the guideline on the provision of

use Society	l l		2	women over 40" I wonder if these can be cross referenced	information about contraception for women in perimenopausal and postmenopausal phase which references the Faculty of Sexual & Reproductive Healthcare clinical guidance on contraception for women aged over 40 years.
Sheffield Teaching Hospitals NHS Foundation Trust	FULL	58	28	In women aged 40-45 with menopausal symptoms including a change in menstrual cycle the suggestion is that an FSH will diagnose the menopause – should read perimenopause I see many women confused by FSH results – I suggest that in the Recommendations section we include the advise that appears earlier in the text that there is considerable fluctuation if FSH levels and they may be difficult to interpret. It seems that many GP do FSH and that it really is no helpful and although not hugely expensive an unnecessary cost	Thank you for your comment. The concern about misinterpretation of FSH levels is discussed in the linking evidence to recommendation section of the guideline, and the GDG do not believe that this level of detail is necessary to present in the recommendation. The term 'menopause' has been corrected to 'perimenopause'.
Primary Care Women's Health Forum	Full	60	24	Women with premature ovarian insufficiency may require higher doses of HRT. It would be helpful to clarify this. Equally as women get older the dose of oestrogen may be reduced.	Thank you for your comment. The protocol for the review did not include a review of HRT doses and therefore the GDG cannot provide guidance on this.
Poole Hospital NHS Trust	Full	61	12 22	It is also important that women and health professionals recognise that the onset of the menopause is an ideal time to review modifiable factors that may influence their risk of developing the health conditions mentioned above (lines 8-11)	Thank you for your comment. The GDG agreed with your comment and have highlighted this in the care pathway and updated recommendations.
Bayer PLC	Full	61	4	Under the introduction to the *'information and advice'* section, the recommendations for effective contraception in peri-menopausal women are not covered. This is despite the fact that in table 10, (p62 of the full guideline), it is reported that *'fertility issues'* was identified in the included studies as a topic that was *"found helpful by women or would have been helpful if they had received it"*. We suggest that that it is important to cover this here as	Thank you for your comment. A recommendation has been added to the guideline on the provision of information about contraception for women in perimenopausal and postmenopausal phase which references the Faculty of Sexual & Reproductive Healthcare clinical guidance on contraception for

				agreed by the developers during the scoping of this clinical guideline.	women aged over 40 years.
British Menopause Society	Full	61	12 22	It is also important that women and health professionals recognise that the onset of the menopause is an ideal time to review modifiable factors that may influence their risk of developing the health conditions mentioned above (lines 8-11)	Thank you for your comment. The GDG agreed with your comment and have highlighted this in the care pathway and updated recommendations.
British Menopause Society	full	61	12	Lifestyle changes—mentioned and hugely important but I cannot find any explanation of what lifestyle changes are recommended. Important to emphasise need for healthy weight, not smoking, minimal alcohol and regular exercise for symptom control and improved later health	Thank you for your comment, links to relevant NICE guidance have been included in the guideline.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	62	General	Very helpful but headings not ideal and difficult to read.	Thank you for your comment. This section has been edited to improve readability.
British Psychological Society	FULL	62 6	29 34	From the review of qualitative studies highlighting the information needs of women (p.62), more information about HRT was highlighted in 4 studies versus 2 studies for non-HRT options. However, in the Recommendations section 6.9 (p. 67), it is not sufficiently clear that non-HRT treatment options are available and information should be provided about them. Currently, the	Thank you for your comment. The GDG discussed the use of non-pharmacological options at great length and agreed that this should be clearly reflected in the recommendations. The recommendation has been amended accordingly.

		7	35	closest recommendation to this is phrased “lifestyle changes and interventions that could help general health and wellbeing”. This is insufficient and should be changed or extended so that health professionals know that information and the option of psychological interventions (e.g. CBT) can be, and should be, made available for VMS, as well as for anxiety and depression that occur from bothersome VSM. This information should be offered to menopausal women and their family or carers alongside information about HRT to allow them to have a fully informed choice.	
University College London Hospitals NHS Foundation Trust	Full	64	20	Sentence does not make sense – correct grammar	Thank you for your comment, this has been amended.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	64	22	Change ‘these’ to ‘this’	Thank you for your comment, this paragraph has been revised for clarity.

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University College London Hospitals NHS Foundation Trust	Full	64	23	Typo mid-sentence “women 2 felt”	Thank you for your comment, this has been amended.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	64	23	Remove ‘2’	Thank you for your comment, this has been amended.
University College London Hospitals NHS Foundat	Full	64	32	Typo at beginning of line “400”	Thank you for your comment, this has been amended.

ion Trust					
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	64	32	Remove '400'	Thank you for your comment, this has been amended.
British Menopause Society	Full	64	39	The number 3 is after 'RCT'	Thank you for your comment, this has been amended.
University College London Hospitals NHS Foundation Trust	Full	66	2	Typo "ion"	Thank you for your comment, this has been amended.
Clinical	F	6	2	Change 'ion' to 'in'	Thank you for your comment, this has been amended.

Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	full	6			
British Menopause Society	Full	66	7	The phrase 'in menopause' is not precise and conflicts with your clearer explanations in section 4.2. I suggest you search for this phrase throughout the document and replace with 'perimenopausal or postmenopausal' or both as appropriate	Thank you for your comment, this sentence has been amended for clarity. In this instance, it is referring to all women with a diagnosis of women so the GDG believe that the terminology is appropriate.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	66	12	Change 'highlighting' to 'highlight'	Thank you for your comment, this has been amended.
London	F	6	1	Please amend references to "smear "...they are cervical screening tests (	Thank you for your comment, this has been amended.

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Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

North West Healthcare NHS Trust	ull	6	4	done using liquid based techniques)	
British Menopause Society	full	66	14	Please amend references to “smear “...they are cervical screening tests (done using liquid based techniques)	Thank you for your comment, this has been amended.
Royal College of Nursing	Full	66	14	Please amend references to *“smear”,* this is an outdated term used generally only by lay people...they are now called cervical screening tests (done using liquid based techniques).	Thank you for your comment, this has been amended.
British Menopause Society	Full	67	39	Tiredness and loss of energy should be included here as many women don't appreciate it can be a menopausal symptom	Thank you for your comment. The symptoms of tiredness and loss of energy are difficult to define from the perspective of an evidence review, and often arise as the result of other menopausal symptoms such as vasomotor symptoms. As such, the GDG did not prioritise these for inclusion in the review.
Poole Hospital NHS Trust	Full	67	39	Tiredness and loss of energy should be included here as many women don't appreciate it can be a menopausal symptom	Thank you for your comment. The symptoms of tiredness and loss of energy are difficult to define from the perspective of an evidence review, and often arise as the result of other menopausal symptoms such as vasomotor symptoms. As such, the GDG did not prioritise these for inclusion in the review.
NCRI - Breast CSG	FUL	68	GEN	Information and advice the breast cancer patients who are very likely to develop menopausal symptoms as a result of treatment. Our survey of breast cancer patients found that fewer than 25% of patients, many with severe	Thank you for this comment. A recommendation is included which suggests that these women should be referred to a healthcare professional with expertise in

Menopause

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Working Group on Symptom Management	L		ERAL	menopausal symptoms, had ever been spoken to by a health care professional about their hot flushes. The recommendations could emphasise the importance of health care professionals being proactive with this group of women. (Management of hot flushes in UK breast cancer patients: comparing the clinician and patient perspective Fenlon et al MATURITAS 81(1):138 · MAY 2015)	menopause. The recommendations about the provision of information and advice pertain to this group of women also.
King's College Hospital NHS Foundation Trust	Full	68117	419	Access to menopause services: Many Clinical Commissioning Groups (CCGs) restrict funding for menopause hospital appointments to an initial assessment visit and one follow up visit. While this would be sufficient for providing a plan of management for the majority of menopause patients, a significant proportion may end up having limited access to specialist follow up (particularly women with complicated medical background or those where no local expertise is available). Would it be possible to suggest that funding should be considered for ongoing follow up, where required, for patients with complex medical background or those who have no local specialist expertise.	Thank you for your comment. This has been forwarded to the NICE implementation support team to inform their support activities for this guideline.
British Menopause Society	Full	68117	419	Access to menopause services: Many Clinical Commissioning Groups (CCGs) restrict funding for menopause hospital appointments to an initial assessment visit and one follow up visit. While this would be sufficient for providing a plan of management for the majority of menopause patients, a significant proportion may end up having limited access to specialist follow up (particularly women with complicated medical background or those where no local expertise is available). Would it be possible to suggest that local CCGs consider funding ongoing follow up, where required, for patients with complex medical background or	Thank you for your comment. This has been forwarded to the NICE implementation support team to inform their support activities for this guideline.

				those who have no local specialist expertise.	
British Menopause Society	Full	68	7	Women who are likely to undergo menopause early eg after cancer treatment. Should be given information about menopause and fertility. I think it is important that such women are referred to a fertility specialist to discuss the option of egg or embryo freezing.	Thank you for your comment. The GDG believe that the recommendations currently address all of the points raised in this comment.
British Menopause Society	Full	68	9	Women in this category should also be given information about age specific risks of HRT as many have preconceived ideas based on media publicity relating to potential risks in older women where the risk/benefit profile maybe very different.	Thank you for your comment. The recommendation highlight the importance of individualising the care of a women which includes taking into account the modifying influence of age on risk. Where applicable, age has been highlighted in the recommendations.
Poole Hospital NHS Trust	Full	68	9	Women in this category should also be given information about age specific risks of HRT as many have preconceived ideas based on media publicity relating to potential risks in older women where the risk/benefit profile maybe very different.	Thank you for your comment. The recommendation highlight the importance of individualising the care of a women which includes taking into account the modifying influence of age on risk. Where applicable, age has been highlighted in the recommendations.
British Menopause Society	Full	69	7	I think tiredness should be included as a common presenting symptom. It is very common	Thank you for your comment. The symptoms of tiredness is difficult to define from the perspective of an evidence review, and it often arises as the result of other menopausal symptoms such as vasomotor symptoms. As such, the GDG did not prioritise these for inclusion in the review.
Clinical Effectiveness Unit of Faculty of Sexual	Full	69	7.2	This is a clear and useful introduction	Thank you for this comment.

& Reproductive Healthcare					
British Menopause Society	Full	69	12	Regardless of whether or not fatigue, palpitations and anxiety are caused by the menopause per se or are a secondary response to sleep disturbance, they are frequently reported menopausal symptoms	Thank you for your comment. The symptoms of fatigue, palpitations and anxiety are difficult to define from the perspective of an evidence review, and often arise as the result of other menopausal symptoms such as vasomotor symptoms. As such, the GDG did not prioritise these for inclusion in the review.
Poole Hospital NHS Trust	Full	69	12	Regardless of whether or not fatigue, palpitations and anxiety are caused by the menopause per se or are a secondary response to sleep disturbance, they are frequently reported menopausal symptoms	Thank you for your comment. The symptoms of fatigue, palpitations and anxiety are difficult to define from the perspective of an evidence review, and often arise as the result of other menopausal symptoms such as vasomotor symptoms. As such, the GDG did not prioritise these for inclusion in the review.
Royal College of Obstetricians and Gynaecologists	Full	69	18	Section 7.2 - Why is percentage and % used in same line?	Thank you for your comment, this has been amended.
British Menopause	Full	69	33	"HRT has been considered to be the most effective treatment " - this statement implies there has been some change in the evidence. There has not, HRT *is* the most effective treatment based on numerous RCTs and	Thank you for your comment. This sentence has been reworded so that the introduction does not presuppose the evidence.

Society	l			reviews of the literature. Whether it is appropriate for a women at any given time is another matter, but it is the most effective treatment.	
Poole Hospital NHS Trust	Full	69	33	"HRT has been considered to be the most effective treatment " - this statement implies there has been some change in the evidence. There has not, HRT *is* the most effective treatment based on numerous RCTs and reviews of the literature. Whether it is appropriate for a women at any given time is another matter, but it is the most effective treatment.	Thank you for your comment. This sentence has been reworded however as this is the introduction to the topic we would not discuss whether HRT is the most effective treatment as this would presuppose the evidence.
British Menopause Society	Full	69	42	VSM should be VMS	Thank you for your comment, this has been amended.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	69	42	Should be VMS, not VSM	Thank you for your comment, this has been amended.
NCRI - Breast CSG Working Group	FULL	69	43	"some women with hormone dependent breast cancer experience severe hot flushing" In our survey 94% of breast cancer patients who responded had hot flushes.£30% of respondents said their flushes were so bad they had considered stopping taking their medication. (Management of hot flushes in UK breast cancer patients: comparing the clinician and patient perspective	Thank you for your comment. The paragraph has been amended to indicate that this is an issue for many women, and that flushing can lead to poor treatment adherence which reduces time to recurrence.

on Symptom Management				Fenlon et al MATURITAS 81(1):138 · MAY 2015) I believe the word "some" does not reflect the patients experience. I think "most" or "many" would be more appropriate. We now know that fewer than 50% complete their 5 years of oestrogen blocking drugs and this leads to a shocking 30% increase in breast cancer mortality (McCowan, Wang et al. 2013 "The value of high adherence to tamoxifen in women with breast cancer: a community-based cohort study." Br J Cancer 109(5): 1172-80).	
Derbyshire Community Sexual Health Service	full	70	General	advise add in acupuncture to the non-drug therapies P147 advise change recommendation to HRT lowers risk of developing diabetes	Thank you for your comment. The importance of giving a women information about non-hormonal treatment options has been added to the recommendation. The recommendation concerning the risk of developing type 2 diabetes is based on the best available evidence identified by the systematic review.
NCRI - Breast CSG Working Group on Symptom Management	FULL	70	1	Alternatives for women with breast cancer. No mention of progesterone/progestins. I find this rather strange. Megace has been used for decades very successfully as an extremely effective treatment for hot flushes in breast cancer. (Loprinzi, Michalak et al. 1994 "Megestrol acetate for the prevention of hot flashes." N Engl J Med 331(6): 347-52. Quella, Loprinzi et al. 1998 "Long term use of megestrol acetate by cancer survivors for the treatment of hot flashes." Cancer 82(9): 1784-8.Bullock, Massey et al. 1975; Use of medroxyprogesterone acetate to prevent menopausal symptoms." Obstet Gynecol 46(2): 165-8. Morrison, Martin et al."The use of medroxyprogesterone acetate for relief of climacteric symptoms." Am J Obstet Gynecol 138(1): 99-104. 1980; Lobo, McCormick et al. 1984 "Depo-medroxyprogesterone acetate compared with conjugated estrogens for the treatment of postmenopausal women." Obstet Gynecol 63(1): 1-5.). (Loprinzi, Levitt et al.	Thank you for your comment. Both of these studies were identified in the systematic review search. However, they were not eligible for inclusion in the network meta-analysis as they were not of long enough duration to allow for an accurate estimation of the intervention's effect (Loprinzi 1994 reported results at 4 weeks follow-up and Bertelli 2002 at 6 weeks follow up). The network meta-analysis protocol specifies that the results from the longest follow-up time point from 12 weeks, but less than 26 weeks, will be included to allow for demonstration of the full treatment effect.

				Bertelli, G., M. Venturini, et al. (2002). "Intramuscular depot medroxyprogesterone versus oral megestrol for the control of postmenopausal hot flashes in breast cancer patients: a randomized study." Ann Oncol 13(6): 883- 8Barton, D., C. Loprinzi, et al. (2002). "Depomedroxyprogesterone acetate for hot flashes." J Pain Symptom Manage 24(6): 603-7.) Many "older" breast cancer oncologists still use it but some newer oncologists have been influences by the arguments that the combined HRT containing progesterone increases the risk of breast cancer. There is evidence from the French E3N cohort that the origin of the progesterone is critical (something you don't mention strangely) with some progesterone HRTs actually protective. (Fournier, A., F. Berrino, et al. (2008). "Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study." Breast Cancer Res Treat 107(1): 103-11.) A recent Nature paper suggests that progesterone may also be protective in breast cancer. (Progesterone receptor modulates ERα action in breast cancer. Mohammed, H et al; doi:10.1038/nature14583)	
Pharma Care Europe	Full	70	4	The statement that "*Herbal preparations, isoflavones and bioidentical hormones are unregulated*" is highly unfounded and generalised. Within Europe, reputable companies ensure that their brands are fully compliant with all legislation related to the sourcing, production, labelling, selling and marketing of food supplements. Food supplements such as Promensil are a highly regulated part of the food industry with numerous control mechanisms to ultimately ensure the health and safety of consumers.	Thank you for your comment. This statement has been edited for clarity in the full guideline and now states that these preparations "are not regulated by the European Medicines Authority".
Pharma Care Europe	Full	70	5	The statement goes on to state *"…and in many instances not subject to any quality control or research studies of sufficient power or quality*". This may be true for some non-reputable products, but is not applicable to reputable and responsible brands such as Promensil®.	Thank you for your comment, this sentence has been amended. However, the review protocol did not consider differences between the formulations, and therefore the GDG are unable to make comments about specific brands such as Promensil®.

				Quality Control: Promensil sources its active Red Clover Isoflavones from a single high quality European source, the specification of which includes identification compliance to the USP monograph (for "Powdered Red Clover Extract"), a standardised content of total isoflavones (40% +/- 10%), a standardised ratio of the four key isoflavones (Genistein + Biochanin A/Daidzein + Formononetin) as well as maximum limits for Loss on drying, Sulphated ash, Residual solvents and Heavy metals (As, Cd, Hg, Pb). With particular respect to the standardised level of active red clover isoflavones provided by Promensil, this has been further substantiated in the following study: ➢ *Determination of phytoestrogens in dietary supplements by LC-MS/MS. Clarke DB et al. Food Add Contam 2008; 25(5):534-547*. Summary results – DEFRA analysis confirms Novogen Red Clover isoflavones (Novogen is the former name of Promensil) contains a standardised 40mg level of Red Clover isoflavones. 19 out of 28 (70%) UK isoflavone supplements contained less than the required 40mg minimum effective level of isoflavones. This standardised content is a key factor. It is important that healthcare professionals understand the quality and level of active ingredients (recommended 80mg as a starting dose; 40mg as a maintenance dose) when making their recommendations. Research studies: Promensil and Red-Clover Isoflavones have more than 15 years' worth of clinical research covering all areas of Menopausal related symptoms.	
Pharma Care Europe	Full	70	6	The statement finishes by stating "*They may not be safer than standard preparations, evidence on efficacy and side effects is incomplete*". Safety/side-effects of Promensil/Red Clover Isoflavones: Promensil is one of	Thank you for this comment. The GDG have amended their recommendation to take account of certain preparations where more data relating to safety are available.

				the UK's leading brands for non-HRT based menopause management and is safely taken by thousands of women across the country. In addition there have been numerous studies carried out investigating the safety of red clover isoflavones with respect to both breast and endometrium health. Further studies on Breast safety include: • *Red Clover isoflavones are safe and well tolerated in women with a family history of breast cancer. Powles T. et al. Menopause Int. 2008;14:6-12*. Summary results – No oestrogenic increase in breast density seen over 3 years when Red Clover isoflavones (Promensil) taken by women with a first-degree relative with breast cancer compared to placebo (Randomised double-blind, placebo controlled study). • *Isoflavones and women's health. Powles T. Breast Cancer Res 2004;6(3):140-142*. Summary results – No oestrogenic increase in breast density with Red Clover Isoflavone use - indicates they are unlikely to cause increased risk of breast cancer (Expert commentary). Further studies on Endometrium safety include: • *A double-blind randomised study of the effects of Red Clover isoflavones on the endometrium. Hale et al, Menopause 2001; 8(5):338-346*. Summary results – No increase in endometrial thickening by endometrial biopsy over 3 months (Randomised double-blind, placebo controlled study). • *Effects of a Red Clover extract (MF11RCE) on endometrium and sex hormones in post-menopausal women. Imhof M et al. Maturitas 2006;55:76-81*. Summary results – Significant decrease of 14.7% in endometrial thickness in postmenopausal women (Randomised,	In relation to the studies presented here: • Powles 2008 was a study in health women and therefore did not meet the protocol • Powles 2004 was a commentary and therefore did not meet the protocol • Endometrium safety was not included as a specific outcome of interest • Jeri A 2002 could not be accessed via the usual document sourcing methods • Nachtigall 2006 was a review and therefore did not meet the protocol for inclusion • Nachtigall 1999 could not be accessed via the usual document sourcing methods • Unpublished data were not considered for inclusion in the review.

				double-blind, placebo controlled study). • *Effects of Red Clover isoflavones (Promensil) versus placebo on uterine endometrium, vaginal maturation index and the uterine artery in healthy postmenopausal women. Woods R et al. J Br Menopause Soc, Suppl S2, 2003:23*. Summary results – No increase in endometrial thickness after 8 weeks (Randomised, double-blind, placebo controlled study). Efficacy, in relation to Promensil/Red Clover Isoflavones and Vasomotor Symptoms: in addition to those studies already considered within this NICE Guidance, the following research has also been carried out: • *The use of an isoflavone supplement to relieve hot flushes. Jeri A. The Female Patient 2002;27:35-37*. Summary results – Frequency of hot flushes reduced by 48.5% and Severity of hot flushes reduced by 47% (Randomised double-blind, placebo controlled study). • *Complementary and hormonal therapy for vasomotor symptom relief: a conservative clinical approach. Nachtigall LE et al. JOGC 2006;28(4):279-289*. Summary results – Red Clover isoflavones recommended option for mild to moderately symptomatic women combined with lifestyle modifications (Vasomotor symptom clinical treatment algorithm). • *Non-prescription alternative to hormone replacement therapy. Nachtigall L et al. The Female Patient 1999;24:45-50*. Summary results – 56% reduction in frequency of hot flushes, 43% reduction in severity of hot flushes and 52% reduction in severity of night sweats. On-going research In addition to these studies described above, in 2012 PharmaCare and its agents in Italy (NAMED SpA) commissioned a study in Italy entitled “Effect of	

				oral administration of red clover on menopausal symptoms of the syndrome induced by adjuvant hormonal treatment in women diagnosed with breast cancer". The primary objectives of this study are two-fold: • Improving the quality of life by reducing symptoms of menopausal syndrome induced by antineoplastic treatment, and • Demonstration of non-toxicity and of additional non-interference related to the treatment. The conclusion of the study is imminent and results expected later in 2015.	
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	70	7	Change comma to semicolon	Thank you for your comment, this has been amended.
British Menopause Society	Full	70	15	VSM should be VMS	Thank you for your comment, this has been amended.
Sheffield Teaching	FULL	70	15	Replace VSM with VMS Add acupuncture to the non drug treatments	Thank you for your comment, this has been amended.

Hospitals NHS Foundation Trust					
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	70	15	Should be VMS, not VSM	Thank you for your comment, this has been amended.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	70	30	Suggest change 'patient' to 'woman'	Thank you for your comment, this has been amended.

Menopause

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British Menopause Society	Full	70	42	I find it hard to understand why severity of hot flushes is not considered. Most studies in this area have looked at severity as it is not uncommon for HRT to reduce severity but not frequency. I accept a scoring system was not appropriate as there are so many different options in this area.	Thank you for your comment. Frequency of flushing was decided as a measure for this outcome rather than severity, since the latter was not as widely reported and diverse scales have been used that would make the synthesis of evidence problematic and less precise (see section 8.8 of the full guideline for a discussion of this issue). This was discussed at length with the GDG at the time of protocol development.
British Psychological Society	FULL	70	42	The Society has concerns over the appropriateness of the choice of outcome measure used in the meta-analysis in the consultation document. Firstly, there is a disparity between the outcome measures outlined in the initial scoping document (i.e. frequency or intensity of VSM) and the outcome used in consultation document (i.e. only frequency of VMS). It is unclear why the decision was made to exclude research that has measured intensity of symptoms. Research shows that intensity, interference, or how troublesome hot flushes / night sweats (HFNS) are the main reason that women seek treatment with regards to menopausal symptoms (Hunter & O'Dea, 1997), not their frequency. Therefore, using frequency as the only main outcome measure for the review is limiting the usefulness and appropriateness of the guidelines. The use of problem ratings for of hot flushes is recommended as more clinically relevant due to the impact on quality of life (Archer et al, 2011). Through exclusion of studies using interference/bothersome/problem-ratings as the outcome, the conclusions and recommendations do not reflect the full range of appropriate and relevant evidence that should be considered as outlined in the scope. In addition, it excludes interventions that have been	Thank you for your comment. Frequency of flushing was agreed as the measure for this outcome rather than severity since the latter was not as widely or consistently reported, thus making the synthesis of evidence problematic and less precise (see section 8.8 of the full guideline for a discussion of this issue). The GDG acknowledge the limitations and discuss this in the linking evidence to recommendation section of the guideline.

				tested using these rating outcomes, when in fact; the North American Menopause Society recommends interventions that are based on bothersomeness of symptoms, impact on sleep and quality of life (Shifren et al, 2014). Such exclusions "biases the choice of studies in favour of HRT and against self-management interventions". It is interference/bother that is associated with QOL and help-seeking to a greater extent than frequency (Ayers et al, 2013).	
NCRI - Breast CSG Working Group on Symptom Management	FULL	71	30	Same point as above. The use of progesterone should at least be reviewed.	Thank you for your comment. As stated in this section of the guideline, progesterone was included as a possible intervention in the network meta-analysis. It is also stated in the protocol contained in Appendix D.4.
British Menopause Society	Full	71	39	I think you need to introduce 'frequency of' before 'vasomotor symptoms' in this line	Thank you for your comment. The text has been amended.
British Menopause Society	Full	72	4	This list is by no means complete: two of the earliest seminal RCTs are not included, Coope et al BMJ 1975; 4:139-43 and Whitehead & Campbell in Clinics in Obstetrics & Gynaecology (Edited by Greenblatt R, Studd JWW)1977; 4: 31-47? More recently Panay N et al Climacteric 2007;10:120-31	Thank you for your comment. Please refer to the excluded studies list in Appendix G of the full guideline. The Coope 1975 study was excluded from the review because data were presented in graphical format and not accompanied by numbers. Panay 2007 and Whitehead and Campbell 1977 were subsequently excluded because no measure of uncertainty/variance was reported.

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Poole Hospital NHS Trust	Full	72	4	This list is by no means complete: two of the earliest seminal RCTs are not included, Coope et al BMJ 1975; 4:139-43 and Whitehead & Campbell in Clinics in Obstetrics & Gynaecology (Edited by Greenblatt R, Studd JWW)1977; 4: 31-47? More recently Panay N et al Climacteric 2007;10:120-31	Thank you for your comment. Please refer to the excluded studies list in Appendix G of the full guideline. The Coope 1975 study was excluded from the review because data were presented in graphical format and not accompanied by numbers. Panay 2007 and Whitehead and Campbell 1977 were subsequently excluded because no measure of uncertainty/variance was reported.
Royal College of Pathologists	Full	72	7	Nielsen 2009 study oestradiol quoted as 0.16 nmol/L should be 160 pmol/L	Thank you for your comment. The units for biochemistry tests have been standardised based on the on the recommendations from UK Pathology Harmony.
British Menopause Society	Full	72	11	I find it amazing that of all the studies into testosterone only a preparation unavailable to prescribe is described. There are also good studies with testosterone implants that could have been included. In addition why is further research into other less costly transdermal testosterone gels not a research question?	Thank you for your comment. The review protocol allowed for the inclusion of all types of testosterone doses and preparations. The data presented are those that reported the outcomes that were prioritised for inclusion in the review. The GDG did not prioritise testosterone for inclusion in a research recommendation.
British Menopause Society	Full	72	11	You state you have chosen frequency of sexual function as an outcome but these studies report frequency of satisfying sexual activity. It is therefore important that you include the phrase 'satisfying' in this table and your later discussions/conclusions	Thank you for your comment. This is correct and the text has been amended where appropriate.
Sheffield Teaching Hospital	FULL	73	General	Purdie inc criteria replace VSM with VMS	Thank you for your comment, this has been amended.

s NHS Foundation Trust					
Royal College of Pathologists	Full	73	General	Geller 2009 study FSH mIU/ml should be IU/L	Thank you for your comment. The units for biochemistry tests have been standardised based on the on the recommendations from UK Pathology Harmony.
Royal College of Pathologists	Full	74	General	Speroff 2003 study FSH 40 IU ; should be IU/L ; E2 level of no more than 20 pg/mL should be oestradiol no more than 73 pmol/L unless E2 defined in abbreviations as oestradiol. Also same comment for Guttuso 2003.	Thank you for your comment. The units for biochemistry tests have been standardised based on the on the recommendations from UK Pathology Harmony.
Royal College of Pathologists	Full	75	General	E2<30pg/ml should be oestradiol < 110 pmol/L ; E2 comment as above	Thank you for your comment. The units for biochemistry tests have been standardised based on the on the recommendations from UK Pathology Harmony.
Royal College of Pathologists	Full	76	General	Geller 2009, Tice 2003 FSH mIU/ml should be IU/L; Yang 2007 oestrogen E2 should be oestradiol < 73 pmol/L	Thank you for your comment. The units for biochemistry tests have been standardised based on the on the recommendations from UK Pathology Harmony.
Royal College of Pathologists	Full	77	General	Amsterdam 2009 FSH mIU/ml should be IU/L; Zheng 2013 E2<30pg/ml should be oestradiol < 110 pmol/L ; E2 comment as above	Thank you for your comment. The units for biochemistry tests have been standardised based on the on the recommendations from UK Pathology Harmony.

Royal College of Pathologists	Full	78	General	Qu 2009, Morrison 2004, Speroff 2003 FSH should be IU/L ; E2 level of no more than 20 pg/mL should be oestradiol no more than 73 pmol/L	Thank you for your comment. The units for biochemistry tests have been standardised based on the on the recommendations from UK Pathology Harmony.
Royal College of Pathologists	Full	80	general	Lin 2011 FSH mIU/ml should be IU/L	Thank you for your comment. The units for biochemistry tests have been standardised based on the on the recommendations from UK Pathology Harmony.
Royal College of Pathologists	Full	81	General	Zheng 2013 E2<30pg/ml should be oestradiol < 110 pmol/L ; E2 comment as above	Thank you for your comment. The units for biochemistry tests have been standardised based on the on the recommendations from UK Pathology Harmony.
Royal College of Pathologists	Full	82	General	Amsterdam 2009 FSH mIU/ml should be IU/L; Zheng 2013 E2<30pg/ml should be oestradiol < 110 pmol/L ; E2 comment as above	Thank you for your comment. The units for biochemistry tests have been standardised based on the on the recommendations from UK Pathology Harmony.
Royal College of Pathologists	Full	83	General	Tice 2003 FSH mIU/ml should be IU/L	Thank you for your comment. The units for biochemistry tests have been standardised based on the on the recommendations from UK Pathology Harmony.
Royal College of Patholo	Full	84	Gener	Qu 2009 E2 level of no more than 20 pg/mL should be oestradiol no more than 73 pmol/L; FSH mIU/ml should be IU/L	Thank you for your comment. The units for biochemistry tests have been standardised based on the on the recommendations from UK Pathology Harmony.

gists			al		
Derbyshire Community Sexual Health Service	full	89	General	I worked out ? CAD is short for Canadian dollars but not sure what SEK is	Thank you for this comment. SEK refers to Swedish Krona, from the ISO 4217 International Currency Code. We've amended the guideline so that International currency codes are spelt out in full in brackets at the first use.
Sheffield Teaching Hospitals NHS Foundation Trust	FULL	89	General	What is SEK – CAD is Canadian dollars not in abbreviations	Thank you for this comment. SEK refers to Swedish Krona, from the ISO 4217 International Currency Code. We've amended the guideline so that International currency codes are spelt out in full in brackets at the first use.
Derbyshire Community Sexual Health Service	Full	90	General	– acupuncture costs are based on an initial consultation fee then 12 treatments at weekly intervals ? repeated over 5 years – this overestimates its costs – our local acupuncture clinic does 6 treatments at fortnightly intervals then one top up treatment every 3 months which is effective at lower cost.	Thank you for this comment. As noted, the acupuncture costs are based on an initial consultation fee of £65 followed by 11 sessions at £40 each. In footnote f to Table 35 is states that's "It is assumed that acupuncture is for 13 weeks (one cycle only) and that no further treatment costs are incurred in subsequent cycles". It is assumed that any treatment benefit obtained in the first cycle is maintained throughout the 5 years and therefore, if anything, the model is more likely to underestimate the cost to achieve a treatment gain sustained over 5 years. However, although the costs of acupuncture are likely to be underestimated for this reason this does not

					have an important bearing on the health economic results. This has been added to the discussion in the relevant section of the health economic appendix.
Sheffield Teaching Hospitals NHS Foundation Trust	FULL	90 92	General	RE Acupuncture costs are based on 12 sessions at weekly intervals after initial assessment ? repeated over 5 years – our local clinic provides 6 sessions fortnightly and one top up at 3m – which will attract a much lower cost. When considering the cost effectiveness of acupuncture the alternatives eg ssri and gabapentin show a 3 month cost , this would be on going at the same rate for these medications whereas for acupuncture cost effectiveness lasts for 3m and requires a top up at around 3 months. When this is considered acupuncture costs are very favourable. This data does not consider long term discontinuation rates of any of these medications nor does it consider discontinuation rates of tamoxifen/aromatase inhibitors because of se and the cost to the NHS of managing recurrences because of this. Acupuncture effectiveness data in women with breast cancer- no data – is there any to include here?	Thank you for this comment. As noted, the acupuncture costs are based on an initial consultation fee of £65 followed by 11 sessions at £40 each. In footnote f to Table 35 is states that's ""It is assumed that acupuncture is for 13 weeks (one cycle only) and that no further treatment costs are incurred in subsequent cycles"". Although not stated, it is assumed that any treatment benefit obtained in the first cycle is maintained throughout the 5 years and therefore, if anything, the model is more likely to underestimate the cost to achieve a treatment gain sustained over 5 years. The costs of gabapentin and SSRI's are however assumed to continue throughout the 5-year timeframe of the model - discontinuation of gabapentin and SSRI's is taken into account although there are some limitations to this as noted in the discussion section of Appendix L. The GDG do not understand the comment about tamoxifen/aromatase inhibitors. However, they were not excluded from the model because of their side effects or costs; tamoxifen/aromatase inhibitors were not evaluated treatments. Alternatively, if this suggesting that in women with breast cancer there

					might be lower discontinuation of these breast cancer treatments with some treatments (e.g. acupuncture) than other comparators and that this could lead to a differential impact on breast cancer outcomes, then the evidence was not available to model this - the economic model was based on data in the network meta-analysis and there was no acupuncture data included in the network meta-analysis for women with breast cancer.
Sheffield Teaching Hospitals NHS Foundation Trust	FULL	91	General	Acupuncture effectiveness- no data given on effectiveness of acupuncture in the management of VMS	Thank you for your comment. Acupuncture was included in the protocol as an intervention for the management of short term symptoms, although the data did not meet the inclusion criteria for the review.
Sheffield Teaching Hospitals NHS Foundation Trust	FULL	91	13	Table xx should read 15	Thank you for your comment, this has been amended.
British Menopause	Ful	92	15	I am staggered that you have found that there is uncertainty as to the efficacy of oral HRT on VMS. This conclusion ripples down through all the rest of the document – economic conclusions and recommendations. This is a major	Thank you for your comment. For the outcome of vasomotor symptoms the results from the network meta-analysis found a large degree of uncertainty for

Society	I			surprise. I feel that this needs a major revisit or a much clearer explanation of the decision of the GDG with regard to the concluded uncertainty.	the efficacy of oral oestrogen plus progestogen, rather than showing conclusively that it is ineffective. Therefore the GDG believe that it was important that the treatment choices available to patients were not restricted because of this finding.
British Menopause Society	Full	92	15 16	Is there really 'a degree of uncertainty' regarding efficacy for e+p alleviating vasomotor symptoms? Raised elsewhere	Thank you for your comment. Although a number of publications evaluating oestrogen plus progestogen for the treatment of VMS were identified by the literature search, several were subsequently excluded when they failed to report key characteristics such as standard errors or standard deviations required to consider uncertainty in their estimates of effect (see Appendix K.2.4). The exclusion of some of these publications then limited the comparisons with oestrogen plus progestogen that could be included in the treatment network. A discussion of the limitations of the analysis is presented in Appendix K.4 of the full guideline. Overall, the results of the analysis found that the treatment effect for oestrogen plus progesterone was associated with a degree of statistical uncertainty.
Pfizer	Full	92	26	In Section 7.7.1 of the full guidance the Committee states: *"Low quality evidence due to high heterogeneity within the network 25 demonstrated that women treated with non-oral oestradiol plus progestogen or with 26 bazedoxefine plus oestradiol were less likely to discontinue treatment than if they were 27 treated with placebo or tibolone."* The Committee appear to have mistakenly stated that women treated with bazedoxefine plus oestradiol are less likely to discontinue treatment instead	Thank you for your comment. All references to 'bazedoxifene' have now been replaced with 'conjugated oestrogens plus bazedoxifene'. All other references to bazedoxifene have also replaced with 'conjugated oestrogens plus bazedoxifene'.

				of bazedoxefene plus oestrogens. Bazedoxifene (BZA) alone is not currently available to be prescribed to women in the UK and the only licensed combination which includes BZA is conjugated oestrogens and bazedoxifene (CE/BZA, 0.45mg/20mg). Therefore Pfizer suggests that any reference to BZA alone should be removed from the Guideline to safeguard against the possibility of confusing users. Furthermore, in line with comment 2, Pfizer proposes that the committee replace the current nomenclature with "conjugated oestrogens with bazedoxifene". .	
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	92	39	Should be 'drawn'	Thank you for your comment, this has been amended.
British Psychological Society	FULL	93 104	general	HRT is not generally recommended as a treatment for depression or low mood - the recommendation should be qualified, e.g. HT might improve low mood that is a consequence of flushes and night sweats.	Thank you for your comment. This recommendation has been edited for clarity.
British	F	9	1	This paragraph needs rewording. It makes very little sense.	Thank you for your comment. The paragraph has

Menopause Society	full	3	10		been edited to improved clarity.
British Menopause Society	full	97	3943	Q1.Transdermal E/P most cost effective inn women with a uterus. This will have a big impact om practice as more expensive than oral. However that is what NICE guidelines are all about.	Thank you for this comment. The cost-effectiveness implications for this recommendation are discussed in section 8.8.3 of the full guideline. Please note that the recommendation has been amended so that it more clearly allows for the provision of both oral and transdermal preparations.
British Menopause Society	full	98	1	Q1. Non oral best in women without uterus. Same as above comment.	Thank you for your comment. The developers do not receive comments in order so are unclear as to what this comments refers to.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	100	2, 3	Should it be 'the GDG wanted to draw the attention of health care professionals to the need to accommodate…' Committee appears several times again in this section – should it be GDG as per earlier sections for consistency?	Thank you for your comment. The text has been amended to GDG throughout the guideline for consistency.
British Menopause	full	100	22	Q!. Will be difficult to recommend due to safety warning	Thank you for your comment. The GDG acknowledges the potential issues associated with the provision of these treatments and has amended the

Society	l		23		recommendation in order to highlight these more clearly.
British Menopause Society	full	100	38	Q!. SSRIs . this will be a change of practice. However important to get the message out.	Thank you for your comment. This has been forwarded to the NICE implementation support team to inform their support activities for this guideline.
British Menopause Society	full	100	49	Q1. As stated recommending St Johns Wort could be very controversial due to its interactions	Thank you for your comment. The GDG discussed the possible interactions between St John's Wort and tamoxifen for women with a history or at risk of breast cancer and this has now been highlighted in the recommendation.
British Menopause Society	Full	101	7/8	women with a history of or at high risk of breast cancer - refer to a specialist - but what as a specialist should we be advising??	Thank you for this comment. Women with a history or at risk of breast cancer should be referred to a healthcare professional with expertise in menopause. The GDG recommend that health professionals who care for women who had or at risk of breast cancer should get advice on the treatment of menopausal symptoms as described in sections 1.13 of the NICE guideline on early and locally advanced breast cancer and section 1.7 of the NICE guideline on familial breast cancer.
Clinical Effectiveness Unit of Faculty of Sexual &	Full	101	12	Should be ‘versus’	Thank you for your comment, this has been amended.

Reproductive Healthcare					
Menopause UK	Full	102	7	***13.6 Low mood and anxiety*** The guideline recognises that women commonly experience depression and mood changes at times of hormonal change such as the menopause (7.2). Certainly, low mood and anxiety are very commonly reported by women seeking advice from Menopause UK's members' professional and peer support services and fora. ▪ We welcome recommendation 14: "Consider offering HRT to alleviate low mood in menopausal women". ▪ We question whether the evidence fully supports the inclusion of recommendation 15: "Consider CBT to alleviate low mood and anxiety in menopausal women". ▪ We question the conclusions drawn at 7.7.2.3. "Comparison of psychological treatments vs usual care". The appropriateness of CBT for low mood and anxiety in menopause is more controversial than the current wording of the guidelines suggest. The comments from a visitor called 'Hot Flush' to our website illustrate the debate succinctly http://menopauseuk.org/2014/10/13/151/ This is an area where there seems to be a considerable gap between the	Thank you for your comment. The GDG reviewed moderate quality evidence from one RCT which compared CBT and usual care in women in menopause, which demonstrated that CBT was significantly more effective than usual care in reducing anxiety and low mood at 26 weeks follow-up. Please refer to table 30 in Appendix I for the quality assessment of this data. For the outcome of anxiety, the mean difference between groups was 0.15 lower (95% CI -0.24 to -0.06), and for low mood the mean difference was 0.15 lower (95%CI -0.28 to -0.02). The recommendation has been amended following consultation in order to improve clarity, and stress the importance of having non-hormonal therapies available as an option for women who are experiencing reduced quality of life as a result of their menopausal symptoms. Further, the GDG acknowledge that there are cross-cultural differences in experiences and that reactions to menopausal symptoms may vary from one woman to another. However, this guideline aims to raise awareness of all potential treatment options, whilst recognising they may not suit every women.

				experiences that many women talk about, and what the published research evidence says. One of the goals of Menopause UK is to highlight these gaps, to inform the development of a stronger and more comprehensive evidence base that provides answers to women's questions, concerns and experiences. If more women share their experiences of menopause, then in time, women's questions can become research questions, and eventually drive the development of information and treatment options that help women. We recognise that the interpretation of the published evidence relating to low mood and anxiety among menopausal women is a difficult task, for a number of reasons: ▪ There is a lack of published high quality studies investigating causes and treatments for low mood and anxiety among menopausal women ▪ Of the well designed studies that have been published, and were considered appropriate for inclusion within the review, the emphasis has tended to be on proving that CBT works rather than investigating what women need or are experiencing ▪ Much of the published work in this area contains questionable assertions and conclusions resulting from flawed interpretation of cross-cultural data.	The review protocol on short term symptoms looked for the evidence on non pharmacological treatment options such as CBT, relaxation and, hypnosis and acupuncture to relief of menopausal symptoms (vasomotor symptoms, low mood, anxiety, and sexual dysfunction). However, not all studies on psychological treatments provided data in line with our protocol to be included in the analysis for all outcomes (for example studies on CBT contributed to the outcomes of low mood and depression).The protocol included "psychological interventions" as a broad category, so as not to miss any relevant outcome data on available therapies (see Appendix D.4). The evidence that met the protocol requirements is presented in Section 8 of the full guideline. There were several topics raised as possible areas for future research recommendations, including the use of psychological therapies for the treatment of menopausal symptoms. While the GDG consider this an important topic, it was not prioritised for inclusion when considered in the context of the full guideline.

				On the latter point, many of the papers reviewed by the GDG quote studies that seem to show that women in South American or African cultures regard the advent of menopause more positively ***and*** are less likely to report problematic menopausal symptoms than European women. This is interpreted by the authors as a causal link. Emerging research into pyschoneuroendocrinology among African women in fact highlights that women from lower income and traditional African households are likely to welcome the menopause because it removes the hardship and personal risk associated with pregnancy. This is compounded by local contextual factors affecting women, including a lack of sexual autonomy, difficulty accessing health care, and cultural and economic differences influencing care-seeking behavior (We would be happy to connect the GDG with leading academics in South Africa who can direct the group to the appropriate sources). The cross-cultural interpretation of these findings is further complicated by important differences in in knowledge and beliefs about reproductive health. If this is the case, it does not follow that these women reported reduced problematic menopausal symptoms ***because*** they approached the menopausal transition with a positive attitude. So it does not follow either that if British women approached the menopause with a positive attitude they could also experience reduced problematic menopausal symptoms. The existence or not of this causal link is central to the choice of therapy. If the link is not proven, it calls into question the rationale for offering CBT to menopausal women for the relief of low mood and anxiety. A number of the papers cited in the guidelines advance this link as proven. **We do not consider that the evidence available to the**	

				reviewers at the current time is strong enough to justify recommendation 15. CBT may well be helpful to some women, providing their low mood and anxiety are psychological in origin. But many women report that, in their experience, low mood and anxiety at menopause is hormonal in origin, and that hormonal therapies had a beneficial effect for them. For these reasons, we would like to see **recommendation 15 deleted**, or at the very least **qualified** to make clear that it refers to cases where low mood and anxiety have been found to be psychological in origin, and we would like to see **a new question included under 1.4 Research Recommendations**: "What is the link between menopause, low mood and anxiety, what are the causes, and which treatments (including hormonal therapy and psychological therapies) are effective in alleviating low mood and anxiety among menopausal women?".	
London North West Healthcare NHS Trust	Full	104 105	General	These recommendations refer to patients with breast cancer on tamoxifen and the interactions with St Joh's wort. Is this then the place to recommend the avoidance of certain SSRIs for breast cancer patients on tamoxifen. (Tamoxifen is rendered ineffective by drugs with CYP450 activity such as paroxetine and fluoxetine) . Whilst this is certainly an area of specialist service (ie prescribing for breast cancer patients with VMS) there are a lot of GPs who are prescribing SSRIs for other indications (depression) to patients with breast cancer on tamoxifen who do not realise the interaction. And the BNF barely mentions it either	1.Thank you for your comment. The GDG agree that it is important to highlight the possible drug interaction between SSRIs with tamoxifen and have revised the following recommendation so that this is highlighted ('Offer menopausal women with, or at high risk of, breast cancer: • information on all available treatment options • information that the SSRIs paroxetine and fluoxetine should not be offered to women with breast cancer who are taking tamoxifen • referral to a healthcare professional with

					expertise in menopause').
British Menopause Society	Full	104 105	General	These recommendations refer to patients with breast cancer on tamoxifen and the interactions with St Joh's wort. Is this then the place to recommend the avoidance of certain SSRIs for breast cancer patients on tamoxifen. (Tamoxifen is rendered ineffective by drugs with CYP450 activity such as paroxetine and fluoxetine) . Whilst this is certainly an area of specialist service (ie prescribing for breast cancer patients with VMS) there are a lot of GPs who are prescribing SSRIs for other indications (depression) to patients with breast cancer on tamoxifen who do not realise the interaction. And the BNF barely mentions it either	Thank you for your comment, this has been clarified in the recommendations.
British Menopause Society	Full	104	18	Given your reluctance to accept oral HRT as effective I find it curious that oral is the first recommendation here rather than transdermal	Thank you for your comment. The recommendation did not intend to imply an order of preference and the recommendation has therefore been amended for clarity.
British Menopause Society	full	104	22	Should there be mention of reasons that oestrogen and progestogen may be needed after hysterectomy, eg with widespread endometriosis or sub-total hysterectomy	Thank you for your comment. The recommendation does not aim to cover all possibilities, and treatment will in part depend on an individual woman's circumstances. A discussion of this is included in the linking evidence to recommendation section of the guideline.
British Menopause Society	full	104	23 29	Excellent—this is a really important message for GPs	Thank you for this comment.
London North West	Full	104	36	Informed consent and documentation for testosterone prescribing. Are we moving towards considering signed consent? There is much being discussed about confusion amongst HCPs about use of off license/unlicensed	Thank you for this comment. The process for obtaining signed consent is the same for all off-label treatment recommendations in NICE guidance. The prescriber

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Healthcare NHS Trust	I			medicines	should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.
British Menopause Society	full	104	36	Informed consent and documentation for testosterone prescribing. Are we moving towards considering signed consent? There is much being discussed about confusion amongst HCPs about use of off license/unlicensed medicines	Thank you for this comment. The process for obtaining signed consent is the same for all off-label treatment recommendations in NICE guidance. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.
Sheffield Teaching Hospitals NHS Foundation Trust	FULL	104	36	Consider testosterone supplementation- could the guidance suggest whether this is t alone or in combination with E2	Thank you for your comment. The term "supplementation" is meant to suggest that treatment with testosterone is in addition to treatment with hormone replacement therapy.
British Menopause Society	Full	104	40	Testosterone is not just for low libido it should also be considered for low mood and tiredness (I guess the difficulty is the lack of RCTs but a number or observational studies and clinical experience would support this view)	Thank you for your comment. Low and very low quality evidence was found for the outcome of low mood and data are presented in Table 14, Appendix I. Tiredness was not prioritised for inclusion in the review protocol so the GDG cannot comment on this.

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Consultation on draft guideline - Stakeholder comments table

1 June 2015 – 13 July 2015

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NCRI - Breast CSG Working Group on Symptom Management	FULL	105	GENERAL	Disappointed by the recommendations for women with breast cancer. Just “St John's Wort” and “see a specialist”. Most breast oncologists would not recommend St John's Wort because of the worries about it interfering with Tamoxifen. But there is good evidence for a number of SSRIs working well to alleviate hot flushes (Venlafaxine, Citalopram) as long as some eg paroxetine are avoided because of its effect on liver function and consequently tamoxifen metabolism.	Thank you for your comment. Where possible, the GDG have asked the reader to be aware of potential drug interactions, and in the case of St John's Wort and SSRIs, these have been explicitly stated. The evidence for using SSRIs for the treatment of vasomotor symptoms did not support its use and this is reflected in the recommendations.
NCRI - Breast CSG Working Group on Symptom Management	FULL	105	GENERAL	Research recommendations. It is excellent that you have identified the urgent unmet need for evidence based research into alternatives for HRT in women with breast cancer. But I find it odd that you are recommending trials into the safety of HRT in women with breast cancer. I thought we knew that ER+ breast cancer is driven by oestrogen, that 10 years of anti-oestrogen therapy is more effective than 5 (eg ATLAS trial), that clinicians go to enormous lengths to ensure ER+ Breast Cancer patents have the absolute minimum levels of oestrogen in their bodies and that we as patients suffer the consequences because it may stop the cancer coming back. How can giving oestrogen be anything but bad??? I think it would be much better for breast cancer patients if progesterone were investigated	Thank you for your comment. The GDG have reviewed and amended this research recommendation to “What is the safety and effectiveness of alternatives to systemic HRT as treatments for menopausal symptoms in women who have had treatment for breast cancer?”
Clinical Effectiveness Unit of Faculty of Sexual & Reprod	Full	105	710	These recommendations are interesting and useful.	Thank you for this comment.

uctive Healthcare					
British Psychological Society	FULL	105	15	The Society has concerns over the phrasing of women with a history of breast cancer being "denied hormonal treatment". We believe that the impetus should be to offer them alternatives first so that they can make informed choices.	Thank you for your comment. The wording of this research recommendation has been amended.
British Menopause Society	Full	106	2	Ironic but welcome that this is included - 3 studies were looking at this very issue, 2 in Stockholm and one in London (Royal Marsden) but were discontinued amid the scares about HRT about 10 years. A call to reopen this question is welcome although somewhat late.	Thank you for this comment.
Poole Hospital NHS Trust	Full	106	2	Ironic but welcome that this is included - 3 studies were looking at this very issue, 2 in Stockholm and one in London (Royal Marsden) but were discontinued amid the scares about HRT about 10 years. A call to reopen this question is welcome although somewhat late.	Thank you for this comment.
Shionogi Limited	Full	107	330	The name 'ospemifene' has been misspelled as 'ospemefine'. Please correct	Thank you for your comment, this has been amended.
British Menopause Society	Full	107	711	Given that many national menopause societies are considering the diagnosis of "Genitourinary Syndrome of Menopause" I wonder if this should at least be mentioned to make the document a little future proof	Thank you for your comment. This has been added to the introduction as suggested.
British Menopause	Full	107	21	Orthogynest pessaries are no longer available. Withdrawn from UK market in November 2013	Thank you for your comment. This has been removed.

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Society	I				
The Yes Yes Company Ltd	Full	107	21 27	There is evidence that the quality of life of menopausal and post menopausal women with symptoms of Urogenital Atrophy affects not only their daily life, but also their sexual health and wellbeing and ultimately their relationships. Clarifying Vaginal Atrophy's Impact on Sex and Relationships (CLOSER) survey: emotional and physical impact of vaginal discomfort on North American postmenopausal women and their partners. http://www.ncbi.nlm.nih.gov/pubmed/23736862 Recommendations for non-hormonal preparations and over the counter products should take into account the points and evidence referenced in Comment No 2. Recommendations without any brand recognition or reference to pH and osmolality values could have a negative economic impact on the NHS. If patients independently choose unsuitable over the counter products they may return to their GP with further conditions such as UTIs and Thrush caused by the use of incorrectly pH balanced products, and severe irritation and inflammation, and dyspareunia caused by lubricants and moisturisers that are hyper-osmotic. This irritation can be similar to thrush and anti-fungal medication may be prescribed unnecessarily. Clinical Practice – Acute Vulvovaginitis http://www.nejm.org/doi/full/10.1056/NEJMcp053720 Urinary Tract Infections in Post Menopausal Women http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3246510 As a result of this evidence, we propose that no products with pH values greater than pH4.5 should be prescribed or recommended. Patients should be advised to look for OTC products that clearly state the pH value on the pack.	Thank you for your comment. The GDG agree that issues relating to sexual health and wellbeing are important to consider in women with premature ovarian syndrome. At the time of protocol development, the GDG prioritised the topics for review – recognising that not every aspect of care could reasonably be covered by the guidance. In recognition of this, a recommendation has been added to the guideline about referral to healthcare professionals who have the relevant experience to help a woman manage all aspects of physical and psychosocial health related to their condition.
Novo	F	1	2	Point 1 – “The aim of this review question was to assess both the safety and	Thank you for your comment. This statement reflects

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Nordisk	u l l	0 7	9 3 0	efficacy of local oestrogen treatment and ospemefine for vaginal atrophy." Novo Nordisk recommends amending this point: "The aim of this review question was to assess both the safety and efficacy of local oestrogen treatment and oral selective oestrogen receptor modulator, ospemifene, for vaginal atrophy." As ospemifene would be a new product to the UK market, it is important to reflect the pharmacological properties and method of administration early in the clinical introduction of the review, facilitating easy differentiation between therapies.	the review question which the GDG are not able to change following completion of the review. However, the point has been taken and this is clarified in the discussion of the review.
Royal College of Pathologists	F u l l	1 0 8	1 2	FSH IU/l should be IU/L	Thank you for your comment. The units for biochemistry tests have been standardised based on the on the recommendations from UK Pathology Harmony.
British Menopause Society	f u l l	1 0 8	2 2	Oestriol is used in many of the studies - should this not say "oestradiol or oestriol were the most ....."	Thank you for your comment. The GDG have added to the sentence to indicate oestriol was also used in several of the studies.
Poole Hospital NHS Trust	f u l l	1 0 8	2 2	Oestriol is used in many of the studies - should this not say "oestradiol or oestriol were the most ....."	Thank you for your comment. We have added to the sentence to indicate oestriol was also used in several of the studies.
Shionogi Limited	F u l l	1 0 8	3 1 3 2	The name 'ospemifene' has been misspelled as 'ospemefine'. Please correct	Thank you for your comment, this has been amended.
Novo Nordisk	F u	1 0	3 1	Title: "Ospemefine" Novo Nordisk recommends the addition of "- oral selective oestrogen receptor	Thank you for your comment. The text has been amended where this was considered an appropriate

	Full	810910	27 38	modulator" to the title lines, in order to provide clear comparison and differentiation with local oestrogens.	addition.
Shionogi Limited	Full	108	32 41	As the licensed indication for ospemifene is specifically for the 60 mg dose, trials that do not include this dose have no clinical significance. Our suggestion is therefore to exclude the Voipio 2002 publication from the review as this study did not include any 60 mg dose groups. This would apply throughout the document. The publications by Portman 2013 and Portman 2014 described the results of the dyspareunia stratum and the dryness stratum respectively of the same study. The publication by Constantine did not describe an individual study, but is a review publication about the endometrial safety of ospemifene in six randomized, double-blind, placebo controlled, parallel-group studies. The study reported by Simon, 2013 was a 40-week extension study in women with a uterus of the 12-week study originally reported by Bachmann, 2010. All studies were multi-site studies. Even the phase 2 study reported by Rutanen 2003 was a 2-site study Excluding the Voipio study and considering the Constantine publication did not report a study, but was a review, we suggest the following text for lines 32-41: "*A total of 5 RCTs comparing ospemifene with placebo were included in this review (Bachmann, 2010; Rutanen, 2003; Goldstein, 2014; Simon, 2013; Portman, 2013 and Portman, 2014 reporting on different strata in the same study). Three of these studies (Bachmann, 2010; Portman 2013 and 2014 and Rutanen 2003) assessed short-term (< 52 weeks) outcomes of*	Thank you for your comment. The review of evidence was presented during the guideline development before a license was granted for 60 mg of ospemifene. Therefore, the review protocol was set up to look at all the evidence independent of dosage within the population of interest. The study by Voipio 2002 was in line with the protocol as no restrictions on the dosage of ospemifene were applied and results from this study were presented separately in the evidence statements. However, the GDG agree with your comment about Constantine 2005 study and this is now removed from the updated version of the full guideline along with some clarification on the study design and the baseline characteristics of the included population. We have also included a statement in the section 8.11.4.3 of the full guideline explaining that Portman 2013 and 2014 reported results from a parallel-group design trial that separated women in each trial based on the most bothersome symptom reported (dyspaneuria or vaginal dryness).

				ospemifene treatment; one (Simon, 2013) was an extension study of a 12 week study (Bachmann, 2010) and assessed long-term (≥ 52 weeks) outcomes; and one assessed both short- and long-term outcomes (Goldstein, 2014). All studies were multi-site studies, with three of the studies conducted in the United States and two in Europe. The majority of subjects were 55 to 64 years of age (57% ospemifene and 59% placebo), with the median age in the overall groups being 59.0 years (EPAR Senshio, 2015). All studies reviewed included at least one dose group with 60 mg ospemifene".	
Novo Nordisk	Full	109	26	Novo Nordisk recommends that a paragraph is included to reflect the clinical evidence for recorded plasma estradiol (E2) levels consistent with baseline levels, for postmenopausal women during treatment with β-estradiol vaginal tablets. • The randomised trial investigated the pharmacokinetics of 10µg and 25µg 17 β-estradiol vaginal tablets in postmenopausal women with vaginal atrophy. The trial included 58 women with vaginal atrophy who were randomized in equal numbers between the two parallel treatment groups: 10µg and 25µg 17 β-estradiol vaginal tablets. Blood samples were measured using GCMS methodology. 29 10µg subjects completed the 12-week trial. Two of the 25µg group discontinued. The mean E2 levels for 10µg subjects remained in the published reference range for postmenopausal women during the first two weeks of daily loading and after the next 10 weeks on the maintenance twice weekly dose. References: Eugster-Hausmann M et al. *Climacteric* 2010; 13(3): 219–227 – Minimized estradiol absorption with ultra-low-dose 10µg 17 β-estradiol vaginal tablets Santen RJ et al; *Steroids* 2007; 72: 666–671 Superiority of gas chromatography/ tandem mass spectrometry assay	Thank you for this comment. Recorded plasma estradiol (E2) was not an outcome included in the protocol (see appendix D), therefore evidence on E2 was not reported.

				(GC/MS/MS) for estradiol for monitoring of aromatase inhibitor therapy	
Shionogi Limited	Full	109	27 34	The name 'ospemifene' has been misspelled as 'ospemefine'. Please correct	Thank you for your comment, this has been amended.
Shionogi Limited	Full	109	28 32	The results were from 4 rather than 5 different RCTs with the two strata (vaginal dryness and dyspareunia) of one RCT reported in two different publications (Portman 2013 and Portman 2014 respectively). Correction of typo ('less one year') Based on this and the exclusion of the Voipio study (see comment 11), we suggest the following text for lines 28-32 "*Pooled analysis of 4 RCTs with 1968 women showed a significant reduction in the percentage of parabasal cells from 60 mg treatment with ospemifene compared to placebo during treatment over a period of less than one year. The evidence was of high quality.*"	Thank you for your comment. The number of studies reflect the number of publications reported the relevant outcome. We have included a statement in the section 7.11.4.3 of the full guideline explaining that Portman 2013 and 2014 reported results from a parallel-group design trial that separated women in each trial based on the most bothersome symptom reported (dyspaneuria or vaginal dryness). The sample size is now checked for clarity. Voipio 2002 study matched our agreed review protocol as no restrictions on the dosage of ospemifene were applied and results from this study were presented separately in the evidence statements.
Shionogi Limited	Full	109	33 38	The results were from 4 rather than 5 different RCTs with the two strata (vaginal dryness and dyspareunia) of one RCT reported in two different publications (Portman 2013 and Portman 2014 respectively). Correction of the total number of subjects on 60 mg ospemifene in these studies to 1968 (instead of 1984) Based on this and the exclusion of the Voipio study (see comment 11), we suggest the following text for lines 33-38 "*Pooled analysis of 4 RCTs with 1968 women showed a significant increase in the percentage of superficial cells from 60 mg treatment with ospemifene compared to placebo during treatment over a period of less than one year.*	Thank you for your comment. The number of studies reflect the number of publications reported the relevant outcome. We have included a statement in the section 7.11.4.3 of the full guideline explaining that Portman 2013 and 2014 reported results from a parallel-group design trial that separated women in each trial based on the most bothersome symptom reported (dyspaneuria or vaginal dryness). The sample size is now checked for clarity. Voipio 2002 study matched our agreed review protocol as no

				The evidence was of high quality."	restrictions on the dosage of ospemifene were applied and results from this study were presented separately in the evidence statements.
Shionogi Limited	Full	109	39 43	If the Voipio study (40 subjects rather than 16 as misstated in the current text) is excluded for the reasons outlined in comment 8, intermediate cells are reported only by Rutanen 2003. We would normally recommend deleting this section since no clinically relevant information can be obtained from the effect on intermediate cells if data on superficial and parabasal cells are available, however, based on Rutanen 2003, this section could be replaced with: "*One RCT with 159 women reported a significant reduction in the percentage of intermediate cells at ospemifene doses of 30, 60 and 90 mg compared to placebo during treatment over a period of less than one year. Evidence was of low quality.*"	Thank you for your comment. Intermediate cells was an outcome selected by the GDG at the protocol stage and the evidence was presented for this outcome when data were available. The review of evidence was presented during the guideline development before the license for 60 mg of ospemifene was granted. Therefore, the review protocol was set up to look at all the evidence independently of dosages for the treatment of ospemifene for the population of interest. The study by Voipio 2002 was in line with the protocol and was presented to the GDG. The number of participants in the evidence statements accurately reflects the sample size of groups compared in each row in the GRADE table rather than the total sample size of the study.
Shionogi Limited	Full	109	44 46	The co-primary endpoint of the two studies mentioned was the effect on dyspareunia (Bachmann 201, Portman 2013) or vaginal dryness (Bachmann 2010, Portman 2014), <u>chosen by the subjects as their Most Bothersome Symptom</u>. The total number of subjects in the two pivotal efficacy trials that chose dyspareunia as their Most Bothersome Symptom was 847 and the number of subjects that chose vaginal dryness as their most bothersome symptom was 536. We therefore recommend to replace lines 44-46 with: "*Pooled analysis of two RCTs with 847 women showed a significant reduction in the severity of dyspareunia selected as Most Bothersome Symptom with 60 mg ospemifene compared to placebo during treatment over a period of less than one year. Evidence was of high quality.*	Thank you for this comment. The evidence statement refers to the outcome of dyspareunia as reported by both studies (Bechmann 2010, Portman 2014) in an Intention to Treat analysis. Evidence was assessed as moderate quality, and was downgraded due to a serious risk of bias.

				Pooled analysis of two RCTs with 536 women showed a significant reduction in the severity of vaginal dryness selected as Most Bothersome Symptom with 60 mg ospemifene compared to placebo during treatment over a period of less than one year in one study only. Evidence was of moderate quality."	
Shionogi Limited	Full	110	13	pH was measured in three studies only: Bachmann 2010, Portman 2013 and 2104 (same study, different strata) and Goldstein 2014. We suggest the following text for lines 1-3: "*Pooled analysis of 3 RCTs with 1889 women showed a significant decrease in vaginal pH with 60 mg ospemifene compared to placebo over a treatment period of less than 1 year. Evidence was of high quality.*"	Thank you for your comment. The number of studies reflect the number of publications reported the relevant outcome. The GDG has included a statement in section 7.11.4.3 of the full guideline explaining how Portman 2013 and Portman 2014 report results from a parallel-group design trial that separated women in each trial based on the most bothersome symptom reported (i.e. dyspaneuria or vaginal dryness). Evidence was considered of moderate quality due to serious risk of bias.
Shionogi Limited	Full	110	46	We are concerned about the bias in reviewing here. Only one of the two pivotal studies looking at vaginal dryness as Most Bothersome Symptom is reviewed here. Data are missing from the other pivotal efficacy study which included patients who selected vaginal dryness as their MBS (Bachmann 2010). This study demonstrated a statistically significant decrease in the severity of vaginal dryness with 60 mg ospemifene compared to placebo over a treatment period of 12 weeks (p=0.021). Since this has now been addressed in our suggestion (see comment 13) for the replacement of lines 44-46 on page 109, we propose to delete these sentences.	Thank you for your comment. Results on the outcome of vaginal dryness as reported by Backmann 2010 study are now included and the evidence statement has been edited as appropriate.
Shionogi Limited	Full	110	79	It is unclear which six RCTs and which 3708 women are included here, but in the entire Phase 2/3 study program for Senshio® (which included other dose levels than 60 mg), there were only 1710 women with an intact uterus (Senshio® EPAR). There was no statistical testing done on increases in endometrial thickness in any of the five RCTs included in this review (Bachmann, 2010; Rutanen, 2003; Goldstein, 2014; Simon, 2013; Portman, 2013 and Portman, 2014), but all publications use the term 'slight' to describe	Thank you for your comment. The sample size has been corrected to reflect the population of women with intact uterus. However, Simon 2013 and Goldstein 2014 were not included in the sample size calculations as they report long term outcomes (greater than one year of treatment).

				the increase in endometrial thickness. Based on the five RCTs included in this review, we suggest the following text for lines 7-9: "*Five RCTs which included 1142 women who were randomized to the 60 mg ospemifene group (770 with an intact uterus) and 834 women who were randomized to placebo (471 with an intact uterus) demonstrated a slight increase in endometrial thickness associated with 60 mg ospemifene treatment compared to placebo during a treatment period of less than one year. Evidence was of moderate quality.*"	
Shionogi Limited	Full	110	10 12	Since in the entire Phase 2/3 study program for Senshio® (which included other dose levels than 60 mg), there were only 1710 women with an intact uterus, it is unclear where the number of 1944 women is derived from. Based on the five RCTs included in this review (Bachmann, 2010; Rutanen, 2003; Goldstein, 2014; Simon, 2013; Portman, 2013 and Portman, 2014), we suggest the following text for lines 10-12: "*In a pooled analysis of five RCTs which included 1142 women who were randomized to the 60 mg ospemifene group (770 with an intact uterus) and 834 women who were randomized to placebo (471 with an intact uterus) there were no endometrial carcinomas, complex hyperplasias, or simple hyperplasias with atypia in either the ospemifene group or the placebo group during a treatment period of less than one year. Evidence was of moderate quality.*"	Thank you for your comment. The sample size has been corrected to reflect the population of women with intact uterus. However, Simon 2013 and Goldstein 2014 were not included in the sample size calculations as they report long term outcomes (greater than one year of treatment).
Shionogi Limited	Full	110	13 19	The 4 RCTs that report Treatment Emergent Adverse Events (TEAEs) are described in Bachmann 2010, Portman 2013 and 2014, Goldstein 2014 and Simon 2013. Apart from Bachmann 2010, all RCTs report a higher percentage of women discontinuing treatment due to adverse events in the 60 mg ospemifene group than in the placebo group. We suggest the following text for lines 13-19: "*A pooled analysis of 4 RCTs found there was a higher incidence of*	Thank you for your comment. The GDG presented data on adverse events separately for the studies with a duration less than a year (Bachmann 2010, Portman 2013 and Portman 2014) and longer than a year (Goldstein 2014 and Simon 2013) in line with the review protocol. The evidence statements have been separated to reflect outcomes reported in short and long term.

				treatment-related adverse events with ospemifene 60 mg compared to placebo during a treatment period of less than one year. Withdrawals due to adverse events were reported to be higher in the 60 mg ospemifene group than the placebo group in 3 out of the 4 RCTs. Quality of evidence was moderate."	
British Menopause Society	Full	110	27	Space missing after 'months'	Thank you for your comment, this has been amended.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	110	27	Should be 'months were'	Thank you for your comment, this has been amended.
Shionogi Limited	Full	110	3334	There is no mention of the endometrial carcinoma (stage II, grade 2) that was found in this study. Could you please provide the rationale for that or include it in the guidelines?	Thank you for the comment. This has been added to the evidence statement.
Shionogi	Fu	11	38	The name 'ospemifene' has been misspelled as 'ospemefine'. Please correct	Thank you for your comment, this has been amended throughout the documents.

Limited	ll	0			
Shionogi Limited	Full	110	38	There is no mention of the long term efficacy of ospemifene on physiology as described in Goldstein 2014. Long term efficacy is however mentioned under local oestrogens. With 'changes in the vagina' classified as a long-term condition (see Scoping document, section 3.1.i) and no formal limitation of use for Senshio, we feel it is relevant to review the long term efficacy of 60 mg ospemifene: "Statistically significant improvements were seen for all primary and secondary efficacy measures and were sustained through week 52 with ospemifene vs. placebo" (Goldstein 2014).	Thank you for your comment. The data for long term efficacy of ospemifene on visual evaluation of vagina as reported by Golstein 2014 were not included in the review. This is because no information on the baseline scoring of these outcomes was reported which meant that an estimate about whether any difference in the improvement in these outcomes could not be calculated, nor attributed to the intervention under examination.
Shionogi Limited	Full	110	39 45	It is unclear where the number 2560 comes from. There are two clinical trials that have included women with a uterus for up to one year, the study reported by Goldstein (2014) which included 363 women on 60 mg ospemifene and 63 women on placebo, and the study reported by Simon (2013) in which women with a uterus continued for another 40 weeks from the study originally reported by Bachmann (2010) and included 69 women on 60 mg ospemifene and 49 women on placebo. Both studies reported the increase in endometrial thickness in the 60 mg ospemifene group as 'slight' and no statistical testing for significance was done in either study. We suggest the following text for lines 39-45: "*Pooled analysis of two RCTs with 544 women, which included 432 women in the 60 mg ospemifene group and 112 in the placebo group, showed a slight increase in endometrial thickness associated with 60 mg ospemifene treatment compared to placebo over a treatment period of 1 year. Evidence was of high quality.* *One study reported a participant who received ospemifene 60 mg to have simple endometrial hyperplasia without atypia on biopsy 3 months after the last dose of the study drug. No cases of endometrial carcinoma were*	Thank you for your comment. The sample size in this evidence statement has been corrected as suggested. However, the quality of evidence was low due to high risk of bias and serious imprecision as assessed using the GRADE quality assessment approach.

				reported for each of the two studies. Quality of evidence was moderate."	
Derbyshire Community Sexual Health Service	full	111	General	ovestin I believe there are 15 doses per pack	Thank you. Based on a one applicator dose (0.5mg Estriol in 0.5g of cream) a day, then there would be 30 doses per pack. The table has been amended to reflect this.
Sheffield Teaching Hospitals NHS Foundation Trust	FULL	111	General	Ovestin contains 30 doses per pack not 3 , costs need amending also	Thank you. Based on a one applicator dose (0.5mg Estriol in 0.5g of cream) a day, then there would be 30 doses per pack. We've amended the table to reflect this.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	111	16	Costs for Ovestin cream are incorrect – should be 30 doses per tube so 14p per dose, not £1.48 we think.	Thank you. Based on a one applicator dose (0.5mg Estriol in 0.5g of cream) a day, then there would be 30 doses per pack. We've amended the table to reflect this.

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UK Clinical Pharmacy Association	Full	111	19	Note that Ortho-gynest pessaries have been discontinued - confirmed with Janssen	Thank you. The references to this product have been deleted in Tables 14 and 15.
Novo Nordisk	Full	111	19	Table 16: Dose Vagifem®: Novo Nordisk requests the removal of the reference to 25 microgram vaginal tablet specifically, as this is no longer available in the UK and is therefore inconsistent with the current SmPC. In addition, manufacture of the 25 microgram tablet has ceased. This is to ensure product is available at the lowest effective dose, consistent with FDA/ EMA guidelines on therapies for post-menopausal women. (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003348.pdf, and http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm135339.htm	Thank you for this comment. The reference to the 25 microgram vaginal tablet has been deleted as suggested.
Novo Nordisk	Full	112	610	Point 4 – "In addition there is now a new agent, ospemifene, which has recently been licensed for use in the USA and Europe (www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_Initial_authorisation/human/002780/WC500177633.pdf), although it does not currently have marketing authorisation in the UK." Novo Nordisk recommends adding ospemifene's approved European Medicines Agency indication to this statement: "Treatment of moderate to severe symptomatic vulvar and vaginal atrophy (VVA) in post-menopausal women who are not candidates for local vaginal oestrogen therapy", in order to provide clarity that the license is not the same as existing agents and define use in the treatment cascade.	Thank you for your comment. The guideline now reflects ospemifene's license status.
Shionogi	Fu	11	9	It is incorrect that ospemifene does not have marketing authorisation in the UK. The recent issuing of a Marketing Authorisation in the European Union	Thank you for your comment. The guideline now reflects ospemifene's license status.

Limited	Ll	2	10	by the European parliament on 15 January 2015 (http://ec.europa.eu/health/documents/community-register/2015/20150115130408/dec_130408_en.pdf) allows marketing in the United Kingdom	
Novo Nordisk	Full	112	34	Point 1 – "The GDG concluded that, given the effectiveness of vaginal lcal oestrogen in relieving" Novo Nordisk recommends amending the miss-type of "lcal" to local.	Thank you for your comment, this has been amended.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	112	34	Should be 'local'	Thank you for your comment, this has been amended.
The Yes Yes Company Ltd	Full	113	12 19	The GDG discussed the role of local oestrogen for women where systemic HRT is contra-indicated such as those with a history of breast cancer, and concluded that local oestrogen should still be considered as there is minimal systemic absorption of low dose preparations, although the decision should be discussed with a health professional with expertise in the field as even very small amounts of oestradiol may decrease the effect of aromatase inhibitors which are used in the treatment of breast cancer. Moisturisers and lubricants were considered a safe option to local oestrogen by the CDG. This conclusion does not take into account that some moisturisers and	Thank you for your comment. The GDG carefully considered your comment in light of the fact that they did not conduct a specific review of the safety of paraben. However, the GDG consider it unlikely that enough parabens would be absorbed in order to have systemic effects or putative drug interaction. The text in the guideline has been amended.

				lubricants contain Parabens which are endocrine disruptors and known to mimic oestrogen and may have the same effect on aromatase inhibitors. Paraben esters: review of recent studies of endocrine toxicity, absorption, esterase and human exposure, and discussion of potential human health risks. http://www.ncbi.nlm.nih.gov/pubmed/18484575 Parabens have also been found in breast tumours and can be absorbed through the mucosa especially when the lubricant also contains glycols which act as penetration agents. Barr L, Metaxas G, Harbach CAJ *et al*. Measurement of paraben concentrations in human breast tissue at serial locations across the breast from axial to sternum. *Journal of Applied Toxicology*, January 12 2012 (published online) http://onlinelibrary.wiley.com/doi/10.1002/jat.1786/abstract It is probably not generally known that Replens MD, the vaginal moisturiser most often prescribed for Vaginal Dryness in England and Wales contains Methylparaben. Ingredients: 2.5g of Replens MD Vaginal Moisturiser contains: Purified water Ph. Eur. 78.82% w/w, Polycarbophil, mineral oil, glycerin, hydrogenated palm oil glyceride, Carbomer Homopolymer Type B, sorbic acid, methylparaben, sodium hydroxide. (taken from Boots.com July 2015) It has pH of pH2.88 and Osmolality of 2011 mOsm/kg. The WHO has concluded that the osmolality of water-based lubricants should preferably be 1200 mOsm/kg or less. As a result of the above evidence, we recommend that only products containing no Parabens should be prescribed for all patients, but especially where systemic or local oestrogen is contraindicated.	

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Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	113	12	Comments on use in women with breast cancer are very helpful.	Thank you for this comment.
Shionogi Limited	Full	113	21	The name 'ospemifene' has been misspelled as 'ospemefine'. Please correct	Thank you for your comment, this has been amended.
British Menopause Society	Full	113	32	why discuss a product that doesn't have UK marketing status?	Thank you for your comment. This sentence has been amended to reflect ospemifene's current UK licensed status.
Shionogi Limited	Full	113	32	It is incorrect that ospemifene does not have marketing authorisation in the UK. The recent issuing of a Marketing Authorisation in the European Union by the European parliament on 15 January 2015 (http://ec.europa.eu/health/documents/community-register/2015/20150115130408/dec_130408_en.pdf) allows marketing in the United Kingdom. Please see also our general comment no. 7.	Thank you for your comment. This sentence has been amended to reflect ospemifene's UK licensed status.
Shionog	F	1	4	As 60 mg ospemifene, licensed under the tradename Senshio® in all EU and	Thank you for this comment. The text has been

i Limited	ull	13	044	EEA-EFTA states, is currently not yet commercially available, there is no price available in the UK or anywhere else in Europe. 60 mg ospemifene is available in the US under the tradename Osphena® for a different indication (the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause) and as with most other medicines, the price in the US is not a guidance for the price in Europe. The sentence "However, the GDG understand that where it is available it is at a high cost" is based on speculation and we respectfully ask the GDG to delete this sentence from the guidelines. Since women who are candidates for local vaginal oestrogens are by default excluded from using ospemifene (the indication in all EU and EEA-EFTA states for 60 mg ospemifene reads "for the treatment of moderate to severe symptomatic vulvar and vaginal atrophy (VVA) in post-menopausal women who are not candidates for local vaginal oestrogen therapy"), and for women who are not candidates for local oestrogen there is currently only one prescription treatment available, i.e. 60 mg ospemifene, it is not appropriate to compare ospemifene with local oestrogens. As a result, we request deletion of lines 40-44.	deleted as requested.
British Menopause Society	full	114	67	The statement that "the GDG wished to emphasise the importance for health professionals of discussing urogenital atrophy with women in menopause" is very welcome and should be in the recommendations.	Thank you for your comment. Recommendation 1.3.1 advises healthcare professionals to give information about and discuss the symptoms of menopause with women which may include urogenital atrophy.
Poole Hospital NHS Trust	full	114	67	The statement that "the GDG wished to emphasise the importance for health professionals of discussing urogenital atrophy with women in menopause" is very welcome and should be in the recommendations.	Thank you for your comment. Recommendation 1.3.1 advises healthcare professionals to give information about and discuss the symptoms of menopause with women which may include urogenital atrophy.
Clinical Effectiveness Unit of	Full	114	7.11.9	These are very helpful and we are pleased that the recommendation supports long-term use, rather than intermittent use. We wondered if recommendation 26 might include the practical point that treatment takes many months to improve atrophy when it is first started.	Thank you for your comment. The short term outcomes were measured at the 3-month timepoint to allow detection of the treatment effect. A sentence has been added to the linking evidence to

Faculty of Sexual & Reproductive Healthcare					recommendations section of the full guideline which explicitly makes this point.
British Menopause Society	Full	114	16 24	long term use defines as unto a year. in recommendations - continue as long as needed - ? upto 1 year?	Thank you for your comment. This statement in the linking evidence to recommendation section of the guideline has been amended so that it accurately reflects the evidence and is consistent with the recommendations.
Shionogi Limited	Full	114	20	As of 15 January 2015, 60 mg ospemifene has been licensed in in all EU and EEA-EFTA states (including the UK) for the treatment of moderate to severe symptomatic vulvar and vaginal atrophy (VVA) in post-menopausal women who are not candidates for local vaginal oestrogen therapy (see also our general comment no.7). As a result, and also because there is no effective and safe treatment available for this particular group of patients, other than ospemifene, we respectfully ask the GDG to formulate a recommendation for 60 mg ospemifene (Senshio®) and align with the wording in section 7.11.9 “Recommendations”.	Thank you for your comment. Given that ospemifene has been granted a license for use in the UK, the GDG re-discussed the evidence for its use.
The Yes Yes Company Ltd	Full	114	26 27	This recommendation considers low-dose vaginal oestrogen for women for whom HRT is contraindicated but does not take into account the many women who choose for personal reasons not to use any form of HRT. Vaginal moisturisers and lubricants can offer an alternative for these women but health professionals should be aware of which products have the correct pH of greater than pH4.5 and osmolality values below 1200 mOsm/kg as this information is now available.	Thank you for your comment. The GDG did not review specific types of moisturisers and lubricants but do consider them an option for the treatment of vaginal dryness as stated in the recommendation.

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				Please visit https://www.yesyesyes.org/yestimonials-cancer-treatment for feedback from a sample of many women who have had cancer and either are contraindicated or choose not to take any HRT through choice.	
The Yes Yes Company Ltd	Full	114	31 34	We recommend that Point 26 should contain a further bullet point explaining to women that lubricants and vaginal moisturisers are an option for the treatment of Urogenital Atrophy. Point 27 Advises women that moisturisers and lubricants can be used alone or in addition to vaginal oestrogen for vaginal dryness, but there is no mention of Urogenital Atrophy.	Thank you for your comment. The recommended has not been amended as requested because dryness is the only symptom of urogenital atrophy that is relieved by moisturisers.
Breast Cancer Now	FULL	115	General	In the Review and Referral section of the main guideline, there is no specific mention of breast cancer patients. It is important that women who experience menopausal symptoms as a result of their breast cancer treatment are appropriately referred to specialist clinicians who are able to advise them appropriately. We would suggest that this should be explicitly mentioned in this part of the guideline so that women are offered appropriate support and treatment as quickly as possible.	Thank you for your comment. A recommendation about the referral of women with or at risk of breast cancer to a healthcare professional with expertise in menopause is included in the guideline.
British Menopause Society	full	115	115	Q! This is good as it will reaffirm and give people confidence	Thank you for this comment.
Clinical Effectiveness Unit of Faculty of Sexual	Full	116	41	Mention 'NHS Cervical Screening Programme'	Thank you for your comment. While this sentence was referring to the NHS programme, it is now explicitly stated in the guideline.

& Reproductive Healthcare					
Derbyshire Community Sexual Health Service	full	117	General	remove 'hypnotherapy' and 'relaxation techniques' from the list - I cant see any evidence for their effectiveness discussed in the document. Also this section is a little confusing as recommendation lumps acupuncture with CBT when acupuncture has been assessed for VMS and CBT for low mood. This really needs clarifying in the summary.	Thank you for your comment. This is now amended. This review question on review and referral leads to a recommendation that women should be provided with information about non-hormonal, psychological and non-pharmacological therapies. This information is in line with the other recommendations given in the guideline, such as those of CBT for low mood.
Sheffield Teaching Hospitals NHS Foundation Trust	FULL	117	general	Hypno herapy and relaxation are included in the list – but there is no evidence to support their use in this document. CNBT and acupuncture grouped together but acupuncture was assessed for VMS and CBT for mood. Please clarify in the summary	Thank you for your comment. This is now amended. The GDG did not find evidence to support a recommendation for the use of CBT for reducing the frequency of vasomotor symptoms as discussed within section 8.2.7 of the full guideline. However, the guideline does include a recommendation about providing information about all of the types of treatments for menopausal symptoms that may be available to a women, taking into account her individual circumstances and personal preferences.
British Menopause Society	full	117	7	Is this for systemic HRT or other systemic treatment only, What about vaginal estrogen—annual review is currently recommended	Thank you for your comment. The GDG consider an interval of 3 months after the initiation of all treatments for short term symptoms gives the healthcare professional the opportunity to assess clinical effectiveness and tolerability and act on alternative treatment options if needed. Thereafter review for all treatments, including vaginal oestrogen, should be

					conducted annually unless there are clinical indications for earlier review.
Breast Cancer Now	FULL	117	15	We are pleased to see the reference to non-hormonal treatments such as counselling, acupuncture and relaxation techniques. However, the guideline currently states that information about these alternatives to HRT should be provided to women who have contraindications to HRT. We would suggest that this information should be given to all women seeing a clinician with menopausal symptoms. In addition, some women may wish to avoid HRT so this information should not be limited to those who have contraindications.	Thank you for your comment. The GDG agrees that non-hormonal options are important for some women and therefore the recommendation about giving information to women with menopause has been amended to reflect this.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	118	12	Change to 'the woman'	Thank you for your comment, this has been amended.
Clinical Effectiveness Unit of Faculty of Sexual	Full	121	18	This sentence is not clear	Thank you for your comment. This sentence has been amended for clarity.

& Reproductive Healthcare					
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	121	24	This sentence does not make sense	Thank you for your comment. This section of the guideline has been amended for clarity.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthc	Full	121	41 42	This sentence is not clear	Thank you for your comment. This section of the guideline has been amended for clarity.

are					
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	123	11	Sentence needs correct punctuation for clarity	Thank you for your comment, this sentence has been amended for clarity.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	123	27	Clarify ' as well as increased BMI' in this sentence	Thank you for your comment. This has been amended for clarity.
Clinical Effectiv	Fu	12	10	Take out word 'group'	Thank you for your comment. This has been corrected.

eness Unit of Faculty of Sexual & Reproductive Healthcare	l l	4			
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	F u l l	1 2 4	1 1 1 3	Not clear which study is saying what	Thank you for your comment. This has been amended for clarity.
Clinical Effectiveness Unit of Faculty of	F u l l	1 2 4	3 1	Should be 'perimenopausal'	Thank you for your comment. This has been corrected.

Sexual & Reproductive Healthcare					
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	125	21	Change to ‘ difference in VTE risk’	Thank you for your comment. This has been corrected.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive	Full	125	33	Add ‘with the no treatment’	Thank you for your comment. This has been corrected.

Healthcare					
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	126	13	Remove 'of' from sentence	Thank you for your comment. This has been corrected.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	126	19	Comment re 'on the PE' is not clear	Thank you for your comment. PE refers to pulmonary embolism and this is spelled out in full at the beginning of the chapter.
Clinical	F	1	3	Needs reworded	Thank you for your comment. This has been reworded

Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	full	26	5		as requested.
British Menopause Society	full	127 128	General	Q1. Very helpful. Word needs to be spread widely not to stop transdermal HRT prior to operations.	Thank you for this comment.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthc	Full	127	810	The micronized progesterone studies have had a lot of publicity suggesting benefit – are the data 'very low quality'	Thank you for your comment. GRADE is used to assess the quality of evidence by outcome rather than by study. Following the GRADE criteria, , the quality of evidence for the outcome of VTE in the comparison of micronized progesterone (combine with oestrogen) versus no HRT use was rated as very low due to serious risk of bias and very serious imprecision associated with the effect size. Please refer to Table 45 in Appendix I for details on the explanations in downgrading the quality of this evidence.

are					
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	127	18	Change to 'in association with'	Thank you for this comment. This has been amended as requested.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	127	27	Should be 'hepatic'	Thank you for your comment. This has been amended to "'hepatic synthesis".
Clinical Effectiv	Fu	12	40	Add 'to be significantly different'	Thank you for your comment. This has been amended as suggested.

eness Unit of Faculty of Sexual & Reproductive Healthcare	ll	7			
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	127	43 45	Sentence could be clearer	Thank you for your comment. This has been edited for clarity.
Clinical Effectiveness Unit of Faculty of	Full	128	7	Double negative – needs changed. Baseline risk needs to be explained as relating to non-users.	Thank you for your comment. This has been amended.

Sexual & Reproductive Healthcare					
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	128	9	Should be 'contraindicated'	Thank you. This has been amended.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive	Full	128	16	Should be 'with a previous'	Thank you for your comment. This has been amended.

Healthcare					
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	128	26	Should be 'one of those studies included more than half a million'	Thank you, this has been amended.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	128	41	Should be 'the main reasons….were'	Thank you, this has been amended.
British	f	1	G	10.1.9. Q1 This will be easy to implement in practice as so clear.	Thank you for this comment.

Menopause Society	ull	29	eneral		
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	129	21	The GDG	Thank you for your comment, this has been amended.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	129	22	Change to 'need for'	Thank you, this has been amended.

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Besins Healthcare	Full	129	27	We believe it is important to differentiate between 'Progestogen' and 'Progesterone' within the guidelines. We suggest describing them as synthetic and "body-identical" progesterone as this may help to distinguish the two product types. This should be accompanied by appropriate definitions of each product type along with supportive evidence. The supportive evidence is provided below. Based on observational studies it is suggested that progestogens and body-identical progesterones should not be regarded as equal in terms of their effect on breast cancer risk in HRT. This is discussed in the following study: Fournier, et al; Unequal risks of breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. Brest Cancer Res. Treat 107, 103-111 (2008) This point of differentiation is of particular importance in the following statement "Oral HRT (either oestrogen alone or oestrogen plus progesterone) increases the risk of VTE and this can occur immediately after starting HRT treatment". This statement should read "Oral HRT (either oestrogen alone or oestrogen plus progestogen) increases the risk of VTE and this can occur immediately after starting HRT treatment. It is suggested that no significant effect on VTE is observed with transdermal estradiol and progesterone" This aspect if supported by the ESTHER Study (http://www.ncbi.nlm.nih.gov/pubmed/17309934)	Thank you for your comment. The GDG agree with your comment and have made the differentiation between progesterone and progestogen throughout the guideline. Where evidence is reported, the terminology used in the publication is replicated in text. The two terms and a description are given in the glossary of the full guideline. In the review of breast cancer risk, the GDG are aware that there are some emerging data to suggest that different progestogens may impact risk to a different degree. However, this was not considered within the review (see protocol in Appendix D.7.5). In the review of VTE risk, findings on different types of progesterone and progestogens in combined HRT were inconclusive. Some observational studies showed an increased risk for some specific preparation of progesterone or progestogen when combined with oestrogen, while other studies found no significant difference. Therefore, the GDG decided not to differentiate the direction of their decision making on HRT type.
Clinical Effectiveness	Full	130	1	Does the GDG endorse that use of transdermal HRT is safe in high risk women, if as stated earlier, it has no greater than baseline risk?	Thank you for your comment. The evidence identified by the systematic review was of moderate to very low quality and therefore definitive conclusions cannot be

Unit of Faculty of Sexual & Reproductive Healthcare	l				drawn. However, the GDG discussed the importance of well-known risk factors for VTE such as age, genetic abnormalities, obesity, smoking or the presence of an inherited thrombophilia impacting on the clotting cascade with increase in coagulation (thrombophilias) and agreed that these should be taken into consideration when the prescription of HRT is considered.
Poole Hospital NHS Trust	full	131	general	A number of meta-analyses are missing here - Salpeter 2006 and Cochrane review (Boardman) 2015. why are these not included?	Thank you for this comment. The systematic review on cardiovascular disease associated with HRT use was led by the evidence that met the inclusion criteria set out in the relevant systematic review protocols (Appendix D). The evidence in this comment has been checked and was not included for the following reasons: • Salpeter et all 2006 was considered a meta-analysis but not a systematic review. In addition, most of the studies reported CHD as an adverse event and not as primary outcome. • Boardman 2015 Cochrane review was published after the cut off time point for the literature searches. . However, the publication has been examined and doesn't meet the the protocol of this review due to differences in the inclusion criteria for population characteristics and outcomes.

					The analysis for both reviews pooled all HRT types whereas the GDG considered different types of HRT separately (for example, results from trials reporting the effect of oestrogen plus progestogen intervention and the effect of oestrogen alone on CHD effect). In addition, the GDG considered results separately for trials that haven't provided subgroups by different type of HRT. Although these references were not considered eligible for inclusion in the review, each individual study within each publication was eligible and already included in the evidence base (PEPI 1995; WHI 2002; WHI 2004, DOPS 2012).
Besins Healthcare	Full	131	30	We wondered why results from two key recent RCTs were not included in the analysis. These are described below: 1) KEEPS trial (http://www.ncbi.nlm.nih.gov/pubmed/25069991) A Randomized controlled trial, the KEEPS trial (ClinicalTrials.gov: NCT00154180) was performed in nine U.S. academic centers in postmenopausal women between 6 and 36 months from last menses without prior cardiovascular disease (CVD) events who had a coronary artery calcium (CAC) score less than 50 to assess atherosclerosis progression and CVD risk factors after MHT initiated in early menopause and whether menopausal hormone therapy (MHT) protects against CVD in healthy postmenopausal women aged 42 to 58 years. Of 727 randomly assigned women, 89.3% had at least 1 follow-up CIMT and 79.8% had CIMT at 48 months. Mean CIMT increases of 0.007 mm/y were similar across groups. The	Thank you for your comment. The studies that are mentioned here do not report outcomes that were considered eligible for inclusion in this review. The review protocol is presented in Appendix D.

					percentages of participants in whom CAC score increased did not differ significantly across groups. No changes in blood pressure were observed with oral CEE or transdermal E2. Low- and high-density lipoprotein cholesterol levels improved and levels of triglycerides, C-reactive protein and sex hormone–binding globulin but not interleukin-6 increased with oral CEE. Insulin resistance (measured by fasting glucose and HOMA-IR) decreased with transdermal E2. Serious adverse events did not differ by treatment (breast cancer, endometrial cancer, myocardial infarction, TIA, stroke, or venous thromboembolic disease). Four years of early MHT did not affect progression of atherosclerosis despite improving some markers of CVD risk. 2) ELITE trial (http://www.ncbi.nlm.nih.gov/pubmed/25380275). This study aims to present data from the Early versus Late Intervention Trial with Estradiol (ELITE) in postmenopausal women, the only clinical trial designed to specifically test the timing hypothesis of postmenopausal hormone therapy (HT). The timing hypothesis posits that HT effects depend on the temporal initiation of HT relative to time since menopause. ELITE is a randomized, double-blind, placebo-controlled trial with a 2 × 2 factorial design. Six hundred forty-three healthy postmenopausal women without cardiovascular disease were randomized to oral estradiol or placebo for up to 6 to 7 years according to time since menopause (<6 or ≥10 y). Carotid artery intima-media thickness (CIMT) and cardiac computed tomography were conducted to determine HT effects on subclinical atherosclerosis across menopause strata. Participants in the early and late postmenopausal strata were well-separated by mean age (55.4 vs 65.4 y) and median	

time since menopause (3.5 vs 14.3 y). Expected risk factors (age, blood pressure, and body mass index) were associated with CIMT at baseline in both strata. In the early postmenopausal group, but not in the late postmenopausal group, we observed significant associations between CIMT and factors that may play a role in the responsiveness of atherosclerosis progression according to timing of HT initiation. These include low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, sex hormone-binding globulin, and serum total estradiol. The ELITE randomized controlled trial is timely and unique. Baseline data indicate that ELITE is well-positioned to test the HT timing hypothesis in relation to atherosclerosis progression and coronary artery disease. Preliminary results (Table 1) were presented at last IMS Congress in Cancun (May 2014).

Onset of HRT:	Early (< de 6 years since MNP)		Late (> de 10 years after MNP)	
	Tx	Po	TX	Po
CIMT:	0,0044	0,0078	0,0100	0,0088
(CI 95%)	(0,0026-0,0061)	(0,0060-0,0096)	(0,0085-0,0115)	(0,0073-0,0103)
p	0,007		0,29	

MNP: menopause; HT: Hormone Replacement Therapy; TX: treatment;
Po: placebo; CI: confidence interval; p: statistical significance.
IMS: International Menopause Society.

Table 1. CIMT (Carotid Intima-Media Thickness) progression in mm/year, versus placebo,with 1 mg/day oral micronized estradiol in association with 90 mg/day progesterone gel vaginally applied, in function of early or late onset of treatment. (ELITE study preliminary

				results).	
British Menopause Society	Full	131	31	States 5 RCTs included in Table 18. Which 5? Why was HERS trial and PHASE trial not included? (Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 1998; 280: 605-13 / Clarke SC, Kelleher J, Lloyd-Jones H, et al. A study of hormone replacement therapy in postmenopausal women with ischaemic heart disease: the Papworth HRT Atherosclerosis Study. Br J Obstet Gynaecol 2002; 109: 1056-62) Why was the study of Brownley et al included? (only 68 women and blood pressure as the CVD outcome)	Thank you for this comment. The five RCTs included are: Shierbeck 2012; The WHI 2002 and 2004; Cherry 2014; Brownley 2004, and the Writing group for the PEPI trial 1995. The review on HRT use and cardiovascular diseases is led by the evidence that meets the inclusion criteria set out in relevant systematic review protocols (Appendix D). One of the primary criterion for including evidence for this question was the initiation of HRT before the age of 65 years. After checking the evidence suggested in your comment: 1) HERS trial. This study did not meet the inclusion criteria because it included women aged 50-80 years with no subgroup analysis on women who have initiated HRT use before age 65 years (the main inclusion criterion for this review question). Please see details in excluded studies list (Appendix G). 2) PHASE trial. This study does not meet the inclusion criteria because no subgroup analysis was given based on the women who have initiated HRT use before the age of 65 years. The information on the age range of included women cannot be extrapolated to assume that those would fall under the review protocol criteria. Exclusion reason has now been reported in excluded studies list (Appendix G).

					The study by Brownley 2004 was included in the evidence review because the age range of women was reported between 40 to 69 years at baseline and subgroup analysis of women started using HRT within 5 year menopause was conducted.
Sheffield Teaching Hospitals NHS Foundation Trust	FULL	132	3	Should this table include the Shierbeck study from 2012	Thank you for this comment. This has been added to the table in the guideline.
British Menopause Society	Full	133	General	where is the HERS trial? Raised elsewhere	Thank you for this comment. This study did not meet the inclusion criteria because it included women aged 50 to 80 years with no subgroup analysis on women who have initiated HRT use before age 65 years (this was the main inclusion criterion for this review question). Please see details in excluded studies list (Appendix G).
Royal College of Pathologists	Full	133	11	Ettinger 1996 study; cholesterol 260mg/dL should be 6.734 mmol/L	Thank you for this comment. This has been amended.
British Menopause	Ful	134	6	Incorrect to state that Schierbeck study compared HRT to placebo. There was no placebo group, only a randomised n-treatment group.	Thank you for this comment. This has been amended.

Society	I				
Sheffield Teaching Hospitals NHS Foundation Trust	FULL	135	8	Remove was	Thank you for this comment. This has been amended.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	135	8	Change to 'and was preserved'	Thank you for your comment, this sentence has been amended.
British Menopause Society	Full	135	15	WHI found significantly reduced CHD risk in long term follow up for women aged 50-59 compared with placebo (stated in line 38).	Thank you for this comment. Line 15 to 17 on page 135 is the evidence statement for oestrogen's effect on CHD and stroke among women aged 50-59 during intervention phase (mean 6.8 year follow-up, WHI 2004, oestrogen trial). Evidence showed that there was no significant difference in the risk of CHD or stroke between oestrogen group and placebo group

					among women of this age group during HRT intervention phase. The evidence statement in line 38 referts to the risk of CHD and stroke associated with oestrogen use after the end of treatment (median 5.9 and 6.6 years), among women aged 50 to 59 at study enrolment. This statement was informed by post intervention re-analysis of WHI oestrogen trial (undertaken by the WHI group), which demonstrated that after a median 5.9 and 6.6 years termination of oestrogen use, reduced risk of CHD was found among women who were 50 to 59 years at baseline, while no significant difference was seen for stroke among women of this age group during post-intervention phase.
British Menopause Society	full	135	15 17	There was significantly reduced CHD risk for women aged 50-59 compared with placebo in WHI study - actually stated later (line 36-41).	Thank you for this comment. Line 15 to 17 on page 135 is the evidence statement for oestrogen's effect on CHD and stroke among women aged 50-59 during intervention phase (mean 6.8 year follow-up, WHI 2004, oestrogen trial). Evidence showed that there was no significant difference in the risk of CHD or stroke between oestrogen group and placebo group among women of this age group during HRT intervention phase. The evidence statement for the risk of CHD and stroke associated with HRT after a median 5.9 and 6.6 years' termination of oestrogen use, among women aged 50 to 59 at study enrolment. This statement was informed by post intervention re-analysis of WHI

					oestrogen trial, which demonstrated that after a median 5.9 and 6.6 years termination of oestrogen use, significantly reduced risk of CHD was found among women who were 50 to 59 years at baseline, while no significant difference was seen for stroke among women of this age group during post-intervention phase.
Poole Hospital NHS Trust	full	135	15 17	There was significantly reduced CHD risk for women aged 50-59 compared with placebo in WHI study - actually stated later (line 36-41).	" Thank you for this comment. Line 15 to 17 on page 135 is the evidence statement for oestrogen's effect on CHD and stroke among women aged 50-59 during intervention phase (mean 6.8 year follow-up, WHI 2004, oestrogen trial). Evidence showed that there was no significant difference in the risk of CHD or stroke between oestrogen group and placebo group among women of this age group during HRT intervention phase. The evidence statement for the risk of CHD and stroke associated with HRT after a median 5.9 and 6.6 years' termination of oestrogen use, among women aged 50 to 59 at study enrolment. This statement was informed by post intervention re-analysis of WHI oestrogen trial, which demonstrated that after a median 5.9 and 6.6 years termination of oestrogen use, significantly reduced risk of CHD was found among women who were 50 to 59 years at baseline, while no significant difference was seen for stroke among women of this age group during post-intervention phase.
British	F	1	1	The Brackets are confusing in this line and I wonder if 'with' should be	Thank you for this comment. This has been amended

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Menopause Society	ull	35	8	replaced with 'which'	in the guideline
Sheffield Teaching Hospitals NHS Foundation Trust	FULL	135 147	18 23	Replace with –which Recommendations suggest include that HRT may reduce the risk of developing type 2 dmnhsnhsnnhsnhsjhrbhlfblnnnhs ma0ijdDJOHNH	Thank you this comment. This typo has been corrected. The recommendations were based on both the interpretation of clinical evidence and GDG expert opinion. In accordance with what set out in the protocols (Appendix D) for long-term outcomes such as CVD and type 2 diabetes in this guideline, evidence from both RCTs and observational comparison studies was reviewed. Specifically, for the population of interest to our review (women who have initiated HRT use before age 65), RCT evidence largely showed no significant difference between HRT and placebo groups in the risk of CHD and type 2 diabetes, while comparative cohort studies showed reduced risk for both outcomes among women on HRT.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthc	Full	135	18 20	Not at all clear	Thank you for this comment. We have amended this sentence.

are					
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	135	38	Not clear	Thank you for this comment. We have amended this sentence.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	136	5	Take out word ‘blood’	Thank you for this comment. The Word "blood" here has been removed.
British Menopa	Fu	13	1	Repetition of the previous sentence.	Thank you for this comment. Line 1 on page 137 is not a repetition of the previous sentence, as this line is the

use Society	I I	7		Why were there no references to the large studies showing reduced mortality with HRT? (Salpeter SR, Cheng J, Thabane L, Buckley NS, Salpeter EE. Am J Med. 2009;122:1016-1022 / Tuomikoski et al. Obstet Gynecol 2014; 124: 947-53 / Boardman et al. Cochrane Database Syst Rev 2015; DOI: 10.1002/14651858.CD002229.pub4)	evidence statement about CHD death in association with HRT use, while the previous sentence was about CVD death in association with HRT use. The review on HRT use and cardiovascular diseases is led by the evidence that meets the inclusion criteria set out in relevant review protocols (Appendix D) during guideline development. None of the studies suggested in this comment meet the inclusion criteria. Specifically: • Salpeter SR, 2009; This publication did not meet the review protocol as it was not a systematic review. In addition the outcome reported of total death was not of interest. • Tuomikoski 2014; this study is a non-comparative study and does not meet the interventional review protocol. In addition, the outcomes were reported as standardised mortality ratios which was not the focus of our review question. • Boardman 2015: The Cochrane review by Boardman 2015 was published after the guideline's submission for the public consultation. However, the GDG considered the eligibility of this review for inclusion and it did not meet the inclusion criteria, for example population and outcomes of interest. A discussion about this publication has been added to section 11.2.4 of the full guideline. Each of the individual studies included in Boardman 2015 were also checked for potential inclusion as an additional quality assurance check.

British Menopause Society	Full	139	10 28	These figures appear different from those from the new Cochrane review in that you do not support the window of opportunity theory that giving HRT early in the menopause confers a degree of protection against CVD. This will confuse media, patients and doctors alike if there is no clarity as to why your analysis should be quite so different to the respected output of the Cochrane collaboration.	Thank you for this comment. The data from the cardiovascular risk review (section 11.2 of the full guideline) were re-examined in relation to those reported in Boardman 2015. Among the 4 studies included for the subgroup analysis on women who have started HRT use within 10 years since menopause in Boardman 2015, 3 studies (DOPs 2012; WHI 2002; WHI 2004;) meet the inclusion criteria and were included in the GDG's review. However, the GDG did not pool the data as Boardman 2015 did, rather, they reported the risk associated with HRT among this subgroup of women by preparations of HRT, e.g., by oestrogen alone, by oestrogen plus progestin where possible in accordance with the review protocol (Appendix D). When the analysis was broken down by HRT preparations, evidence showed that there was no significant difference in the risk of CHD associated with oestrogen alone, or associated with oestrogen plus progestin compared with placebo groups among women who have started HRT use within 10 years since menopause (evidence from WHI 2002, 2004, respectively). Although the data showed a trend of reduced risk for coronary heart diseases associated with oestrogen, or oestrogen combined with progestin, statistical significance was not reached. For the other 2 studies (ERT II 1997; DOPs 2012) included in the subgroup analysis of women who have

					started HRT use within 10 years since menopause in Boardman 2015, ERT II 1979 was excluded from the review because only an overall risk estimate for all women with a mean age of 55 years (range of age not reported) was reported and this had been reported in our excluded studies list (Appendix G). For Shierbeck 2012 (DOPS 2012), this study is included in the review but the specific risk estimate for women who have started HRT use within 10 years since menopause was not available in its published report and we did not have access to it during guideline development.
British Menopause Society	Full	139 139	33 37	RCTs show no increased risk in women with pre-existing CHD (HERS (Hulley et al), ESPRIT (Cherry et al), PHASE (Clarke et al), WHISP (Collins P, Flather M, Lees B, Mister R, Proudler AJ, Stevenson JC. Randomized trial of effects of continuous combined HRT on markers of lipids and coagulation in women with acute coronary syndromes: WHISP Pilot Study. Eur Heart J 2006; 27: 2046-53)) There is evidence of dose dependency for stroke risk with low doses not increasing the risk. (Grodstein et al. Arch Intern Med 2008; 168: 861-66)	Thank you for your comment. Data from the evidence review including RCTs and cohort studies were not consistent. Meta-analysis from two cohort studies showed an increased risk of CHD among current HRT users who have had an MI (RR: 1.04 [95% CI: 1.02-1.91], while RCT evidence from Cherry 2014 showed no difference, HR: 1.23 (95%CI: 0.63-2.41). The publications suggested by this comment have been checked, although none of studies meet the inclusion criteria, specifically: - Hulley, S., Grady, D., Bush, T., Furberg, C., Herrington, D., Riggs, B., Vittinghoff, E., Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group, JAMA, 280, 605-613, 1998 Participants aged 55-80 years were included at

					baseline, no subgroup analysis for women who have initiated HRT use before age 65 years was performed. - Collins, P., Flather, M., Lees, B., Mister, R., Proudler, A.J., Stevenson, J.C., WHISP (Women's Hormone Intervention Secondary Prevention Study) Pilot Study Investigators. Randomized trial of effects of continuous combined HRT on markers of lipids and coagulation in women with acute coronary syndromes: WHISP Pilot Study Outcomes of the study were risk factors of CVD, not CVD events itself. - Cherry,N., Gilmour,K., Hannaford,P., Heagerty,A., Khan,M.A., Kitchener,H., McNamee,R., Elstein,M., Kay,C., Seif,M., Buckley,H., ESPRIT team., Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial, Lancet, 360, 2001-2008, 2002 Participants (current HRT users) aged 50-69 years were assessed, no subgroup analysis on women younger than 65 years of age was conducted. For the risk of stroke associated with HRT use, evidence on dosage was not stated in protocol therefore relevant evidence on dosage was not reviewed.
London North	Fu	14	6	Very important conclusion. Would the guideline be prepared to advise on use of HRT in women under 65 who have had a cardiovascular event such as	Thank you for your comment. While women with existing heart diseases were included in the review if

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West Healthcare NHS Trust	ll	1	13	MI or angioplasty?	they started HRT use before age 65, the findings from RCTs and cohort studies were not consistent. Meta-analysis from two cohort studies showed an increased risk of CHD among current HRT users who have had an MI (RR: 1.04 (95% CI: 1.02-1.91). RCT evidence from Cherry 2014 showed no difference, HR: 1.23 (95%CI: 0.63-2.41). However, the GDG did not feel that this evidence was compelling enough to draft a negative recommendation.
British Menopause Society	full	141	6 13	Very important conclusion. Would the guideline be prepared to advise on use of HRT in women under 65 who have had a cardiovascular event such as MI or angioplasty?	Thank you for your comment. While women with existing heart diseases were included in the review if they started HRT use before age 65, the findings from RCTs and cohort studies were not consistent. Meta-analysis from two cohort studies showed an increased risk of CHD among current HRT users who have had an MI (RR: 1.04 (95% CI: 1.02-1.91). RCT evidence from Cherry 2014 showed no difference, HR: 1.23 (95%CI: 0.63-2.41). However, the GDG did not feel that this evidence was compelling enough to draft a negative recommendation.
Royal College of Nursing	Full	141	6 13	Would the guideline be prepared to advise on use of HRT in women under 65 who have had a cardiovascular event such as myocardial infarction (MI) or angioplasty? This would be helpful.	Thank you for your comment. While women with existing heart diseases were included in the review if they started HRT use before age 65, the findings from RCTs and cohort studies were not consistent. Meta-analysis from two cohort studies showed an increased risk of CHD among current HRT users who have had an MI (RR: 1.04 (95% CI: 1.02-1.91). RCT evidence from Cherry 2014 showed no difference, HR: 1.23 (95%CI: 0.63-2.41). However, the GDG did not feel that this evidence was compelling enough to draft a

					negative recommendation.
British Menopause Society	full	141	7	Not only is there no evidence of an increased Cardiovascular risk in women under 65 with HRT there is convincing evidence of a possible reduction as laid out in previous 10 pages or so.	Thank you for your comment. The GDG carefully considered the strength and quality of the evidence available from both RCT and observational studies, separated by HRT preparation wherever possible. While they noted a trend toward cardiovascular risk reduction, the data did not provide robust evidence of a protective effect.
Poole Hospital NHS Trust	full	141	7	Not only is there no evidence of an increased Cardiovascular risk in women under 65 with HRT there is convincing evidence of a possible reduction as laid out in previous 10 pages or so.	Thank you for your comment. The GDG carefully considered the strength and quality of the evidence available from both RCT and observational studies, separated by HRT preparation wherever possible. While they noted a trend toward cardiovascular risk reduction, the data did not provide robust evidence of a protective effect.
British Menopause Society	Full	141	20 21	take into account raised BP - how?	Thank you for your comment. This recommendation has been amended for clarity.
British Menopause Society	Full	141	20	Not a helpful statement. Does not give guidance on how to manage women with CV risk factors	Thank you for your comment. This recommendation has been revised in light of stakeholder feedback. Please note the specific management of cardiovascular risk factors (for example, hypertension) is outside the scope of the guideline.
Clinical Effectiveness Unit of	Full	142	Gener	Very helpful although see previous comments about 'women on any HRT'	Thank you for this comment. Many studies did not specify the type of HRT and this has now been clarified in the recommendations.

Faculty of Sexual & Reproductive Healthcare			al		
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	143	General	Need consistent abbreviations for T2DM in this section	Thank you for your comment, this has been amended.
Clinical Effectiveness Unit of Faculty of Sexual &	Full	143	22	Should be 'menopause'	Thank you for your comment, this has been amended.

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Reproductive Healthcare					
Royal College of Pathologists	Full	144	25	Bonds 2006 study; kg/m2 should be kg/m^2 (also page 148 table21); triglycerides mmol/l should be mmol/L	Thank you for your comment. The units have been amended.
Royal College of Pathologists	Full	145	general	De Lauzon-Guillain 2009 study; Kg/m2 should be kg/m^2 ; Zhang 2002 glucose should be mmol/L not mml/l or mmol/l	Thank you for your comment. The units have been amended.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	146	67	Sentence not clear	Thank you for your comment. The units have been amended.
Clinical	F	1	1	Sentence not clear	Thank you for your comment. The units have been

Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	ull	46	214		amended.
Royal College of Pathologists	Full	146	19	Refers to T2D this occurs several times in later lines, abbreviation is T2DM listed	Thank you for your comment, this has been amended.
British Menopause Society	full	147	General	Q1. This is very helpful and will give excellent guidance to primary care regarding obesity and chance of developing type 2 diabetes	Thank you for this comment.
British Menopause Society	Full	147	201	associated wit a lower risk of developing T2DM - C/W NEXT LINE - NOT ASSOCIATED WITH AN INCREASED RISK - which one?	Thank you for your comment. This sentence has been corrected.
Menopause UK	Fu	14	26	***10.4 deals with Type Two diabetes management***	Thank you for your comment. The treatment of long-term sequelae of oestrogen depletion caused by

	I I	7		The evidence review focuses on the impact of HRT on glycemic control. The conclusion is that HRT does not negatively affect control of blood sugar levels. However, the review also acknowledges that fluctuations in sex hormones during the menopausal transition "can have an influence on blood sugar levels". In addition, the draft guidelines note that the ability of women with T2D to self-manage their blood sugar based on symptoms during the menopausal transition can be complicated because unfamiliar events such as hot flushes can be hard to distinguish from symptoms of hypoglycaemia. No advice or further information is offered to women or health care practitioners on monitoring or managing this situation. Conversations with women who have diabetes suggest that awareness of the impact of menopause on diabetes management is low amongst both women and healthcare practitioners. We suggest that the guidelines should include advice to practitioners caring for women with T2D around the time of menopause, at least covering the provision of information to women and raising awareness of the impact of menopause amongst healthcare practitioners. We further suggest that an additional Research Recommendation be added: “What is the impact on menopause of long term conditions such as diabetes?”.	menopause is outside the scope of the guideline.
Royal	F	1	3	Glycosylated haemoglobin is incorrect terminology should be glycated	Thank you for your comment. Glycated has been

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College of Pathologists	ull	48	2	haemoglobin; HbA_{1c} not HbAl1c; correct units in use in other NICE guidelines for diabetes mellitus use correct units of HbA_{1c} mmol/mol not %. This needs to be corrected throughout remainder of document, Table 21, page 150 line 25, 29, page 151 line 9. HbA_{1c} 10% should be 86 mmol/mol	amended in the guideline. HbA1c was reported as a percentage because this is how the studies reported the outcome. Percentages are used throughout the updated suite of NICE guidance on diabetes management.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	150	25 26	Significantly greater or significantly less	Thank you for your comment. The result of the supplementary evidence showed that over a two year period, women who were taking HRT experienced a positive effect on control of T2DM as their HbA1c levels were significantly reduced compared to women who did not take HRT.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	151	10	Should be 'groups. These…'	Thank you for your comment, this has been amended.

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Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	151	46	Should be 'associated' and 'a reduction in ..'	Thank you for your comment. This has been amended.
NCRI - Breast CSG Working Group on Symptom Management	FULL	152	GENERAL	It is interesting that your argument in favour of HRT use for menopause in normal women is based primarily on the risk of dying from breast cancer rather than developing it. As a patient with breast cancer, there is some chance that something other than breast cancer will kill me - but I would much rather not have had the breast cancer in the first place. Never mind the health economic impact (I must have cost the NHS a fortune) I have had 10 years of hot flushes, fatigue, broken sleep, inability to work to my full potential, I would much rather not have had breast cancer	Thank you for your comment. The review protocol did not consider the primary aetiology of breast cancer so when the GDG reviewed the evidence on breast cancer, it was not possible to examine whether HRT treatment was the underlying cause of the breast cancer. The GDG appreciates your concern and acknowledges that everyone would prefer to be disease free.
British Menopause Society	Full	152	13	Why ask the question in women taking HRT for menopausal symptoms only as most women who do so will use HRT for a short duration? What about women who may need to consider longer duration of exposure for osteoporosis prevention? It is longer duration of therapy that is associated with increased risk of diagnosis.	Thank you for this comment. The GDG discussed how the duration of HRT treatment required to relieve menopausal symptoms may vary from woman to woman. That is the reason why the protocol was set up to examine the effect of HRT duration on the risk of breast cancer. Longer term data were considered

					when available.
British Menopause Society	Full	152	16	Within this first paragraph I think it would be helpful for you include death rates. I suggest this because you cover mortality later on but the context of what death rates are in the UK at the moment would provide context for readers	Thank you for your comment. The survival rates as quoted in NICE CG80 (Early and locally advanced breast cancer) are provided at the end of the paragraph.
British Menopause Society	Full	152	16	The whole section (10.5.2 lines 16 to 45 page 152 and lines 1 to 5 page 23) is difficult to read and jumps between facts. If this is to provide more detailed information for GPs I think they will find this very confusing.	Thank you for your comment. This introduction has been revised in order to improve clarity.
British Menopause Society	Full	153	26	There are in fact 6 RCTs of HRT. The one missed out (although limitations to the trial design) but should be included for completion is the Nachtigall study from 1992 (Obstet Gynaecol 1992 80(5) 827).	Thank you for your comment. This RCT was excluded from the systematic review because it only reported results from the post-intervention phase. In addition, during the 12 year post-stopping phase, there was a high proportion of women in the placebo arm who switched over to the HRT arm. More specifically, 38% of the original placebo users switched to use HRT and were counted as HRT users in the analysis. The primary RCT from 1979 was excluded from the review because the study did not report estimates for breast cancer and no cases of cancer were reported in the treatment group
British Menopause Society	Full	153	28	Schierbeck et al did give details of the type of HRT	Thank you for your comment. The details of the type of HRT used in this study have been added.
Poole Hospital NHS Trust	Full	153	28	Schierbeck study did not have placebo group, they had a randomised no treatment group. They also specified type of HRT (one of the few non-CEE studies)-.	Thank you for your comment. This is now corrected.

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British Menopause Society	Full	153	41	It should be made quite clear for all the RCTs whether breast cancer was an a priori hypothesis, a secondary outcome or a safety outcome as this will have bearing (amongst other factors) as to the validity of the findings from individual trials and whether the breast cancer data has any relevance in informing clinical advice	Thank you for your comment. The information on whether the outcome of breast cancer was a primary, secondary or safety outcome is important in the interpretation of results has been added in the text for clarity.
British Menopause Society	Full	154	1	Table 22 – I am concerned that the last column on duration of intervention is based on the median / mean follow-up. This is *not* the same as duration of exposure, which is not stated for all of the trials (it is definitely not for the WHI study, which is really the only of the RTC date that can be used with any reliability in terms of risk of diagnosis as it was (along with WISDOM) the only study sufficiently powered to detect change in diagnosis rates). This should be amended as it will be mis-interpreted.	Thank you for your comment. This information has now been amended.in the description of studies (section 11.5.4. in the full guideline).
British Menopause Society	Full	155	14	Significant reduction in breast cancer seen with estrogen alone during cumulative follow up (Manson et al, 2013)	Thank you for your comment. The GDG agree with your statement and this is described in section 11.5.6 where the evidence statements are presented by outcome. However, when the GDG considered the clinical benefits and harms across all of the included randomized and observational studies they concluded that HRT with oestrogen alone is associated with little or no increase in the risk of breast cancer and this was reflected in the recommendation.
British Menopause Society	Full	156	general	WHI does provide evidence for a duration effect as risk of breast cancer diagnosis was only increased in women allocated to combined HRT who had been using HRT prior to study entry (they had a 3-month washout period before restarting HRT if allocated to receive it). In the WHI study information is only provided about duration of follow-up. If the duration of exposure is calculated, for the oestrogen only arm of the RCT the median duration of exposure is 4.6 years and for the combined arm of the study, 3.2 years. This means sufficiently powered RCT date shows no increased risk of diagnosis with just under 5 years exposure to CEE and just over 3 years exposure to	Thank you for your comments. Based on the information presented in Manson 2013, both arms of the WHI trial had a proportion (although different proportion) of women who reported prior use of HRT. However, given that results were not presented for the subgroups of women with different exposures to HRT (including previous exposure to HRT), conclusions could not be drawn in relation to duration effect of HRT in the incidence of breast cancer based on WHI

				CEE + continuous MPA (2.5mg).	data. This is noted in the discussion of results in the linking evidence to recommendation section of the guideline.
British Menopause Society	Full	156	6	I think there should be a clear statement about which of the 6 RCTs were sufficiently powered to detect a change in the risk of breast cancer diagnosis (only WHI and WISDOM, the latter was stopped prematurely before meaningful date could be accrued). This should also include whether breast cancer diagnosis was an a priori hypothesis, secondary or safety outcome, blinded or open label (e.g.Schierbeck et al 2012) – these are all factors that negate the 'gold standard' of randomisation.	Thank you for your comment. The GDG agrees with your comment about these aspects of quality assessment that compromise the evidence reviewed. The quality of evidence was assessed using the GRADE approach as described in the NICE Guidelines Manual. More specifically, risk of bias, including randomization and allocation concealment were taken into consideration and are described in footnotes of the relevant GRADE profiles. The adequacy of a RCT's power to detect a difference in the outcomes and the uncertainty around this effect estimate was assessed using the domain of imprecision following the GRADE approach (please see Methods in Chapter 2 for further details). Finally, although the studies in which breast cancer diagnosis was a primary versus secondary versus safety outcome may provide different measures of precision, the review protocol was not set up to look at any differences between these studies. Furthermore, no studies were excluded based on this criterion.
British Menopause Society	Full	156	105 6	I have always found it hard to conclude the effect of HRT on breast cancer from the studies identified and I think the fact that all the studies quoted are low or very low quality except for a few which are moderate quality reinforces it is very hard to conclude anything in this area. Should this be more explicitly stated early on in this section?	Thank you for your comment. The quality of the studies is discussed in the linking evidence to recommendation section of the guideline. However, the synthesis of evidence from both randomized and observational studies showed similar direction in the effects and the GDG reached their conclusions based on the risk of breast cancer for the different types of

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					HRT.
British Menopause Society	Full	156	10	Only WHI is sufficiently powered to draw conclusions about risk of breast cancer diagnosis. If the writers of the guidance want to discuss post-intervention follow-up from WHI, ESPRIT and the Schierbeck study this ought to be highlighted rather than stating low quality evidence or very low quality evidence…….again I think if reading this for further information as a GP this is very confusing. For the ESPRIT and Schierbeck studies breast cancer was a safety outcome and breast 'monitoring' interventions etc are not commented upon on the papers. I would not include this is evidence and certainly not the post-intervention results.	Thank you for your comment. The GDG agree that the conclusions drawn from the interventional phase of a trial should be considered separately from the post interventional follow up that is why the evidence statements were presented separately. However, the GDG still consider it important to look at the HRT effect in the post interventional follow up period and interpret the data in light of the study limitations.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	157	25	Not clear – 'oestrogen's' ??	Thank you for your comment. This has now been amended.
London North West Healthcare NHS Trust	Full	158	General	Again really important information and major finding of guideline	Thank you for this comment.

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British Menopause Society	Full	158	General	Again really important information and major finding of guideline	Thank you for this comment.
Royal College of Nursing	Full	158	General	We are pleased to have this important information and major findings of the guideline.	Thank you for this comment.
British Menopause Society	Full	158	3	All studies (observational and RCTs) are able to report is the risk of breast cancer diagnosis. We do not know the true incidence of breast cancer. This is really important as HRT probably promotes the growth or pre-existing cancers rather than initiating malignant change.	Thank you for your comment. This has been corrected.
British Menopause Society	Full	158	16	Why start talking about progestogens alone? They are not used for the management of vasomotor symptoms as far as I know in the general population. They were used for iatrogenic symptoms in breast cancer patients but this practice stopped after the publication of the first WHI paper in 2003 that confirmed the additional of a progestin to oestrogen conferred the increased risk of breast cancer diagnosis with HRT.	Thank you for your comment. The review protocol was set up to look at all types of HRT including progestogens alone. This evidence statement summarised the evidence from a meta-analysis of 3 studies evaluating progesterone (without further details on the duration of treatment) that showed no significant difference in the risk of breast cancer compared to control arm. The sentence has been amended for clarity.
British Menopause Society	Full	158	17	Which WHI data is this statement referring to? In the WHI RCT, the median duration of exposure for women allocated to receive combined HRT who did not have prior (pre-trial) HRT exposure was 3.2 years and their risk of diagnosis was not increased in analyses according to age group (Manson et al 2013) supplementary data.	Thank you for your comment. This inconsistency has been corrected.
Clinical	F	1	1	3 times more – 3x what? Either use RR or absolute numbers as below.	Thank you for your comment. We have amended this

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Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	ull	58	8	Please clarify.	sentence to include the absolute risk of breast cancer.
British Menopause Society	Full	158	29	Which data is this paragraph referring to? It is really confusing to mix up the observational and RCT data. The writers of this guidance need to decide whether they are going to use the 'gold standard' of RCT data (the best being the interventional phase of the WHI) and support raising exploratory questions with the wealth of observational evidence available (with all the constraints of inherent bias).	Thank you for your comment. This paragraph refers to evidence from the observational cohort studies and has been clarified in the text.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	158	29	Please clarify type of HRT	Thank you for your comment. A number of the individual studies did not specify the type of HRT used, which has now been reflected in the risk tables where appropriate.

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British Menopause Society	Full	158	35	I'm assuming this is referring to observational data but it is unclear from the guidance.	Thank you for your comment. The paragraph refers to comparative cohort studies, which has now been clarified.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	158	37	'More than or equal to'	Thank you for your comment. The text has been amended.
British Menopause Society	Full	159	19	'this' should be replaced with 'these'	Thank you for your comment, this sentence has been amended.
Clinical Effectiveness Unit of Faculty of Sexual	Full	159	20	'Question'	Thank you for your comment, this has been amended.

& Reproductive Healthcare					
British Menopause Society	Full	159	21	Change 'several thousand of patients' to 'several thousand patients'	Thank you for your comment, this has been amended.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	159	28	Take out ' due to'	Thank you for your comment, this has been amended.
British Menopause Society	Full	159	48	The best quality data about the impact of HRT on mammographic breast density is from the placebo-controlled PEPI trial (Greendale GA et al 1999 Annals Int Med and JNCI 2003). Overall this shows breast mammographic density increases with HRT exposure occurs over the first 12 months of exposure only and that changes with unopposed oestrogen are not significantly increased compared with placebo and of the order of a 3% to 5% increase with combined HRT (synthetic and micronized progestin, cyclic or	Thank you for this information which expands on the comment made by the GDG in the linking evidence to recommendation section of the guideline. The guideline did not review the data for breast density and the comment was included as a good practice point only.

				continuous). However, whilst the latter is statistically significant the clinical significance of this has not been prospectively assessed. So to state that density increases with combined HRT makes the detection of small cancers more difficult is no more than an assumption. The WHI investigators did produce a paper about increased recall and investigations for women taking HRT but it is inappropriate to compare the 'screening' practice of the USA with the UK as there are significant differences in practice and quality assurance (e;g much higher recall rates and open biopsy rates in the US compared with the UK and so on).	
British Menopause Society	full	160	general	The GDG are to be congratulated on producing such clear and concise recommendations on this emotive topic where the evidence has been so contradictory. This will be a huge help to those women considering the use of HRT	Thank you for this comment.
Poole Hospital NHS Trust	full	160	general	The GDG are to be congratulated on producing such clear and concise recommendations on this emotive topic where the evidence has been so contradictory. This will be a huge help to those women considering the use of HRT	Thank you for this comment.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthc	Full	160	3	Please clarify – baseline is over 7.5 years which is confusing with figures in table	Thank you for your comment. A note has been added to the table to indicate that the absolute risk differences in the table are also over 7.5 years. This length of time was used as it was the average study duration time and therefore was most representative for our evidence (see Section 3.3.4).

are					
British Menopause Society	Full	160	6	At no time in the guidance is any reference made to the fact that WHI (randomised trial) showed in terms of overall cancer risk with combined therapy this is associated with a reduced risk of diagnosis of colorectal cancer (for 10,000 women allocated combined HRT 9 additional breast cancers, 6 less colorectal and 1 less endometrial cancer so overall 4 cancers more; for unopposed oestrogen 7 less breast cancers, 2 additional colorectal so overall cancers 8 less). Breast cancer isn't the only cancer outcome	Thank you for your comment. The GDG agrees that breast cancer is not the only cancer outcome that could be considered for inclusion in the review. However, the decision about which outcomes to prioritise for inclusion in the review was made on the basis of which outcome is the most controversial.
British Menopause Society	full	160	12	A really useful summary	Thank you for this comment.
British Menopause Society	Full	160	15	Please refer to comment 1	Thank you for this comment. The developer does not receive these comments in order so is unable to determine which previous comment you refer to.
British Menopause Society	Full	160	17	Please refer to comment 2	Thank you for this comment. The developer does not receive these comments in order so is unable to determine which previous comment you refer to.
King's College Hospital NHS Foundation Trust	Full	160	19	Breast cancer risk and type of progesterone: there is reference to the increased risk of breast cancer with oestrogen and progestogen use but not to the potential differential effect of different progesterone / progestogen preparations. The Fournier et al. 2008 study - E3N breast cancer risk with different hormone therapies - is included in the Table and reference list but not in the conclusions or recommendations.	Thank you for your comment. The evaluation of potential differences between formulations containing progesterone was included in the protocol. However, the data did not allow for the consideration of differences between progesterone preparations.
British	F	1	1	Breast cancer risk and type of progesterone: there is reference to the	Thank you for your comment. The evaluation of

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Menopause Society	ull	60	9	increased risk of breast cancer with oestrogen and progestogen use but not to the potential differential effect of different progesterone / progestogen preparations. The Fournier et al. 2008 study - E3N breast cancer risk with different hormone therapies - is included in the Table and reference list but not in the conclusions or recommendations.	potential differences between formulations containing progesterone was included in the protocol. However, the data did not allow for the consideration of differences between progesterone preparations.
British Menopause Society	Full	160	19	Please refer to comment 3	Thank you for this comment. The developer does not receive these comments in order so is unable to determine which previous comment you refer to.
British Menopause Society	Full	161	General	? tibolone and breast cancer risk	Thank you for your comment. The research recommendation has been amended so that it is limited to alternatives to conventional systemic treatments in this population. Therefore, it is not appropriate to include tibolone in the proposed research question.
NCRI - Breast CSG Working Group on Symptom Management	FULL	161	GENERAL	It is good to see the call for a registry of women taking the various different preparations of HRTs and SERMs. I would also like to see progesterone alone eg megace.	Thank you for your comment. The current research recommendation allows for the inclusion of progesterone alone.
Sheffield Teachin	FUL	162	5	Re the LNG IUS – replace secreting with releasing. Recent faculty guidance on intrauterine devices recommends 5 yr use of th LNG IUS as add back for HRT – (out of license) ref FSRH GUIDANCE 2015 Intrauterine contraception	Thank you for your comment. The text has been amended as suggested.

g Hospitals NHS Foundation Trust	L				
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	162	5	Correct terminology is 'levonorgestrel-releasing'	Thank you for your comment. This has been amended.
UK Clinical Pharmacy Association	Full	163	333 334	Some HRT products are licensed for indication - osteoporosis prophylaxis. The statement that HRT products in the UK are not licensed for osteoporosis treatments needs to be modified.	Thank you for your comment. We have changed the sentence to allow for HRT products which are licensed for prophylaxis.
Sheffield Teaching Hospital	FULL	175	29	Replace no with non	Thank you for your comment, this has been corrected.

s NHS Foundation Trust					
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	175	29 35	No current users: ? should be non-current users	Thank you for your comment, this has been corrected.
Sheffield Teaching Hospitals NHS Foundation Trust	FULL	175	35	Replace no with non	Thank you for your comment, this has been amended.
Clinical Effectiveness Unit of	Full	175	36	“4five”: check and reword	Thank you for your comment, this has been amended.

Faculty of Sexual & Reproductive Healthcare					
Royal College of Pathologists	Full	175	38	3two should this be 3	Thank you for your comment, this has been amended.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	175	39	“women used HRT”: should be “using”?	Thank you for your comment, this has been corrected.
Clinical Effectiveness	Full	176	5	“3two”	Thank you for your comment, this has been amended.

Unit of Faculty of Sexual & Reproductive Healthcare	I				
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	176	10	"no current users": reword	Thank you for your comment, this has been corrected.
Clinical Effectiveness Unit of Faculty of Sexual	Full	176	21	"3ahundred": reword	Thank you for your comment, this has been amended.

& Reproductive Healthcare					
British Menopause Society	Full	176	46	Unnecessary 's' on the end of 'fracture'	Thank you for your comment, this has been amended.
British Psychological Society	FULL	177	15 19	The Society believes that there is a clear under-representation of current evidence for psychological treatments into managing menopausal symptoms (HFNS, VMS), particularly that of Cognitive Behaviour Therapy (CBT). It is advised that "evidence from randomised control trials (RCTs) of CBT for VMS should be included in the main document and appendices." Currently, this information is referred to in the section "Review and Refer" for women who have contradictions to HRT. However, the evidence is also relevant for women going through a natural menopause as a viable alternative for those who prefer not to have HRT. It is suggested that the evidence from relevant trials (Mann et al, 2012; Ayers et al, 2012; *Duijts et al, 2012*) be included in the main document that links with the summary recommendations with a suggested change to 'women with menopausal symptoms who prefer non hormonal options and/or have contraindications to HRT'.	Thank you for your comment. The systematic review of evidence for the treatment of short term symptoms included psychological interventions such as cognitive behavioural therapy (see Appendix D.4). A discussion of the evidence is presented in section 9.2 of the full guideline. For the outcome of vasomotor symptoms, data from Mann 2012, Ayers 2012 and Dujits 2012 studies were not included in the NMA because the treatment arms of these studies could not be connected to other treatments in the network (connectedness of treatments is a basic requirement of a network meta-analysis)..
British Menopause Society	Full	177	19	Lower risk of hip fracture is supported by RCTs, not just cohort studies. (Cauley JA, Robbins J, Chen Z, Cummings SR, Jackson RD, LaCroix AZ, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA*	Thank you for your comment. Cauley 2003 and Jackson 2006 were included in the review. Results for hip fracture from both of the studies showed a reduction in the risk of hip fracture overall or stratified

				2003;290:1729-38 / Jackson RD, Wactawski-Wende J, LaCroix AZ, et al. Effects of conjugated equine estrogens on risk of fractures and BMD in postmenopausal women with hysterectomy: results from the Women's Health Initiative randomized trial. J Bone Miner Res 2006; 21: 817-28	by age. However, there was uncertainty around the estimate of effect observed as the 95% confidence intervals crossed either one or two of the thresholds of minimal important differences thus making the result imprecise (please see Methods section 3.3.3 in the full guideline for more information). On this basis, only hip fracture in prospective cohorts were discussed.
British Menopause Society	full	178	26 40	Conclusion states (line 28) "...lower risk of fragility fracture and this lower risk is preserved when HRT is discontinued" Recommendations say (line 39) " is maintained during treatment but decreases once treatment stops"	Thank you for your comment. This text has been amended for clarity.
Poole Hospital NHS Trust	full	178	26 40	Conclusion states (line 28) "...lower risk of fragility fracture and this lower risk is preserved when HRT is discontinued" Recommendations say (line 39) " is maintained during treatment but decreases once treatment stops"	Thank you for your comment. This text has been amended for clarity.
King's College Hospital NHS Foundation Trust	Full	178	37	Consider HRT as first line intervention for prevention / treatment in women with POI and those under 60 years of age particularly in the presence of menopausal symptoms.	Thank you for your comment. The evidence review considered the increased risk of developing osteoporosis associated with HRT, but did not specifically include studies that evaluate the use of HRT for the prevention of fractures in women who are under 60 or have premature ovarian syndrome.
British Menopause Society	Full	178	37	Consider HRT as first line intervention for prevention / treatment in women with POI and those under 60 years of age particularly in the presence of menopausal symptoms.	Thank you for your comment. The evidence review considered the increased risk of developing osteoporosis associated with HRT, but did not specifically studies that evaluate the use of HRT for

					the prevention of fractures in women who are under 60 or have premature ovarian syndrome.
British Menopause Society	full	179	General	Consideration should be given to the Rocco studies showing increased risk of dementia in women with oophorectomy who do not receive oestrogen but beneficial effect of taking estrogen	Thank you for your comment. Because the study by Rocco 2007 used a case control design, it did not fit the inclusion criteria of the systematic review.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	179	4	Incidence given per 1000 women: are these and baseline figures per 1000 women per year?	Thank you for your comment. The baseline figures quoted are for the total study duration. This has been clarified in the table captions.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive	Full	179	31	“maybe” should be may be	Thank you for your comment, this has been amended.

Healthcare					
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	180	27	"versus no use who had previously discontinued HRT": meaning is unclear	Thank you for your comment, this has been amended.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	180	28	17b should be 17ß	Thank you for your comment, this has been amended.
Clinical	F	1	3	10.5 (plus 4.9): meaning unclear	Thank you for your comment, this has been amended.

Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	full	80	536		
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	180	43	"in US": ?should be "in the US"	Thank you for your comment, this has been amended.
British Menopause Society	full	182	general	There is no mention of the Mayo clinic series (Rocca W,Neurology 2007) which reports increased risk of dementia amongst women who have early BSO and no Oestrogen replacement. Although not an RCT this provides useful additional information about the risks of BSO.	Thank you for your comment. Because the study by Rocco 2007 used a case control design, it did not fit the inclusion criteria of the systematic review which was discussed and agreed by the GDG at the time of protocol development

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Poole Hospital NHS Trust	full	182	general	There is no mention of the Mayo clinic series (Rocca W,Neurology 2007) which reports increased risk of dementia amongst women who have early BSO and no Oestrogen replacement. Although not an RCT this provides useful additional information about the risks of BSO.	Thank you for your comment. Because the study by Rocco 2007 used a case control design, it did not fit the inclusion criteria of the systematic review which was discussed and agreed by the GDG at the time of protocol development.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	182	17	"to very": ?to very low	Thank you for your comment, this has been amended.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	183	4	"for those used HRT treatment" reword	Thank you for your comment, this has been amended.

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Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	183	32	“although” should be removed for sense of sentence, we think	Thank you for your comment, this has been amended.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	185	108	Sarcopenia section useful and clear	Thank you for this comment.
British Menopause	ful	188	37	Muscle mass can also be an important factor in fracture prevention.	Thank you for your comment. The introduction has been amended as suggested.

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Society	l				
Poole Hospital NHS Trust	full	188	37	Muscle mass can also be an important factor in fracture prevention.	Thank you for your comment. The introduction has been amended as suggested.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	189	13	Oophorectomy not just for cancer: need to include benign indications here	Thank you for your comment. This has been amended in the guideline.
The Daisy Network	FULL	189	20	Sexual problems in POI Although sexual problems in POI are mentioned briefly in the guideline, we believe that specific recommendations should be made in the full guideline about the management of psychosexual problems. We believe that the guidelines should include the following points: • During assessment of women with POI, sexual well being should be routinely addressed. • Referral for psychosexual counseling should be offered. • Adequate replacement of systemic estrogen and local estrogen is	Thank you for your comment. Whilst the developers acknowledge that this is a very important area for consideration, it was not prioritised for review following the stakeholder consultation workshop at NICE and the public scoping process.

				important for sexual function. • Androgen replacement may be considered, although there is currently insufficient evidence specific to POI regarding the efficacy and long term effects of androgen replacement. Sexual dysfunction is a common problem among women with POI with decreased sexual well-being, and increased dyspareunia [van Der Stege, 2008; De Almeida, 2011] . Sexual dysfunction is more complex when POI is diagnosed at younger age [Graziottin, 2004] and is also affected by the underlying etiology of POI. Management should include psychosexual counseling, estrogen replacement (both systemic and local if necessary) and consideration given to androgen replacement. Women with POI have been shown to have lower androgen levels compared with control groups [Janse, 2012], however there are only limited data investigating the role of androgen replacement in POI. No studies have explored the effect of testosterone replacement on sexual function in POI. van der Stege JG, Groen H, van Zadelhoff SJ et al. Decreased androgen concentrations and diminished general and sexual well-being in women with premature ovarian failure. Menopause 15, 23–31 (2008). De Almeida DM, Benetti-Pinto CL, Makuch MY. Sexual function of women with premature ovarian failure. Menopause 18, 262–266 (2011). Graziottin A, Basson R. Sexual dysfunction in women with premature menopause. Menopause 11, 766–777 (2004). Janse F, Tanahatoe SJ, Eijkemans MJ, Fauser BC. Testosterone concentrations, using different assays, in different types of ovarian insufficiency: a systematic review and meta-	

				analysis. Hum. Reprod. Update 18, 405–419 (2012).	
The Daisy Network	Full	189	23	We believe that current evidence supports additional investigations at the time of diagnosis of POI, to investigate underlying cause and assess risk of long term complications: (1) FMR1 Gene premutation The most frequently identified single-gene mutation associated with POI is the Fragile X mental retardation 1 (FMR1) gene premutation. The FMR1 premutation has been identified in 11% of familial POI and 3% of sporadic cases [Marozzi, 2000, Murray, 2000, Bussani, 2004]. Screening for the FMR1 premutation should therefore be considered in women diagnosed with POI to identify those patients and family members who may be at risk of having children with Fragile X syndrome. Those with identified premutation should be referred for family genetic counseling. Marozzi A, Vegetti W, Manfredini E et al. Association between premature ovarian failure and fragile x premutation. Hum. Reprod. 15, 197–202 (2000). Murray A. Premature ovarian failure and the FMR1 gene. Semin. Reprod. Med. 18, 59–66 (2000). Bussani C, Papi L, Sestini R et al. Premature ovarian failure and fragile X premutation: a study on 45 women. Eur. J. Obstet. Gynecol. Reprod. Biol. 112, 189–191 (2004). (2) Adrenal autoantibodies Autoimmune POI is associated with ovarian, adrenal or other steroidogenic cell autoantibodies resulting in an autoimmune lymphocytic oophoritis and is estimated to be responsible for approximately 5% of POI cases (Silva, 2014).	Thank you for your comment. Supplementary investigations such as these were not prioritised for inclusion in the scope at the time of protocol development for this review.

				Adrenal autoimmunity is thought to account for 60–80% of autoimmune POI. 4-5 % of women with POI will be positive for adrenal autoantibodies (La Marca, 2010). Positive adrenal antibodies suggest autoimmune oophoritis as the underlying mechanism and identify those patients who are at risk of developing adrenal insufficiency and should thus be referred to an endocrinologist for regular testing of adrenal function. Silva CA, Yamakami LY, Aikawa NE, Araujo DB, Carvalho JF, Bonfa E. Autoimmune primary ovarian insufficiency. Autoimmun. Rev. 13, 427–430 (2014). La Marca A, Brozzetti A, Sighinolfi G, Marzotti S, Volpe A, Falorni A. Primary ovarian insufficiency: autoimmune causes. *Curr Opin Obstet Gynecol.* 22: 277-282 (2010). (3) Thyroid antibodies (TPO-Ab) Up to 30% of women with POI suffer from additional autoimmune disorders including 25% who have hypothyroidism. POI is associated most commonly with thyroid autoimmunity (14–27%) when adrenal autoimmunity is absent (Hoek, 1997; Kim, 1997). Screening for thyroid antibodies should be recommended. It has been advised that thyroid stimulating hormone levels should be checked on a yearly basis if thyroid peroxidase antibodies are positive (Welt, 2008). Hoek A, Schoemaker J, Drexhage HA. Premature ovarian failure and ovarian autoimmunity. *Endocr Rev* 1997;18: 107-134. Kim TJ, Anasti JN, Flack MR, Kimzey LM, Defensor RA, Nelson LM. Routine endocrine screening for patients with karyotypically normal 464 spontaneous premature ovarian failure. *Obstet Gynecol* 1997;89: 777-779. Welt CK. Autoimmune oophoritis in the adolescent. *Ann N Y Acad Sci*	

				2008;1135: 118-122.	
The Daisy Network	Full	189	23	Bone Health in POI Preservation of bone health is of crucial importance in the management of women with POI. We believe this should be highlighted in the guidelines along with recommendations for when bone mineral density (BMD) testing is required. NICE guidelines for osteoporosis currently recommend BMD testing in women at high risk for osteoporosis such as untreated POI. The prevalence of osteoporosis in POI has been estimated at 8-14% compared to zero in controls (Bachelot, 2009; Popat, 2009). Given the high prevalence of osteopenia or osteoporosis at the time of diagnosis in POI, the evidence suggests that routine assessment of BMD at diagnosis may be justified. Bachelot A, Rouxel A, Massin N, Dulon J, Courtillot C, *et al*. Phenotyping and genetic studies of 357 consecutive patients presenting with premature ovarian failure. *Eur J Endocrinol* 2009;161: 179-187 Popat VB, Calis KA, Vanderhoof VH, Cizza G, Reynolds JC, *et al*. Bone mineral density in estrogen-deficient young women. *J Clin Endocrinol Metab* 2009;94: 2277-2283.	Thank you for your comment. The GDG recognises the importance of preserving bone health in women with premature ovarian insufficiency and have highlighted the health benefit of bone protection associated with HRT or combined oral contraceptive pill use in the recommendation about management of POI. However, the timing and frequency of risk assessment for different long term outcomes such as osteoporosis for women with POI was outside the scope of the guideline.
Clinical Effectiveness Unit of Faculty of Sexual &	Full	190	7	“and they were in remission” ?should be “and were in remission”	Thank you for your comment, this has been amended.

Reproductive Healthcare					
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	190	11	"secondary" ?should be "secondarily"	Thank you for your comment, this has been amended.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	190	18	"and assessed the utility" ?should be "assessed the utility"	Thank you for your comment, this has been amended.

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Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Royal College of Pathologists	Full	191	1	Figure 9 and 10 FSH mIU/ml should be IU/L	Thank you for your comment. We have standardised the units for biochemistry tests based on the on the recommendations from UK Pathology Harmony.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	193	17	"may be not of use" should be "may not be of use"	Thank you for your comment, this has been amended.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthc	Full	193	18	"found to" should be "found to have"	Thank you for your comment, this has been amended.

are					
Royal College of Pathologists	Full	193	20	Oestradiol cut-off < 50pg/mL does not make sense as this would be equivalent to 183.55 pmol/L. Should this be <50 pmol/L	Thank you for your comment. The units for biochemistry tests have been standardised based on the on the recommendations from UK Pathology Harmony.
University Hospitals Southampton NHS Foundation Trust	Full	193 12	25	A cut-off level of FSH above 30 IU/L is quoted to indicate ovarian failure in women <40 years however this may not apply to all aetiologies. This cut-off is reported to have low sensitivity and high specificity; however the actual values are not quoted. This information would be useful to labs providing this analysis to enable them to formulate comments for reports. The ACB audit presented in June 2015 found that FSH values from 8 up to 118 IU/L were in use in UK laboratories to distinguish the premenopause from the perimenopause so guidance is clearly needed.	Thank you for your comment. The GDG reviewed the available evidence which supported the cut-off value of 30 IU/L to indicate ovarian insufficiency in women under 40 years of age; the reference quoted (Jadoul 2011) provided a sensitivity of 38% (95% CI 18 to 62) and specificity of 100 % (95% CI 74 to 100). However the Committee were aware that FSH levels often fluctuate in women with POI and therefore recommended repeating FSH measurement. This comment has been forwarded to the NICE implementation support team to inform their support activities for this guideline.
Royal College of Pathologists	Full	193	27	FSH mIU/ml should be IU/L	Thank you for your comment. The units for biochemistry tests have been standardised based on the on the recommendations from UK Pathology Harmony.
Royal College of Pathologists	Full	193	29	FSH mIU/ml should be IU/L	Thank you for your comment. The units for biochemistry tests have been standardised based on the on the recommendations from UK Pathology Harmony.

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Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	194 6	general	Consideration of economics and recommendations useful and relevant to current clinical practice.	Thank you for this comment.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	194	13	“correct positive diagnosis can be” ?should be “correct positive diagnosis which (or that) can be”	Thank you for your comment, this has been amended.
Clinical Effectiveness Unit of	Full	194	20	“AMH levels of <8.8 more may useful to diagnose POI” reword	Thank you for your comment, this has been reworded for clarity.

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Faculty of Sexual & Reproductive Healthcare					
London North West Healthcare NHS Trust	Full	194	36	AMH levels also higher in patients with PCOS	Thank you for your comment. This text has been amended.
British Menopause Society	full	194	36	AMH levels also higher in patients with PCOS	Thank you for your comment. This text has been amended.
British Menopause Society	full	195	37 41	Q1 this will save money for many units by relying on FSH and not submitting to pressure to do AMH and some units cant offer it .	Thank you for your comment.
The Daisy Network	Full	196	8	Psychological aspects of typical age menopause The draft guidance focuses exclusively on biomedical treatment and pays little attention to non-medical approaches that could and arguably should be	Thank you for your comment. The GDG acknowledge the concerns raised in this comment. The recommendations do not specify the order that treatments should be offered, and note that non-

				offered at the outset, depending on presentation, in typical aged menopause as alternatives, and, in particular as a routine adjunct to young women with POI or a premature (iatrogenically-induced) menopause. There is strong evidence that Cognitive Behavioural Therapy (CBT) significantly reduces the impact as measured by problem-rating of hot flushes for women during the menopause transition (perimenopause) and postmenopause, as well as in breast cancer patients (Ayers et al 2012; Mann et al 2012; Duijts et al 2012). The guidelines would benefit from including these papers in the main document. Psychological management of POI We would advocate the need for routine offers of psychosocial support around diagnosis and also at follow up. This group of young women face emotional turmoil. They often feel confused, sad, jealous of other women's pregnancies and/or old before their time. Psychological counselling can ease this distress. Follow-up is required because needs and attitudes will change over time – eg teenagers are not necessarily worried (yet) about issues such as fertility or even long term partnerships/relationships. Even when the *offer* of psychological support is not taken up when originally proffered, it may well be both welcome and beneficial later; and the offer itself acts as a helpful/supportive form of containment. There is an increasing recognition of the value of 'patient-centred' care within the NHS. This suggests that listening to POI women is likely to result in a number of important benefits, namely: increase compliance with medical treatment (young women seem to be particularly reluctant to take 'synthetic' medication and have particular fears over long term use) which are likely to be cost-effective the NHS in the longer term; as well as serving to counter	hormonal treatments were included in the review on the management of short-term symptoms (see Appendix D.4) in women of typical menopause age. Specifically, the protocol included CBT as a possible treatment for hot flushes and night sweats. Mann 2012, Ayers 2012 and Duijts 2012 considered for inclusion in the review but were subsequently excluded because the treatments were not connected to the network which meant that the relative effects of these treatments could not be compared to the other treatments. The GDG did not prioritise problem-rating for inclusion in the protocol of the review due to the restrictions on the number of outcomes included for each review question. In addition, the selection of outcomes was driven by the Network Meta- Analysis (NMA). A discussion about the decision process on the selection of outcomes and the limitations in the interpretation of the NMA results is provided in section 8.8 of the full guideline. The GDG included a clinical psychologist as an expert advisor and discussed in depth the impact of selecting frequency of vasomotor symptoms and not intensity or problem rating scales for assessing the impact of vasomotor symptoms on women in menopause. Further, the GDG recognise the importance of considering the psychological impact of premature ovarian syndrome and have added a recommendation about referral of women with premature ovarian syndrome to healthcare professionals who have the

				feelings of shame and inadequacy, improving self-esteem and quality of life We are concerned that for women with POI or a premature iatrogenically induced menopause in particular, the psychosocial sequelae – loss of fertility, changes in self image and effect on sexual function (in addition to increased vulnerability to bone fracture, cardiovascular health and cognitive functioning) – the utility of psychosocial support is not given due emphasis. While no RCTs have been conducted, there are several studies both, UK and international, that make this point repeatedly over time (see below). Australian Menopause Society Factsheet: Early Menopause Due to Premature and Unexpected Ovarian Failure Feb 2008 BMJ Best Practice Monograph 1004 2015 Boughton MA. Premature menopause: multiple disruptions between the woman's biological body experiences and her lived body. *Journal of Advances in Nursing* 2002; 37:423-30. Cooper AR, Baker VL, Sterling EW, Ryan ME, Woodruff TK, Nelson LM. The time is now for a new approach to primary ovarian insufficiency. *Fertility and Sterility*, 95 (6) May 2011:1890–1897 Cox L, Liu JH. Primary Ovarian Insufficiency: An update. *Int Journal Women's Health;* 2014; 6:235-243 Davis M, Cartwright B. What is the Best Management Strategy for a 20-year-old Woman With Premature Ovarian Failure? *Clin Endocrinol.* 2012; 77(2):182-186. Davis M, Ventura JL, Wieners M, Covington SN, Vanderhoof VH, Ryan ME, Koziol DE, Popat VB, Nelson LM. The psychosocial transition associated with spontaneous 46,XX primary ovarian insufficiency: illness uncertainty, stigma, goal flexibility, and purpose in life as factors in emotional health. *Fertility and*	relevant experience to help them manage all aspects of physical and psychosocial health related to their condition.

				Sterility 2010; 93 (7):2321-2329. Deeks AA, Gibson-Helm M, Teede H, Vincent A. Premature menopause: a comprehensive understanding of psychosocial aspects. *Climacteric* 2011; 14 (5):565-572 (doi:10.3109/13697137.2011.566390) Farrell E. Premature menopause. 'I feel like an alien'. *Aust Fam Physician.* 2002 May;31(5):419-21. Faubion SS, Kuhle CL, Shuster LT, Rocca WA. Long term health consequences of premature or early menopause and considerations for management. *Climacteric* 2015; 18:1-9 Groff AA, Covington SN, Halverson LR , Fitzgerald RO, Vien Vanderhoof MSN, Calis K, Nelson LM Assessing the emotional needs of women with spontaneous premature ovarian failure, *Fertility & Sterility* 2005; 83:1734-1741. Hunter MS. Psychosocial aspects of Premature Menopause. *Menopause Management:* May/June 2009; 18-21 Islam R, Cartwright R. The impact of premature ovarian failure on quality of life: results from the UK 1958 Birth Cohort, 27th Annual Meeting of the European-Society-of-Human- Reproduction and Embryology ESHRE. Oxford University Press (p108) ISSN:0268-1161, 2011. Liao KL, Wood N & Conway GS Premature menopause and psychological well-being *J Psychosom Obstet Gynaecol* 2000; 21: 167-174. Mann E, Hunter MS, Singer D, Panay N, Pitkin J. Psychosocial adjustment in women with premature menopause: a cross-sectional survey. *Climacteric* 2012; 15:481-9 www.ncbi.nlm.nih.gov/pubmed/22335389 PMID:22335389 Nelson LM. Clinical practice. Primary ovarian insufficiency. New England Journal of Medicine 2009; 360: 606-614. Orshan SA, Furniss KK, Forst C & Santoro N. The lived experience of	

				premature ovarian failure. *J Obstet Gynecol Neonatal Nurs* 2001; 30: 202. Orshan SA, Ventura JL, Covington SN, Vanderhoof VH, Troendle JF, Nelson LM. Women with spontaneous 46,XX primary ovarian insufficiency (hypergonadotropic hypogonadism) have lower perceived social support than control women. *Fertility and Sterility.* 2009; 92(2): 688–693. Panay N, Fenton A. Premature ovarian failure: a growing concern. *Climacteric.* 2008; 11: 1-3. Pitkin J, Rees MC, Gray S et al. Management of premature menopause. *Menopause Int*; 2007; 13:44-45 Groff AA, Covington SN, Halverson LR et al. Assessing the emotional needs of women with spontaneous premature ovarian failure, *Fertility & Sterility* 2005; 83:1734-1741. Schmidt PJ, Cardoso GMP, Ross JL, Haq N, Bondy CA. Shyness, Social Anxiety and Impaired Self-esteem in Turner Syndrome and Premature Ovarian Failure *JAMA* 2006; 295: 1374-1376. Schover LR Premature Ovarian Failure and its consequences: Vasomotor Symptoms, Sexuality and Fertility *Journal of Clinical Oncology* 2008; 25(5):753-8. Singer D. It's not supposed to be this way: psychological aspects of a premature menopause. *Counselling and Psychotherapy Research* June 2012; 2:100-108. Singer D, Hunter MS, Mann E, Pitkin J, Panay N. The silent grief: psychosocial aspects of premature ovarian failure. *Climacteric*, 2011; 14(04), pp. 428 - 437. DOI: 10.3109/13697137.2011.571320 Van der Stege JG, Groen H, van Zadelhoff SJ et al. Decreased androgen concentrations and diminished general and sexual well-being in women with premature ovarian failure. *Menopause*; 2008; 15:23-31	
Clinical Effectiv	Fu	19	11.	Clear, useful introductory section to Mx of POI	Thank you for your comment.

eness Unit of Faculty of Sexual & Reproductive Healthcare	l l	6	2.1		
London North West Healthcare NHS Trust	Full	196	14	We do not have 5-10 percent of our POI patients conceiving spontaneously, find that figure hard to believe	Thank you for your comment. This reference is taken from the American College of Obstetrics and Gynaecology report on Primary Ovarian Insufficiency in Adolescents and Young Women (http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Adolescent-Health-Care/Primary-Ovarian-Insufficiency-in-Adolescents-and-Young-Women).
British Menopause Society	Full	196	14	We do not have 5-10 percent of our POI patients conceiving spontaneously, find that figure hard to believe	Thank you for your comment. This reference is taken from the American College of Obstetrics and Gynaecology report on Primary Ovarian Insufficiency in Adolescents and Young Women (http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Adolescent-Health-Care/Primary-Ovarian-Insufficiency-in-Adolescents-and-Young-Women).
Clinical Effectiveness	Ful	196	37	“involved” should be “involving”	Thank you for your comment, this has been amended.

Unit of Faculty of Sexual & Reproductive Healthcare	I				
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	196	39	Was this a COC taken cyclically? It is clear with the second study quoted next, but not with this one.	Thank you for your comment. Please refer to the evidence tables in Appendix H. Sequential conjugated oestrogen (0.625mg) was given for 14 days, followed by conjugated oestrogen (0.625mg) and medroxyprogesterone acetate (5mg) for the following 14 days (Premaril Plus MP®, Dexxon). Treatment duration was 6 months.
Clinical Effectiveness Unit of Faculty of Sexual	Full	197	9	Clarify that this was a COC taken with a hormone free interval	Thank you for your comment. The OCP regimen ("Standard hormone replacement") was ethinylestradiol 30µg and noresthisterone 1.5mg daily for weeks one to three, followed by seven "pill-free" days (Loestrin 30, Galen Ltd.).

& Reproductive Healthcare					
Royal College of Pathologists	Full	197	20	Guttmann 2001 study units should be 25 hydroxy vitamin D nmol/L ; 1,25 dihydroxy vitamin D pmol/L; deoxypiridine nmol/L or if quoting per mmol of creatinine in urine need to state this nmol/mmol	Thank you for your comment. The units have been standardised as suggested for these outcomes.
London North West Healthcare NHS Trust	Full	199	General	2 very small studies (one with 17 patient and another with 42) provide all the evidence for the statements on use of oral contraceptive versus HRT choice in treatment for POI patients. COC is a poor choice for POI patients….guidlines on COC use recommend stopping COC at 50, so POI patients will need to change treatment to HRT then if they wish to continue above 50 (which would be sensible) . There is also the issue of a 7 pill free break incorporated in the 21 day packs, and whilst we would recommend no pill free breaks(again not addressed in the guideline) this lends itself to misinterpretation by both patient and prescriber.	Thank you for your comment. Some women choose to take the oral contraceptive pill and this is important option for them which is supported by available evidence. The seven day pill break was included in one of the studies, but unclear in the other, so the GDG do not wish to be prescriptive about whether this should be followed.
British Menopause Society	Full	199	General	2 very small studies (one with 17 patient and another with 42) provide all the evidence for the statements on use of oral contraceptive versus HRT choice in treatment for POI patients. COC is a poor choice for POI patients….guidlines on COC use recommend stopping COC at 50, so POI patients will need to change treatment to HRT then if they wish to continue above 50 (which would be sensible) . There is also the issue of a 7 pill free break incorporated in the 21 day packs, and whilst we would recommend no pill free breaks(again not addressed in the guideline) this lends itself to misinterpretation by both patient and prescriber.	Thank you for your comment. Some women choose to take the oral contraceptive pill and this is important option for them which is supported by available evidence. The seven day pill break was included in one of the studies, but unclear in the other, so the GDG do not wish to be prescriptive about whether this should be followed.

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Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	199	1	"a significant decrease in systolic and diastolic BP when comparing use of HRT with the COC at the end of 12 months treatment": suggest reword for clarity. Is this saying that the mean syst/diast BP was lower in the HRT group than in the COC group?	Thank you for your comment. The GDG agree with your interpretation and this statement has been amended for clarity.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	199	78	BMD (BMD): ?should be bone mineral density (BMD)	Thank you for your comment, this has been amended.
Royal College of Patholo	Full	199	7	1,25 hydroxylated Vitamin D3 should be 1,25 dihydroxy vitamin D3	Thank you for your comment, this has been amended.

gists					
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	199	27	"significantly" should be "significant"	Thank you for your comment, this has been amended.
British Menopause Society	full	199	31 45	Q2. RCT at KCL has shown that HRT is superior to COCP with regards to bone density (and symptoms) in women with POI. (submitted for publication. Presented at RCOG world congress of O and G , Brisbane, 2015)	Thank you for this comment. Unpublished evidence is an exclusion criteria of the systematic review. The GDG were aware of this data but understand that it is not yet published.
Royal College of Pathologists	Full	199	32	1,25 hydroxylated Vitamin D3 should be 1,25 dihydroxy vitamin D3	Thank you for your comment, this has been amended.
British Menopause Society	full	200	general	Included in the recommendations on the management of POI it would be helpful to see some clear guidance about the need for these women (under 40) to be referred to a specialist centre for expert advice and ongoing support/DEXA scanning etc.	Thank you for your comment. The GDG discussed the importance of holistic management of women with POI and added a new recommendation on referring women with POI to health professionals with relevant experience who can facilitate management of all

					aspects of physical and psychosocial health related to their condition.
Poole Hospital NHS Trust	full	200	general	Included in the recommendations on the management of POI it would be helpful to see some clear guidance about the need for these women (under 40) to be referred to a specialist centre for expert advice and ongoing support/DEXA scanning etc.	Thank you for your comment. The GDG discussed the importance of holistic management of women with POI and added a new recommendation on referring women with POI to health professionals with relevant experience who can facilitate management of all aspects of physical and psychosocial health related to their condition.
London North West Healthcare NHS Trust	Full	200	45	Strongly disagree COC may be preferred choice for POI in young women, for reasons given above. We have also moved away from COC as a recommended choice in the young, and encouraging LARC (long acting reversible contraception) so this will become an outdated recommendation	Thank you for this comment. The oral contraceptive pill is being offered as a form of hormone replacement for the treatment of symptoms arising from premature ovarian syndrome, rather than as a form of contraception.
British Menopause Society	Full	200	45	Strongly disagree COC may be preferred choice for POI in young women, for reasons given above. We have also moved away from COC as a recommended choice in the young, and encouraging LARC (long acting reversible contraception) so this will become an outdated recommendation	Thank you for this comment. The oral contraceptive pill is being offered as a form of hormone replacement for the treatment of symptoms arising from premature ovarian syndrome, rather than as a form of contraception.
Poole Hospital NHS Trust	full	200	45	COC should not be preferred choice for POI in young women. Evidence base is small, pill free interval not ideal and LARCs now increasingly recommended for longterm contraception in young women.	Thank you for your comment. The evidence review considered the oral contraceptive pill as a form for oestrogen-based hormone replacement for the treatment of premature ovarian syndrome symptoms rather than contraception. LARCs were not considered as part of the evidence review.
Clinical Effectiv	Fu	20	11.	Recommendations and research recommendations are clear and useful.	Thank you for this comment.

eness Unit of Faculty of Sexual & Reproductive Healthcare	l l	0 2 0 1	2. 9 1 1 1. 2. 1 0		
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	F u l l	2 0 0	2 5 2 8 3 5	"OCP": suggest COCP for clarity	Thank you for your comment. The GDG believe that the current terminology is accurate and have therefore no made the suggested change.
University College London Hospitals NHS	F u l l	2 0 0	3 2	Agree there is insufficient conclusive evidence in favour of COCP or HRT but risks of HRT are lower than those of COCP.	Thank you for this comment.

Foundation Trust					
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	Full	200	33	More effective for what? This is a key conclusion and will be the only bit that many clinicians will read, so needs to be clear	Thank you for your comment. This has been now amended for clarity.
The Daisy Network	FULL	200	36	Other recommendations for management and patient information – suggestions to help users overcome any challenges - Management of POI should be in Specialist multidisciplinary clinics (including Consultant gynaecologist, specialist nurse; specialist pharmacist; counsellor; nutritionist and GPs with a special interest, with close links to fertility and oncology/haematology services). - Regular follow up appointments should be undertaken as physiological, social and psychological needs may change significantly over time. - Targeted information aimed at young women with POI is required. Information given must be age-appropriate.	Thank you for your comment. The GDG discussed the importance of holistic management of women with POI and added a new recommendation on referring women with POI to health professionals with relevant experience who can facilitate management of all aspects of physical and psychosocial health related to their condition. The section on information and advice which outlines the information needs for menopausal women is relevant to women with POI.

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				- Information on & link to the Daisy Network www.daisynetwork.org.uk - as a source of information for both patients and health professionals	
King's College Hospital NHS Foundation Trust	Full	200	37	Consider transdermal oestradiol in women at risk of VTE (raised BMI / family hx of thrombosis etc). Consider hormone replacement close to physiological levels in this cohort of patients.	Thank you for your comment. This section refers to management of POI and the GDG concluded that there is very limited evidence for differences in any of the outcomes reported for the treatments of HRT and combined oral contraceptive pill, so both choices should be offered to women with POI by taking into account their preferences and needs. No subgroup analysis was available for data relating to women at risk of VTE therefore the group could not recommend a specific type of treatment for this group. The matching of HRT to physiological levels was not within the scope of the review question.
British Menopause Society	Full	200	37	Consider transdermal oestradiol in women at risk of VTE (raised BMI / family hx of thrombosis etc). Consider hormone replacement close to physiological levels in this cohort of patients.	Thank you for your comment. This section refers to management of POI and the GDG concluded that there is very limited evidence for differences in any of the outcomes reported for the treatments of HRT and combined oral contraceptive pill, so both choices should be offered to women with POI by taking into account their preferences and needs. No subgroup analysis was available for data relating to women at risk of VTE therefore the group could not recommend a specific type of treatment for this group. The matching of HRT to physiological levels was not within the scope of the review question.
British Menopause Society	Full	200	40	Women with POI may benefit from the addition of testosterone. Particularly if they continue to have symptoms of low moods tiredness or loss of libido despite oestrogen replacement.	Thank you for your comment. Testosterone replacement was considered elsewhere in the guideline (see section 8: managing short term symptoms). It was not prioritised for consideration

					specifically in this population of young women.
The Daisy Network	Full	200	60	Information for women with POI It is recommended that HRT should be continued until at least the average age of menopause; however, HRT discontinuation rates amongst women with POI are high, with approximately 7% choosing to stop HRT within 5 years [Maclaran, 2012]. Recent surveys have highlighted the misperceptions surrounding HRT use in women with POI, with 56–79% perceiving that HRT use was associated with breast cancer [Gibson-Helm, 2014]. In the section "Explain to women with POI" the guidance should contain a statement that there is no evidence suggesting an increased risk of breast cancer with HRT used up until the average age of menopause. We feel it is important to highlight both to patients and health professionals that findings from the Women's Health Initiative and Million Women Study regarding risk of breast cancer cannot necessarily be applied to women with POI using HRT. Maclaran K, Panay N. Presentation and management of POF: findings from the West London POF database. Presented at: 15th World Congress of Gynecological Endocrinology. Florence, Italy, 7–10 March 2012, Gibson-Helm M, Teede H, Vincent A. Symptoms, health behaviour and understanding of menopause therapy in women with premature menopause. Climacteric 17, 1–8 (2014).	Young women with ovarian insufficiency should be informed that it is not possible to extrapolate the evidence from studies of older women to this age group, because the incidence of cardiovascular disease, breast cancer and osteoporosis are so low in women under 40 years that it is not possible to study the impact of these therapies on them.
British Menopause Society	full	201	14	The importance of taking HRT should be emphasised (long term health data need citing). Too many women under 40 choose not to take HRT as they are concerned about the perceived risks. They need to be aware that the data that fuels the risks discussed elsewhere are not pertinent to their age group. I feel this needs specific mention under the recommendations in this section.	Thank you for your comment. The GDG has added another point in the recommendation that advises women with POI to start treatment with either HRT or combined oral contraceptive, highlighting how the baseline population risk with diseases such as breast cancer and CVD increase with age but is very low in

					women under the age of 40 years. In addition, more discussion has been added to the LETR section in the full guideline (Chapter 12.2) about how young women with POI should be informed that it is not possible to use the evidence from studies of older women to determine risk in their age group because the incidence of cardiovascular disease, breast cancer and osteoporosis are so low in women under 40 years. Further research is needed in this area to study the long term impact of different pharmacological treatments for POI, preferably through a national register that links to available cancer and mortality registers, as stated in the research recommendation 5 in the short guideline.
Poole Hospital NHS Trust	full	2014	1	The importance of taking HRT should be emphasised (long term health data need citing). Too many women under 40 choose not to take HRT as they are concerned about the perceived risks. They need to be aware that the data that fuels the risks discussed elsewhere are not pertinent to their age group. I feel this needs specific mention under the recommendations in this section.	Thank you for your comment. The GDG has added another point in the recommendation that advises women with POI to start treatment with either HRT or combined oral contraceptive, highlighting how the baseline population risk with diseases such as breast cancer and CVD increase with age but is very low in women under the age of 40 years. In addition, more discussion has been added to the LETR section in the full guideline (Chapter 12.2) about how young women with POI should be informed that it is not possible to use the evidence from studies of older women to determine risk in their age group because the incidence of cardiovascular disease, breast cancer and osteoporosis are so low in women under 40 years. Further research is needed in this area to study the long term impact of different pharmacological

					treatments for POI, preferably through a national register that links to available cancer and mortality registers.
King's College Hospital NHS Foundation Trust	Full	201	4	Could the guidance include suggested recommendations regarding bone density assessment (and repeat assessment) in women with POI? e.g. Consideration should be given to carrying out bone density assessment at presentation for women with POI especially those who present late or have additional risk factors for osteoporosis. A survey carried out on members of the BMS (Mittal et al. 2013) showed that DEXA scans were performed routinely for all new referrals with POI by 42.7% of clinicians, selectively by 31.5% but was not considered by 25.8%. A total of 16.4% indicated they would repeat DEXA every 1-3 years, 36.9% every 3-5 years while 36.9% would not routinely repeat it. It is appreciated that this wide variation in practice is largely due to the lack of good prospective evidence assessing the effect of HRT on bone mineral density and fracture reduction in this cohort of women. However, observational data (e.g. Popat et al. 2014; Svejme et al. 2013, Gallagher 2007) have demonstrated reduced bone density in women with POI (with all causes of POI) as referred to in the draft NICE guidance document and including such guidance in the document may help in guiding clinical practice in this context. The survey by Mittal et al. 2013 also showed wide variations in practice among clinicians with regards to carrying out karyotype assessment and auto-antibody screening in women with POI. Again it is appreciated that there are limitations in the evidence supporting	Thank you for your comment. However, this was outside of the scope of the guideline. A sentence has been added referring people to the NICE osteoporosis - assessing the risk of fragility fracture guidance.

				this, but including recommendations in the NICE guidelines regarding these areas would help guide practice in this area.	
British Menopause Society	Full	201	4	Could the guidance include suggested recommendations regarding bone density assessment (and repeat assessment) in women with POI? e.g. Consideration should be given to carrying out bone density assessment at presentation for women with POI especially those who present late or have additional risk factors for osteoporosis. A survey carried out on members of the BMS (Mittal et al. 2013) showed that DEXA scans were performed routinely for all new referrals with POI by 42.7% of clinicians, selectively by 31.5% but was not considered by 25.8%. A total of 16.4% indicated they would repeat DEXA every 1-3 years, 36.9% every 3-5 years while 36.9% would not routinely repeat it. It is appreciated that this wide variation in practice is largely due to the lack of good prospective evidence assessing the effect of HRT on bone mineral density and fracture reduction in this cohort of women. However, observational data (e.g. Popat et al. 2014; Svejme et al. 2013, Gallagher 2007) have demonstrated reduced bone density in women with POI (with all causes of POI) as referred to in the draft NICE guidance document and including such guidance in the document may help in guiding clinical practice in this context.	Thank you for your comment. However, this was outside of the scope of the guideline. A sentence has been added referring people to the NICE osteoporosis - assessing the risk of fragility fracture guidance.
Bayer PLC	Full	258	gener	Whilst the glossary of the full guideline does state *"Perimenopausal women who wish to avoid pregnancy are advised to use reliable contraception until 2 years have passed without a menstrual period if aged under 50, until 1 year if aged 50 or older, or until the age of 55 years (NICE publication*	Thank you for your comment. A recommendation has been added about information provision on contraception.

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			al	*cks.nice.org.uk/contraception-assessment)",* we suggest that this will be overlooked by many readers as it is not listed as part of a recommendation. This statement, or similar, should be included as part of recommendation 6 regarding the information that should be given to menopausal women	
Sheffield Teaching Hospitals NHS Foundation Trust	FULL	266	General	Typo change progrestogen to progestagen	Thank you for your comment, this has been amended.
British Menopause Society	full	271	general	BMS is British Menopause Society!	Thank you for your comment. The British Medical Society has been spelt out in full to avoid confusion.
Poole Hospital NHS Trust	full	271	general	BMS is British Menopause Society!	Thank you for your comment. The British Medical Society has been spelt out in full to avoid confusion.
Sheffield Teaching Hospitals NHS	FULL	271	general	Change secreting to releasing Include data on the effectiveness of acupuncture in the management of	Thank you for your comment, secreting has been changed to releasing. Acupuncture was included in the protocol for the management of short term symptoms. However, the data were subsequently excluded from the analysis – see Appendix K.2.4 for more details.

Foundation Trust				women with breast cancer???	
Royal College of Surgeons	General	General	General	No comments	Thank you for this comment.
NHS England	General	General	General	No comments	Thank you for this comment.
British Menopause Society	general	General	General	No differentiation between different progestogens on risks/benefits.	Thank you for your comment. The systematic review of data for risk of breast cancer associated with HRT did not differentiate by type of progesterone, as agreed by the GDG at the time of developing the protocol. In the absence of such data, the GDG are unable to make a statement about any potential differences between preparations.
British Menopause Society	gener	Gener	General	baseline DEXA scans? need - not addressed yes /no?	Thank you for your comment. The GDG did not evaluate evidence on the value of baseline DEXA scans as this was not prioritised for inclusion in the scope. However, the GDG did consider evidence on the risk of developing osteoporosis, as presented in

	al	al			Section 11.6 of the full guideline.
British Menopause Society	general	General	General	contraceptive issues not addressed or advised - or referred to FSRH	Thank you for your comment. The GDG agree with your comment and have subsequently addressed this oversight in the draft guidance. A recommendation has been added about information provision on contraception.
British Menopause Society	General	General	General	Education of primary care staff will be the most challenging aspect of altering practice. WHI and Million Women are firmly fixed in the minds of GPs as is the guidance from the CSM which came out following the initial publications from these studies. Many GPs still regard HRT as highly dangerous and actively discourage women from starting it. There will need to be a lot of publicity and education about the benefits of HRT and the importance of treatment for POI.	Thank you for your comment. This has been forwarded to the NICE implementation support team to inform their support activities for this guideline.
The Menopause Exchange	General	General	General	Having just looked at the guidelines again I do not have any comments except to say that with reference to information to women going through the menopause some suggestions for self-help lifestyle changes may be useful.	Thank you for your comment. The GDG did not review the evidence for self-help interventions, so are unable to make suggestions on this topic.
Sheffield Teaching Hospitals NHS	General	General	General	This short docyment is succinct, the text easy to understand however the recommendation to use the tables to inform women will be difficult in practise as these tables are complex.. This document does not include any advice on duration of use of HRT which is a common concern for patients and profesionals, could you address the	Thank you for your comment. The GDG considered duration of HRT use when considering the risk of developing VTE, cardiovascular disease, breast cancer, osteoporosis, type 2 diabetes, dementia and sarcopenia. The risks associated with long-term treatment should be considered in light of the woman's

Foundation Trust	I	I		MHRA advice?	underlying baseline population risk.
NCRI - Breast CSG Working Group on Symptom Management	GENERAL	GENERAL	GENERAL	For anxiety and depression – there are general clinical services for women with these symptoms (offering antidepressants and cognitive behaviour therapy). Women with breast cancer can be referred to these general services but for women with menopausal symptoms and psychological symptoms specialist services are often preferred, for example menopause clinics or cancer support services. Ideally counselling/psychology therapies (CBT) should be made available to women with menopausal symptoms (hot flushes, sleep problems and low mood) following breast cancer by counsellors/psychologists or trained CNSs within menopause or cancer support services.	Thank you for your comment. The evaluation of service provision was outside the scope of the guideline and the GDG recognise that local referral pathways may differ.
Department of Health	General	General	General	No comments	Thank you for your comments.
Royal College of Nursing	General	General	General	The Royal College of Nursing welcomes proposals to develop this guidance. The RCN invited members of the RCN Women's Health Forum to review and comment on the draft guidelines. The comments below are based on views from RCN members who care for women with menopausal conditions.	Thank you for your comments.
British	G	G	G		Thank you for your comment. The GDG acknowledge

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Psychological Society	general	general	general	Comments from Society on the draft guideline were highly consistent in the view that the document: (1) Appears to have a strong bias towards hormone replacement therapy (HRT) as the main and first line treatment for women during the menopause. (2) This bias is reflected in the focus on the frequency measure of symptoms only (rather than severity or problem-rating, interference) resulting in many substantial papers being rejected, and, (3) The lack of inclusion of any evidence for psychological treatments, such as cognitive behavioural therapy (CBT), for hot flushes and night sweats. There is good evidence from at least three randomised control trials (RCTs) that should be included in the guide so that women can make informed choices. Women tend to prefer non-medical options, particularly when they have undergone breast cancer treatments. (4) There was considerable concern and disappointment that the recommendations did not embrace a biopsychosocial perspective on the menopause, but promoted a biomedical model - which might be influenced by the composition of the core development group.	the concerns raised in this comment and have discussed these in light of the full range of stakeholder feedback. Specifically: (1) The recommendations do not specify the order that treatments should be offered, and note that non-hormonal treatments were included in the review on the management of short-term symptoms (see Appendix D.4) (2) Frequency was chosen as an outcome because it allowed inclusion of the most data. The group noted that 38 out of 400 studies were excluded from the analysis because they reported data in terms of intensity (see Appendix G). (3) The review protocol includes CBT as a comparator in the network meta-analysis. However, the form of the data did not allow for its inclusion in the analysis. Only data on the impact of reducing the frequency of flushing was included to permit the undertaking of the NMA. Publications looking at the impact or severity of hot flushes could not be included to allow the formulation of a NMA. (4) (5) The GDG included a clinical psychologist as an expert advisor. The composition of the GDG was available for comment at the time of scope development and advertisements were made in line with the NICE policy on guideline recruitment.

					(6)
British Psychological Society	General	General	General	<u>References:</u> Archer et al, *Climacteric* 2011, 14(5); 515-528 Avis et al (2015) 175(4);531-539 Ayers et al (2013) *Climacteric*, 16; 235-239 Ayers et al (2012), *Menopause,* 19(7); 749-759; *Duijts et al, J Clin Oncology 2012,* 30(33);4124-4133 Gentry-Maharaj et al (2015) *Menopause*, 2(4) Godlee, (2015) *BMJ*;350:h3176 Hunter and O'Dea (1997), *Soc. Sci. Med.* 1997, 45(10); 1541-1548 *Jama,* (2002); Writing Group for the Women's Health Initiative Investigators, 321-333 Mann et al (2012), *Lancet Oncol*, 13;309-318; Menon et al (2007), *Menopause*, 14(3);63-77 Mom et al (2006), *Crit Rev Oncol Hemat*, 57(10); 63-77 Shifren et al (2014) *Menopause*, 21; 1038-1062	Thank you for your comment, but we are unclear of the purpose of providing these references.

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Besins Healthcare	General	General	General	Question 1: Which areas will have the biggest impact on practice and be challenging to implement? We believe that guidelines that do not reflect the evidence base and are not precise with their recommendation are the most challenging to implement. As described above, we feel the evidence base has not fully been reflected in proposing a clear set of guidelines in the use of HRT treatments to manage the vasomotor symptoms of menopause. To offer prescribers and patients greater clarity, the recommendation based on the evidence base should support the use of transdermal preparations as preferred treatments for managing vasomotor symptoms, and in particular patients at risk of VTE. Explaining that women using transdermal preparations are no more likely to experience VTE compared to the general population is an important aspect of the patient consultation in order to allay historical concerns patient may have about treatments for the symptoms of menopause.	Thank you for your comment. The recommendations are based on the best available evidence, taking into account the need for patient preference. As such, the recommendation does not specify a preference for a particular type of preparation. This comment has been forwarded to the NICE implementation support team to inform their support activities for this guideline.
Besins Healthcare	General	General	General	Question 2: What would help users overcome any challenges? Leadership and clarity These guidelines present a significant opportunity to correct the negative perceptions a significant number of women and healthcare professional have about HRT treatments. Perceptions which have resulted in women having to suffer in silence and fear and healthcare professionals being unsure about which is the right course of actions for their patients. Leadership from NICE in proposing clear treatment recommendation in patients presenting with vasomotor symptoms is the first step to realising the opportunity to address the incorrectly held perceptions.	Thank you for your comment. This has been forwarded to the NICE implementation support team to inform their support activities for this guideline.

				Identification and treatment: Akin to the impact that QOF had on long-term conditions (https://www.diabetes.org.uk/Upload/Professionals/Publications/MedicineDigest-Spring.pdf), the identification and treatment of the symptoms of menopause should receive the same degree of attention from primary care health organisations. Similar tools and processes should be recommended to ensure broad implementation of the guidelines.	
Pfizer	General	General	General	Pfizer welcomes the opportunity to review and comment on the draft NICE Menopause Clinical Guideline (CG); we believe that clear guidance on how best to provide care to women for menopause is not currently available for health care professionals (HCPs) in the UK. However, Pfizer believes that in its current form the draft guideline is unlikely to adequately inform HCPs or women on how best to manage symptoms associated with menopause. Additional information should be provided to support HCPs understanding of menopause, the various hormone replacement therapies (HRT) available in the UK and the expected benefits and associated risks of treatment. In particular, Pfizer believe that there may be additional opportunity to provide guidance to HCPs and women on: • Treatment pathway Pfizer proposes that the Committee include Figure 1: Care pathway from the full guidance in the short guidance document • A summary of the types of hormone replacement therapy (HRT) available Pfizer proposes that the Committee include a table that clearly describes:	Thank you for your comment and suggestions for improvement. The guideline is not a comprehensive review of all aspects of treatments related to menopause. In relation to your suggestions: • The short guideline has a specific template and although the care algorithm cannot be included, an interactive online pathway will be developed by NICE to support the implementation of the guideline and this will be available at the time of publication. • The GDG has considered the evidence on benefits and risk of different types of HRT and the treatment options for women with uterus and women without uterus. The purpose of the guideline is to provide best practice advice on the care of menopausal women based on the areas prioritised in the scope. Looking at the differences between the two main types of progestogens used in HRT or looking at the differences between continuous combined

				1. The currently available forms of HRT for women: ▪ With a uterus - oestrogen plus progestogen, and tissue selective oestrogen complexes (TSEC). ▪ Without a uterus - oestrogen alone; and 2. The various HRT formulations available e.g., oral, transdermal and vaginal, etc. 3. The differences between the two main types of progestogens used in HRT, i.e., those most closely resembling progesterone (e.g., dydrogesterone, drospirenone and medroxyprogesterone acetate) and those derived from testosterone (e.g., norethisterone, norgestrel and levonorgestrel). 4. The expected benefits and associated risks for each form of HRT. 5. When it is most appropriate to prescribe continuous combined and continuous sequential HRT. • A summary of the various HRT products available in the UK To help HCPs Pfizer proposes that the Committee includes a table that clearly outlines for each HRT product: 1. The qualitative and quantitative composition 2. The available doses and regimen 3. The marketing authorisation 4. The intended benefits and associated risks • Guidance on managing side effects and tolerability issues associated with HRT 1. Pfizer suggest including guidance on how to best manage women who continue to experience menopausal symptoms or experience complications whilst using HRT; currently, the	and continuous sequential HRT were not areas prioritised in the scope therefore the GDG could not comment on these topics. • It is expected that treatments will be considered in light of product information available in the British National Formulary, where safety considerations are regularly updated. Medicine's quality composition, dosages and marketing information are not routinely included in the guidelines. • The GDG decided that a referral should be made to a healthcare professional with expertise in menopause for women who continue experiencing menopausal symptoms because of the complexity of the individual management under consideration. However they have made specific recommendations for women whose menopausal care has specific contraindications such women with a history or at risk of breast cancer. Women with progesterone intolerance were not prioritised as a group under consideration in the scope.

				recommendations simply advise that these women should be referred to a HCP with expertise in menopause. 2. Guidance would also be strengthened by including information on alternative HRTs that could be used if common or particular tolerability issues// arise (i.e. how to manage menopause in women with progesterone intolerance)	
Pfizer	General	General	General	Pfizer recommend correcting the terminology used to describe the combination of conjugated oestrogens and bazedoxifene (CE/BZA, 0.45mg/20mg). The Committee have used “bazedoxifene plus oestrogen”. Pfizer is concerned that this may lead to misinterpretation by those using the guideline, and therefore request that the Committee amend the terminology to reflect that used by the European Medicines Agency (EMA), namely “conjugated oestrogens with bazedoxifene”. Please follow this link to supporting information on the EMA website.	Thank you for your comment. This has been amended throughout the guideline.
Clinical Effectiveness Unit of Faculty of Sexual & Reproductive Healthcare	General	General	General	Overall, we felt this was a very helpful guidance document which provided clarity on many issues which have been controversial over the years. In particular the sections outlining follow up, greater safety with transdermal HRT and use of vaginal preparations are very welcome. The document emphasises the need for referral to a menopause specialist in many situations which is also welcomed but we are aware that many UK regions do not have such a service. It would be very helpful to acknowledge this lack of expertise in many regions and support the development of specialist services to support excellence in menopause care.	Thank you for your comment. The GDG acknowledge that the availability of services may currently vary because of differences in local commissioning, and care may be delivered by a range of trained healthcare professionals.
Mylan	G	3	2	Risks dependent upon type of HRT used e.g. oral dydrogesterone - selective	Thank you for your comment. This statement in the

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EPD (BGP Products Ltd)	general		62 27	receptor binding activity - no oestrogenic, androgenic or glucocorticoid side effects. HRT in general is associated with an increased risk of breast cancer that is dependent on the duration of taking HRT. However, large observational studies have not found a statistically significant increased risk of breast cancer with oestradiol-dydrogesterone preparations, unlike preparations containing noresthisterone and medroxyprogesterone. 1. Fournier A et al. Unequal risks for breast cancer associated with 9 different hormone replacement therapies: Results from the E3N cohort study, Breast Cancer 10 Research and Treatment, Breast Cancer Res Treat 2008;107:103–11 2. Schneider C et al. Risk of cardiovascular outcomes in users of estradiol/dydrogesterone or other HRT preparationsClimacteric 2009; 12: 514-524 3. Lyytinen H et al. Breast Cancer Risk in Postmenopausal Women Using Estradiol–Progestogen Therapy Obstet Gynecol 2009; 113:(1): 65-73 4. Lyytinen H et al. A case-control study on hormone therapy as a risk factor for breast cancer in Finland: intrauterine system carries a risk as wellInt J Cancer 126:483-489	introduction of the short guideline is based on conclusions made by the GDG following the examination of evidence. For more details about the systematic review of treatment for short term symptoms that was conducted, which considered HRT according to type, please refer to the protocols contained in Appendix D and the evidence presented in section 8 of the full guideline. Similarly, the evidence for the risk of developing breast cancer associated with HRT is presented in Section 11.5 of the full guideline.

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London North West Healthcare NHS Trust	General	145 123	General	We are saying that VTE risk with standard dose transdermal HRT is no higher than baseline. If so why do women at risk of VTE require a referral to haematology? This is confusing and rather contradictory. The full guideline p 123 suggests the progestogen type is also relevant. So the short guideline needs rephrasing?	Thank you for your comment. The evidence did not demonstrate an increased risk of VTE associated with transdermal HRT, but this could not be excluded. Therefore the GDG recommended that healthcare professionals involved in the care of menopausal woman should consider getting haematological advice for high-risk women. The evidence on the effect of progestogen type was unclear.
British Menopause Society	General	145 123	General	We are saying that VTE risk with standard dose transdermal HRT is no higher than baseline. If so why do women at risk of VTE require a referral to haematology? This is confusing and rather contradictory. The full guideline p 123 suggests the progestogen type is also relevant. So the short guideline needs rephrasing?	Thank you for your comment. The evidence did not demonstrate an increased risk of VTE associated with transdermal HRT, but this could not be excluded. Therefore the GDG recommended that healthcare professionals involved in the care of menopausal woman should consider getting haematological advice for high-risk women. The evidence on the effect of progestogen type was unclear.
Mylan EPD (BGP Products Ltd)	General	14	5	Mylan agree with the importance of highlighting that unscheduled vaginal bleeding may be common however Mylan also recommend the inclusion of the following statement “Low (1mg oestradiol , 0.3 CEE/ ultra low (0.5mg oestradiol) dose oestrogen and progestogen are also associated with less endometrial stimulation with high rates of amenorrhea” (1) 1. Gambacciani M, Genazzani AR. Hormone replacement therapy: the	Thank you for your comment. This publication is a review and therefore would not have met the inclusion criteria stated in the protocol (see Appendix D). The recommendation intends to make raise awareness of unscheduled bleeding rather than state the rates associated with various treatments.

				benefits in tailoring the regimen and dose. 195–201 An amenorrhoea rate of 91.4% and 88.2% for Femoston-conti 0.5/2.5 and Femoston 1/5 respectively was seen in the Stevenson et al. Maturitas 2010; 67: 227-232 paper	
Mylan EPD (BGP Products Ltd)	General	14	8	Advice is provided on generally reducing or stopping, however no advice is provided on how this should be done. Interpretation of this recommendation may vary, dosing on alternate days is an unlicensed use of the HRT treatment. Various strengths of oestrogen are available and guidance can be provided to titrate down to lowest effective dose.	Thank you for your comment. Please refer to section 10.8 of the full guideline where the methods used by the various studies are considered. The GDG did not find evidence that either method (gradually reducing or immediately stopping treatment) led to better patient outcomes and therefore recommend both are options.
Menopause UK	General	17	General	***Fig. 1 The Care Pathway*** This diagram has the potential to be the highest impact content of the guidelines. It is a resource to which practitioners are likely to refer to as a decision aid, perhaps without reference to the full guidelines. **Increasing the amount of information contained in the figure, so that it can stand alone as a reference resource** will be important in driving practice change. We suggest the following improvements to remove anomalies and improve user-friendliness: ▪ Recognizing that many health care professionals will hold wrong or outdated beliefs about menopause, and that they will be interpreting the Figure in the context of these beliefs, care should be taken to eradicate any statements	Thank you for your comment. The GDG carefully considered the care pathway in light of this feedback and made changes where this was believed to improve readability.

				that could be misinterpreted. For example, a GP who believes that the risks of HRT outweigh the benefits for the majority of women is likely to arrive at a 'no' decision after the prompt 'assess risk factors for treatment'. Likewise, the prompt 'suitable to continue treatment' is likely to be open to misinterpretation. ▪ Providing more information about diagnosis eg spelling out menopausal symptoms (we know that recognition in primary care is poor) and providing at a glance guidance on how to diagnose including appropriate tests. ▪ Providing more information in the form of process boxes to address the initiation of treatment (summary advice on what to expect, when to leave things, how long things typically take to settle, when to return and seek advice). ▪ Clarifying what constitutes 'treatment failure' – how long should a woman be left without adequate alleviation of symptoms before she is referred to a specialist? This is of particular concern for us given the number of women who contact us having been told, wrongly and for many years, that there is nothing that can be done for them. Skilled graphic design input will be valuable in ensuring that this high-impact Figure achieves its potential as a key element of the guidelines. We strongly suggest that this will be a worthwhile investment as part of the implementation and communication of the guidelines. Menopause UK	

				will be happy to provide further input and suggestions.	
NCRI - Breast CSG Working Group on Symptom Management	GENERAL	38	37	The use of frequency of VMS and exclusion of papers using severity/interference/bother as an outcome for VMS considerably limits the scope of the evidence presented. Consequently some non-medical approaches that have good evidence, such as CBT, relaxation are excluded. The NMA analysis can still use frequency but where relevant the severity/interference/bother measures should be included. Otherwise it appears as though the constraints of the NMA are influencing the evidence considered and consequently the conclusions drawn. The initial scoping document does state that the guide will address frequency and intensity/severity of VMS. As a breast cancer patient suffering from severe hot flushes (every 45min) from my own experience I know that some treatments - especially SSRIs decrease the intensity rather than the frequency of hot flushes. This is very important as the reduced intensity means that some times I can sleep through the flushes rather than being woken. It also allows me to cut down the dose of zopiclone I take. I think it is a mistake to exclude treatments that reduce severity rather than frequency	Thank you for your comment. The GDG discussed the prioritisation of outcomes at length, taking into consideration how each might be used to inform decision-making. It was accepted that while a measure of frequency is not reflective of all aspects of a woman's experience of VMS, it is commonly reported in a consistent manner, as opposed to intensity which can vary by assessment tool. Data on the efficacy of CBT were available for HF/NS from the study by Mann 2012, but this was subsequently excluded because the comparison could not be connected to the network. It should be noted that the outcomes presented in the scope are not considered final, and that a further prioritisation process occurs, based on the requirements of each review question. In summary, the GDG recognises the importance of ensuring that women have access to the range of treatment options that may be available in their area and have therefore highlighted them in information and advice section of the full guideline.
Menopause UK	Gene	104	36	***1.3.8: Altered sexual function/testosterone*** We welcome the inclusion in the guidelines of the beneficial effect that testosterone therapy can have for women. This is a poorly understood	Thank you for your comment. Apart from sexual function and low mood, the GDG did not include the additional outcomes mentioned in this comment so are unable to comment on testosterone's efficacy in these

	r a l			and recognized area. It would be helpful to include additional advice to prescribers to make clear that testosterone has wider therapeutic benefits than just libido. Other important (potential) indications for androgen therapy include e.g. profound fatigue, weakness, headaches, insufficient relief from urogenital symptoms with oestrogen alone. This is of particular importance in surgical menopause (where there is biological plausibility for androgen deficiency), especially POI. There is currently a great deal of misunderstanding in the general medical community when it comes to testosterone therapy and women report very negative and distressing encounters with practitioners on this topic.	wider areas. The GDG were asked to prioritise the most important women related outcomes in relation to menopause that would match the main areas of outcomes defined in the scope. Therefore, the GDG prioritised outcomes that are more specific to the hormonal changes during menopause such as frequency of vasomotor symptoms, low mood, anxiety and altered sexual function.
Menopause UK	G e n e r a l	1 1 5	G e n er al	***Referrals to specialist care*** We suggest the rewording of Recommendations 31 and 32 to be more explicit about the circumstances under which referral is appropriate. This should take into account the belief of many practitioners that 'nothing can be done' based on overestimations of the risks of HRT and false assumptions about contraindications for treatment. The insertion of a table (possibly at the end of the summary of recommendations ending at page 25 and cross refermced on page 115) summarising when to refer is likely to be helpful as an overview: **When to refer for specialist advice**	Thank you for your comment. This recommendation has been updated following stakeholder consultation and now suggests that referral should be considered if the woman has menopausal symptoms and contraindications to HRT or there is uncertainty about the most suitable treatment options for their menopausal symptoms. Defining the expertise and remit of a menopause specialist is defined by the professional societies in this field and defining this is beyond the scope of this guideline development. The GDG accept that this may currently differ according to local pathways and did not review service configuration as part of the guideline. This comment has been forwarded to the NICE implementation support team to inform their support activities for this guideline.

				Multiple treatment failure Abnormal bleeding Confirmed venous thromboembolism Osteoporosis (confirmed or high risk) Premature ovarian insufficiency (all cases of primary menopause or menopause below age 45) Previous or high-risk of hormone-dependent malignancy (suggest GDG consider clarifing 'high risk' e.g. not just one relative) *NB: A suitably qualified practitioner should be able to advise on effective therapy in the presence of all of the above conditions, and they should not be regarded as absolute contraindications for appropriate products* A general concern is the repeated recommendation to refer for specialist advice, when in practice menopause specialists are currently extremely scarce and difficult to identify. We believe that meeting the menopause-related needs of the majority of women should take place in primary care. However, we hear often from women who have failed to find appropriately knowledgeable help in primary and sometimes secondary care. And we hear also from women who describe the difference that specialist menopause care has made to them as literally life-changing. There is currently no definitive information about the location and	

				extent of menopause services. Menopause UK undertook a mapping exercise in 2014. This identified a total of 29 specialist NHS menopause clinics across the UK as whole, of which just 19 are in England. The map, and further information about how it was developed, can be viewed at http://menopauseuk.org/resources/map-of-menopause-services/ The ratio across the UK as a whole is approximately one specialist NHS clinic to every third of a million women of menopausal or post menopausal age. There seem to be large variations in provision: Scotland looks relatively well served with each of its nine specialist clinics serving less than 100,000 women. At the other end of the scale, we could only find two specialist NHS clinics in the North of England, a ratio of 1: 1,250,000 women of menopausal age. The mapping exercise did not look at the quality of care, or women's satisfaction with services, nor did it attempt to measure service volume. The map does not include menopause clinics in primary care, or the service provided by practitioners who are known locally by their colleagues to have a special interest in menopause. One of the reasons why local menopause clinics in primary and community care have proved hard to track down is that the majority aren't formally commissioned. Care might be provided locally in a number of different settings, by professionals from a variety of specialities (gynaecology, endocrinology, sexual and reproductive health), or not at all. We found no evidence of formal planning or deliberate co-ordination in local menopause services.	

				We suggest that the implementation of the guidelines will be greatly assisted by a commitment from local health services to: ▪ review local service provision for menopause ▪ identify lead clinicians and experienced practitioners ▪ clarify and communicate referral routes ▪ monitor levels of service demand and provision. Professional bodies such as the RCOG and representative organisations such as Menopause UK would be well placed to assist with this exercise, which will be key to the effective implementation of the guidelines. The establishment of a working group may be beneficial.	
Menopause UK	General	123	General	***Transdermal v. oral HRT*** Although this is in the VTE subsection, it may be useful to state elsewhere that transdermal HRT is the preferred route for women who suffer with migraine.	Thank you for your comment. The GDG did not consider evidence specifically for women who suffer with migraine and therefore are unable to make a recommendation for this patient group.
NCRI - Breast CSG Working Group on Sympto	GENERAL	177	15 19	It is positive that non-hormonal options are included for breast cancer patients who have VMS but this is only referred to in the Review and Refer section. Breast cancer patients could be offered the non-medical treatments mentioned e.g. relaxation, cognitive behaviour therapy (CBT), acupuncture, earlier in the process. More importantly the evidence for these treatments is not included at all in the appendices nor in the main document. The relevant studies need to be	Thank you for your comment. The systematic review of evidence for the treatment of short term symptoms included a number of non-medical treatments, such as cognitive behavioural therapy (see Appendix D.4). A discussion of the evidence is presented in section 9.2 of the full guideline. Exclusion criteria for studies for the analyses of vasomotor symptoms are reported in

m Management				included e.g. Elkins et al; Fenlon et al; Mann et al; Ayers et al; Duijts et al; Frisk et al; Lee et al; Walker et al and the evidence documented.	Appendices K.2.4 and K.3.1. Frisk et al. reported medians and ranges, which cannot be used for evidence synthesis. Lee et al. reported means without a measure of uncertainty (SD, SE or 95% CI). Walker et al. presented data in graphs only and therefore the data were not in a format we could obtain. Fenlon et al. is a cohort study and therefore is a lower level of evidence than we would include for this review. Elkins, Mann, Ayers and Duijts were excluded because the treatments were not connected to the network and so we were not able to obtain relative effects of these treatments compared to the others.
London North West Healthcare NHS Trust	NICE	General	general	pleased to note that they frequently suggest 'referral to a healthcare professional with expertise in menopause' but do not mention the role of a specialist menopause clinic anywhere. Who will decide what constitutes a 'specialist' and what competence must they demonstrate?	Thank you for this comment. The expertise and remit of a menopause specialist is defined by the professional societies in this field and defining this is beyond the scope of this guideline development. The GDG accept that this may currently differ according to local pathways.
British Menopause Society	NICE	General	general	Suggests women with high-risk of VTE should be referred for assessment to an haematologist but do not include a specialist menopause clinic that also currently offers this expertise. Haematology clinics could probably not cope with this influx of referrals and GPs may not want to fund it. This will result in difficulty in implementation.	Thank you for your comment. The GDG recommended that healthcare professionals involved in the care of menopausal woman should consider getting haematological advice for high-risk women, but accept that local referral pathways may vary.
Gransnet	NIC	Gen	Gen	Our members welcome a more individual approach to diagnosing and managing the menopause. Many of them commented on the lack of empathy and support they received during this difficult time and welcome guidelines	Thank you for your comment. The GDG agree that all care relating to the menopause should take account of each woman's individual circumstances and they

	E	e r a l	er al	that will help other women in the future. “As someone who suffered eight years of misery after being told by my GP to stop (oestrogen only) HRT after three years, I can only say that I wish that this guidance had been available then..” “The female doctor I went to in year 15 just said as a throwaway remark, Oh, bad luck. That is the only 'help' I have had so far from GPs.”	stress the importance of maintaining a respectful and empathetic approach. This should underpin all recommendations. In order to make this point more prominent, the GDG have added a recommendation at the beginning of the guideline, and refer the reader to the NICE guideline on Patient Experience.
Gransnet	NICE	General	General	Although there is a strong focus on the physical effects of menopause, our users felt the psychological effects deserved consideration too. “When I was being treated at the local hospital for post menopausal troubles (hot flushes etc.) one of the things I found most doctors, including my practice G.P.s, were completely unconcerned about, or even interested in, was the psychological effects. Yes - it was great not to have to worry about contraception, but I really went through a grieving process. I couldn't have a baby any more (not that I was desperate for one) but that process was 'dead' to me and it took me quite a while to come to terms with that.”	Thank you for your comment. The GDG agree that maintaining the psychological health of a women with menopause is essential and included psychological outcomes in all of the treatment protocols (see Appendix D). Where data were available, it was reported in the guideline.
Cornwall Menopause Referral Service	NICE	General	General	The overall tone of the document is clear and helpful	Thank you for this comment.
Cornwall Menopause Referral Service	NICE	Gen era	General	The recommendations are easy to follow	Thank you for this comment.

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Cornwall Menopause Referral Service	NICE	General	General	The risk tables do move the published evidence on but something more visual will be needed both when teaching and in counselling women	Thank you for your comment. This has been forwarded to the NICE implementation support team to inform their support activities for this guideline.
NCRI - Breast CSG Working Group on Symptom Management	NICE	general	general	We are very please that Breast Cancer patients have been highlighted in this document as a group requiring special attention. Reference is made throughout the document to breast cancer patients and we wonder whether a dedicated section for this patient group would be helpful. We strongly agree with the recommendations regarding further research for non-HRT alternatives for this patient group.	Thank you for your comment. The GDG considered the presentation of evidence particular to women with breast cancer, but decided not to dedicate a section to these women because there are essentially two issues under consideration (1. women who have/have had breast cancer and 2. whether HRT causes breast cancer) and these should not be combined from an evidence perspective.
Gransnet	NICE	General	General	A lack of consistency re the prescription of HRT seems to be a common theme. "I have begged (and I mean begged) various GP's within my practise for HRT, all of whom have refused. I guess that once the first one said no the rest just went along with his decision, yet none have been able (or willing) to give me a good reason for their refusal except that they have it on record, from me, that my mum was diagnosed with breast cancer aged 59. At 53 the menopause is ruining life and I am not exaggerating. I am permanently tired, irritable, suffering from hair loss, mood swings, re-occurring water infections, insomnia and horrendous hot flushes and night sweats. I would do anything to feel normal again."	Thank you for your comment. The GDG recommended that referral to a healthcare professional with expertise in menopause should be for women who had or at risk of breast cancer (section 11.5 of the full guideline).

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Gransnet	NICE	General	General	A number of women have reported relief from natural remedies – however some are more effective than others (and differ from person to person). Just one example: "[The menopause] was the most horrendous time in my life, night sweats and hot flushes most of the day and night, depression, crying, anxiety and panic attacks… I tried every herb under the sun, acupuncture, massage, reflexology, strict diet of natural oestrogen so like yams and vitamins with phytonutrients.....some things I tried did help....but the one thing that really made a difference eventually (and please be aware, that no natural remedy will ever get rid of all symptom completely) was black cohosh...however you need to take it for a min of two months to start to really notice the difference...Sage dried me up too much, Angus cactus made my nipples really sensitive and enlarged it was quite frightening how I reacted to this one...red clover didn't make much difference....but black cohosh, really really made the difference.."	Thank you for your comment. These treatments were included in the systematic review on the treatment of short term symptoms. The GDG recognise that menopause can be experienced differently by each woman and recommend that health professionals should adopt an individualised approach at all stages of diagnosis, investigation and management of menopause. In addition, the GDG recommend that health professionals should provide information to women and their family members on hormonal, non-hormonal and non-pharmacological treatments of menopause symptoms. In relation to Black Cohosh, the GDG recommend that health professional should make women aware that there is some evidence of its effectiveness to relieve the frequency of vasomotor symptoms compared to placebo but also explain concerns about this treatment such as the uncertainty associated with the multiple preparations and regulation of the industry. Please see the linking evidence to recommendation section of the full guideline for a discussion about their efficacy and associated cost-effectiveness (section 8.8).
Breast Cancer Now	NICE	General	General	We welcome the inclusion of breast cancer patients throughout this guideline. However, given breast cancer patients comprise a significant proportion of the people affected by this guideline, it may be appropriate to dedicate a section to this patient group to ensure that clinicians and patients are able to access this information in the guideline quickly and easily. We are also concerned that information regarding the treatment of breast cancer patients is often not obviously distinguishable from information	Thank you for your comment. The GDG considered the treatment for menopausal symptoms for women who had or are at risk of breast cancer as one group although recognising that there are different clinical considerations among them. However, in terms of contraindications to specific treatments for menopausal symptoms, both women who had or at risk of breast cancer are not eligible for hormonal

				intended for women who are at risk of breast cancer. These are two very separate patient groups and it is important that information for these groups remains separate and distinct to avoid any confusion for patients or clinicians.	treatment and this was the basis for our putting them together for the purposes of our network meta-analysis and decision making.There is a specific section in the short guideline referring to women who had or at risk of breast cancer..
London North West Healthcare NHS Trust	NICE	2	1 2	We consider that there should be a separate specific recommendation about information and support for the young women, whose needs are unique and very different to natural age menopause. Such information needs to be specific and targeted.	Thank you for your comment. The recommendations about giving information cover women in this age group, while issues specific to women with premature ovarian syndrome are discussed in section 12 of the full guideline.
British Menopause Society	NICE	3	2	A poor definition of menopause	Thank you for your comment. A full definition of menopause is given at the beginning of this document in section 1.
Gransnet	NICE	3	1 2	Members would like to see a requirement for GPs to consider HRT prescription alongside other medical conditions and to assess carefully the risks versus the benefits: “I have fibromyalgia and CFS, so lots of joint and muscle issues. When taking HRT my GP had recommended I continue as long as possible as in her experience on stopping joint and muscle pain was exacerbated. On changing surgeries my new GP disagreed so dramatically that he refused to continue to prescribe. I have been in more pain ever since. My suggestion is that, somewhere, in the guidance there is a requirement for GP's to consider HRT prescribing alongside existing medical conditions and to consider the risks alongside the benefits to chronic illness”	Thank you for your comment. The guideline did not specifically consider the impact of HRT in patients with comorbidities. However, it is recommended that women with symptoms and contraindications to HRT be considered for referral to a healthcare professional who is experienced in the management of menopause.
Sheffield Teachin	NIC	3	2 4	remove however	Thank you for your comment, this has been amended.

g Hospitals NHS Foundation Trust	E				
Gransnet	NICE	5	5	Patient centred-care. User feedback says “In my experience many GP's do not always allow patients to make informed decisions. This appears in all NICE guidelines now. It saddens me this is not a requirement, rather a 'should'.”	Thank you for your comment. NICE considers the patient experience to be of upmost importance and the text in this section is based on the rights outlined in the NHS constitution. The GDG refers the reader to the NICE guideline on Patient Experience which discusses shared decision-making in detail.
Gransnet	NICE	6	10 13	Positive feedback: “To be applauded - if GP's take notice.”	Thank you for this feedback.
Sheffield Teaching Hospitals NHS Foundation Trust	NICE	8	20	this line reads that the ovaries stop functioning st the menopause – this is a generalisation as there is still some testosterone production	Thank you for your comment, this has been amended.
London North West	NIC	91	Gen	Oestradiol levels can be useful in conjunction with FSH levels in women over 45 with atypical symptoms (see comment 1.1.5 p10) and also in conjunction with FSH levels in hypogonadotrohic disorders such as	Thank you for this comment. The GDG did not recommend diagnosing menopause using oestradiol or LH measurement in women over 45 because no

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Healthcare NHS Trust	E	0	eral	youngsters with eating disorders who are sometimes are referred to menopause clinics and require a POI diagnosis to be excluded. Is the guideline suggesting there is no place whatsoever for measuring oestradiol levels in menopause diagnosis? Also please mention that LH not indicated (as almost every GP who requests FSH also requests LH)	evidence was found to support this. This is discussed in the linking evidence to recommendation section of the full guideline (section 5.8).
British Menopause Society	NICE	910	General	Oestradiol levels can be useful in conjunction with FSH levels in women over 45 with atypical symptoms (see comment 1.1.5 p10). Is the guideline suggesting there is no place whatsoever for measuring oestradiol levels in menopause diagnosis? Also please mention that LH not indicated (as almost every GP who requests FSH also requests LH)	Thank you for your comment. The evidence from moderate to low quality single studies found that oestradiol was not useful for distinguishing perimenopausal women from premenopausal women (see section 5.7 of the full guideline), and therefore the GDG did not recommend it for use in women over 45 . The GDG did not find evidence for the usefulness of these tests in combination.
Sheffield Teaching Hospitals NHS Foundation Trust	NICE	9	4	? change urogenital atrophy to genitourinary syndrome as per NAMS and ISSWSH 2014	Thank you for your comment. This terminology was discussed at the time of scoping and it was agreed that urogenital atrophy would be used. This has been added to the full guideline and the glossary.
Gransnet	NICE	9	8	User feedback: “Vasomotor symptoms can be both severe and embarrassing. I would suggest that a note to the effect that these can be serious symptoms which can limit day-to-day activities unhelpfully would be appropriate. There remain too many jokes and jokers about these potentially debilitating symptoms.”	Thank you for your comment. A statement to this effect has been added to the full and short guidelines.
Sheffield	NI	9	9	replace dilation with dilatation	Thank you for your comment. This has been amended.

Teaching Hospitals NHS Foundation Trust	CE				
NCRI - Breast CSG Working Group on Symptom Management	NICE	9 2 1	1 9	We would agree that it is imperative to highlight the difficulty of confirming true “menopause” in breast cancer patients who have received chemotherapy and/or are receiving endocrine therapy & draw attentions to the paper by Smith et al - Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: caution & suggested guidelines, JCO, June 1 2006, vol. 24, no. 16. We would emphasise the inaccuracy of LH & FSH measurement on tamoxifen & the need to measure suprasensitive oestradiol levels if patients are receiving aromatase inhibitors if wishing to confirm adequate suppression.	Thank you for your comment. The GDG agree that diagnosis of menopause is difficult in these circumstances, and that the measurement of FSH/LH is confounded by hormonal medication. However, measurement of oestradiol to confirm suppression on aromatase inhibitors is outside the scope of this guideline.
London North West Healthcare NHS Trust	NICE	1 0	General	Fatigue and sleep disturbance which are major menopause symptoms is not mentioned (whereas low mood is)	Thank you for your comment. These outcomes were not prioritised for inclusion in the review as they often arise as the result of vasomotor symptoms such as night sweats (which was included in the review), see the protocols in Appendix D.
Bayer PLC	NICE	1 0	1 0	Please see comment 1 relating to the equivalent recommendation in the full clinical guideline. Suggested adaption to recommendation 1.2.1. 1.2.1. Give information to menopausal women and their family members or	Thank you for your comment. The recommendation 1.3.1 in the full guideline summarises all the issues covered in your comment. The issue of information on contraception is covered by a separate recommendation (1.3.5) and a discussion in the linking evidence to recommendation section of the guideline

				carers (as appropriate) that includes: • an explanation of the stages of menopause • common symptoms (see recommendation 8) and diagnosis • lifestyle changes and interventions that could help general health and wellbeing • the benefits and risks of treatments for menopausal symptoms. • the recommendations regarding effective contraception for women who wish to avoid pregnancy from nationally recognised guidelines such as those from the NICE accredited provider the Faculty of Sexual & Reproductive Healthcare, Clinical Guidance on Contraception for Women Aged Over 40 Years (July 2010).[4] (4) Faculty of Sexual & Reproductive Healthcare (FSRH) Clinical Effectiveness Unit. Clinical Guidance - Contraception for Women Aged Over 40 Years. July 2010. Available from: http://www.fsrh.org/pdfs/ContraceptionOver40July10.pdf. (Last accessed: 8/7/2015).	makes suggestions about the type of information that may be available. The GDG also amended the recommendation 1.3.5 to include the link to the clinical guidance by the Faculty of Sexual & Reproductive Healthcare on Contraception for Women Aged Over 40 Years.
Bayer PLC	NICE	11	12	Please see comment 4 relating to the equivalent recommendation in the full clinical guideline. Recommendation 1.3.2 *states "Offer hormone replacement therapy (HRT) for vasomotor symptoms after discussing the short-term (up to 5 years) and longer-term benefits and risks. Offer a choice of oral or transdermal preparations as follows:* • *oestrogen and progestogen to women with a uterus* • *oestrogen alone to women without a uterus."* It should be made clear that the Levonorgestrel-releasing intrauterine system (IUS) (containing 52mg levonogestrel, releasing 20 micrograms/24 hours) is	Thank you for your comment. The evidence for conjugated oestrogens and bazedoxifene was reviewed as a separate comparison in the NMA for women with a uterus. Based on the included studies, no evidence was found for a reduction in frequency of vasomotor symptoms over oestrogen plus progesterone and therefore the GDG could not make this recommendation.

				licensed for protection from endometrial hyperplasia during oestrogen replacement therapy for 4 years,[5] and therefore the choice for the progesterone component of HRT extends beyond oral or transdermal preparations. (5) Bayer plc. Mirena® 20 micrograms/24 hours intrauterine delivery system - Summary of Product Characteristics (SPC). 1 July 2015. Available from: http://www.medicines.org.uk/emc/medicine/1829. (Last accessed: 8/7/2015).	
Pfizer	NICE	11	13	In Section 1.3.2 the Committee state: *"Offer hormone replacement therapy (HRT) for vasomotor symptoms after discussing the short-term (up to 5 years) and longer-term benefits and risks. Offer a choice of oral or transdermal preparations as follows:* • *oestrogen and progestogen to women with a uterus* • *oestrogen alone to women without a uterus."* Pfizer believes that this recommendation is incomplete and only offers limited guidance to HCPs and women on the types of HRT available. Pfizer proposes that the Committee amends the current text to include TSECs for women with a uterus. Please note: currently the only TSEC licensed in the EU is conjugated oestrogens and bazedoxifene (CE/BZA, 0.45mg/20mg), which is authorised for the treatment of oestrogen deficiency symptoms in postmenopausal women with a uterus (with at least 12 months since the last menses) for whom treatment with progestin-containing therapy is not appropriate.	Thank you for your comment. The evidence for conjugated oestrogens and bazedoxifene was reviewed as a separate comparison in the NMA for women with a uterus. Based on the included studies, no evidence was found for a reduction in frequency of vasomotor symptoms over oestrogen plus progesterone and therefore the GDG could not make this recommendation.
Gransnet	NI	11	25	Our users' experiences prove that many women find menopause psychologically challenging with impact both wide and damaging and anxiety,	Thank you for your comment. The GDG recognise the importance of considering the psychological aspects

	CE			low self esteem, loss of confidence all common. Feedback: “it is important to include in the guidance that these symptoms may not be short lived - some women struggle with psychological issues for many years post menopause. Once confidence is lost and self-esteem lowered it can take many months or indeed years for it to be re-built. It can be particularly difficult for women with premature ovarian insuffience.”	of care and included psychological interventions in the relevant treatment protocols (see Appendix D.4). Specifically, recommendations on the treatment of anxiety and low mood have been made in section 1.4 of the short guideline. An overarching recommendation has been added to the guideline which directs readers to the NICE patient experience guideline which includes recommendations about getting to know the patient as an individual and tailoring healthcare services for each patient.
Gransnet	NICE	12	4	General agreement but also the suggestion that there is a place for medication with high anxiety – “this does not seem to be mentioned.”	Thank you for your comment. The review of treatments for short term symptoms included the outcome of anxiety (see Appendix D.4). However, it did not separate the evidence by level of anxiety. For more information about the management of anxiety please see the NICE guideline on Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults: Management in primary, secondary and community care (CG113).
British Menopause Society	NICE	12	7	Giving testosterone to postmenopausal women with intact ovaries rarely improves libido. Assessment of relationship/sexual function is important and psychosexual counselling may be required	Thank you for your comment. Data on sexual function suggested an improvement in satisfying sexual activity was associated with the use of testosterone in women with menopause, which is reflected in the recommendation. The GDG did not evaluate the efficacy of psychosexual counselling so are unable to comment on this intervention.
Gransnet	NICE	12	10	Comment from a member: “I have urogenital atrophy and found that section very clear and helpful. I particularly appreciate the clear non-judgemental language of the report. In my experience one of the hardest things to bear was the frequently	Thank you for this comment.

				expressed view that suggested that a positive attitude / brisk walk / alternative health remedy was all that was required."	
Royal College of Nursing	NICE	13	General	This guideline refers repeatedly in recommendations to refer to the women to "specialist." It is not clear who will classed as 'specialists'? Will it be special clinics, or nominated health professionals? What education will the person(s) need to be deemed a specialist? What competences will need to be demonstrated and how are they assessed? Our member consider that this will raise issues around funding for education. Menopause experts can be found in many disciplines – sexual health, nursing, primary care medicine, gynaecology, endocrinology etc. Our members are concerned that the role 'specialist' could be interpreted as 'doctor', when the specialist could well be a nurse.	Thank you for this comment. The expertise and remit of a menopause specialist is defined by the professional societies in this field and defining this is beyond the scope of this guideline development. The GDG accept that this may currently differ according to local pathways.
London North West Healthcare NHS Trust	NICE	13	1	states that there is no need to monitor the endometrium with topical estrogen but do not mention specifically that progestogens are not required. Why one recommendation but not the other when both are common misconceptions?	Thank you for your comment. The GDG considered evidence on the use of oestrogens for the treatment of urogenital atrophy, and used this evidence to inform the recommendation on the monitoring of the endometrium. As the group did not evaluate the use of progesterone they cannot make a comment or recommendation about its use.
British Menopause Society	NICE	13	1	This guideline refers repeatedly to a recommendation to refer to "specialist" Who will be the specialists? Will they be special clinics, or nominated health professionals? What education will you need to be deemed a specialist? What competences will need to be demonstrated and how are they assessed? This will raise issues around funding for education. Menopause experts can be found in many disciplines – sexual health, nursing, primary care medicine, gynaecology, endocrinology. It would seem reasonable that	Thank you for this comment. The expertise and remit of a menopause specialist should be defined by the professional societies in this field and defining this is beyond the scope of this guideline development.

				the British Menopause Society would provide guidance on the definition of a Menopause Specialist and develop appropriate training and education.	
Gransnet	NICE	13	328	Some members have had success with complementary therapies and would like to be given more information and access to these. The cost is given as a potential barrier to using them. "I tried acupuncture, and this has helped enormously. It's expensive though. Any other advice will be appreciated." Another commented: " I was on HRT for five years when my GP refused to give me anymore my symptoms quickly returned I consulted a homeopath who successfully treated the hot flushes and made a huge difference to my insomnia"	Thank you for your comment. The guideline included a systematic review of complimentary therapies (see the protocol in appendix D.4). Additionally, the health economic model undertaken for this guideline included a number of complimentary therapies. With the possible exception of St John's Wort in a population of women with breast cancer, the health economic analysis did not suggest that these therapies generated sufficient benefit to represent value for money for the NHS and hence were not recommended.
London North West Healthcare NHS Trust	NICE	13	8	Women with breast cancer - I don't understand why St Johns Wort is singled out as a recommendation for women who have had breast cancer when the evidence according to the guideline is "nil for VMS and moderate to low for mood and anxiety? "The interaction with Tamoxifen is important, but you could say the same for SSRIs and they are not singled out for a recommendation other than not to be used first line? The NICE guideline (guidance.nice.org.uk/cg80) on breast cancer suggests SSRIs as a treatment option so these guidelines conflict .	Thank you for your comment. In the network meta-analysis (NMA) for the group of women with a history/ or at risk of breast cancer, St John's Wort had the highest probability of being the best treatment to relieve vasomotor symptoms compared to all the other treatments included in the network (including SSRIs). However, the GDG recognised the limited data that fitted this NMA and cross-linked to the relevant recommendations in the NICE Guideline on early and locally advanced breast cancer and the NICE Guideline on familial breast cancer in which SSRIs is a treatment option for the relief of menopausal symptoms. In addition, the group discussed how women with a history or at high risk of breast cancer should be offered information about all the available

					treatment options for menopausal symptoms, and referred to a specialist with an interest in menopause for further advice. Lastly, the GDG consider that the potential interaction with SSRIs and tamoxifen is important to state. The GDG has discussed your concern about the conflicting information with the recommendation 1.13.12 in the NICE breast cancer guideline and the recommendation 1.4.26 has been amended to read ' Offer menopausal women with, or at high risk of, breast cancer: • information on all available treatment options • information that the SSRIs paroxetine and fluoxetine should not be offered to women with breast cancer who are taking tamoxifen • referral to a healthcare professional with expertise in menopause.'
British Menopause Society	NICE	13	8	Women with breast cancer - I don't understand why St Johns Wort is singled out as a recommendation for women who have had breast cancer when the evidence according to the guideline is "nil for VMS and moderate to low for mood and anxiety? "The interaction with Tamoxifen is important, but you could say the same for SSRIs and they are not singled out for a recommendation other than not to be used first line? The NICE guideline (guidance.nice.org.uk/cg80) on breast cancer suggests SSRIs as a treatment option so these guidelines conflict .	Thank you for your comment. In the network meta-analysis (NMA) for the group of women with a history/ or at risk of breast cancer, St John's Wort had the highest probability of being the best treatment to relieve vasomotor symptoms compared to all the other treatments included in the network (including SSRIs). However, the GDG recognised the limited data that fitted this NMA and cross-linked to the relevant recommendations in the NICE Guideline on early and locally advanced breast cancer and the NICE Guideline on familial breast cancer in which SSRIs is a treatment option for the relief of menopausal symptoms. In addition, the group discussed how

					women with a history or at high risk of breast cancer should be offered information about all the available treatment options for menopausal symptoms, and referred to a specialist with an interest in menopause for further advice. Lastly, the GDG considered that the potential interaction with SSRIs and tamoxifen is important to state. The GDG has discussed your concern about the conflicting information with the recommendation 1.13.12 in the NICE breast cancer guideline and the recommendation 1.4.26 has been amended to read ' Offer menopausal women with, or at high risk of, breast cancer: • information on all available treatment options • information that the SSRIs paroxetine and fluoxetine should not be offered to women with breast cancer who are taking tamoxifen • referral to a healthcare professional with expertise in menopause.'
Royal College of Nursing	NICE	13	8	*Women with breast cancer*: Our members consider that it is not clear why in the short NICE guideline, St John's Wort is singled out as a recommended complementary therapy for women who have breast cancer when the evidence according to the guideline is "nil for Vasomotor Symptoms and moderate to low for mood and anxiety"? The interaction with Tamoxifen is important, but one could also say the same for SSRIs which are not singled out for a recommendation other than the advice that it they are not to be used as first line treatment? The NICE guideline (guidance.nice.org.uk/cg80) on breast cancer suggests SSRIs as a treatment option so these guidelines seem to conflict.	Thank you for your comment. In the network meta-analysis (NMA) for the group of women with a history/ or at risk of breast cancer**,** St John's Wort had the highest probability of being the best treatment to relieve vasomotor symptoms compared to all the other treatments included in the network (including SSRIs). However, the GDG recognised the limited data that fitted this NMA and cross-linked to the relevant recommendations in the NICE Guideline on early and locally advanced breast cancer and the NICE Guideline on familial breast cancer in which SSRIs is a

					treatment option for the relief of menopausal symptoms. In addition, the group discussed how women with a history or at high risk of breast cancer should be offered information about all the available treatment options for menopausal symptoms, and referred to a specialist with an interest in menopause for further advice. Lastly, the GDG considered that the potential interaction with SSRIs and tamoxifen is important to state. The GDG has discussed your concern about the conflicting information with the recommendation 1.13.12 in the NICE breast cancer guideline and the recommendation 1.4.26 has been amended to read ' Offer menopausal women with, or at high risk of, breast cancer: • information on all available treatment options • information that the SSRIs paroxetine and fluoxetine should not be offered to women with breast cancer who are taking tamoxifen • referral to a healthcare professional with expertise in menopause.'
London North West Healthcare NHS Trust	NICE	13	15 16	The evidence for review at 3 months and thereafter annually is based purely on cost. But it is poorly considered, as if a patient may need a further review at 6 months, and may then be considered a case of" treatment ineffective " so then referred to a special clinic which will incur greater cost. Can there not be an option for more regular visits within the first year, which would also encourage compliance with treatment?	Thank you for this comment. No clinical evidence was found for this topic and it is difficult to suggest an optimal frequency. The GDG relied extensively on their clinical experience, expert opinion and existing guidance in order to make these recommendations. The GDG did not think that their recommendations would represent a change in the current practice and therefore would not result in additional resource implications for the NHS.

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Consultation on draft guideline - Stakeholder comments table

1 June 2015 – 13 July 2015

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British Menopause Society	NICE	13	15 16	The evidence for review at 3 months and thereafter annually is based purely on cost. But it is poorly considered, as if a patient may need a further review at 6 months, and may then be considered a case of" treatment ineffective " so then referred to a special clinic which will incur greater cost. Can there not be an option for more regular visits within the first year, which would also encourage compliance with treatment?	Thank you for this comment. No clinical evidence was found for this topic and it is difficult to suggest an optimal frequency. The GDG relied extensively on their clinical experience, expert opinion and existing guidance in order to make these recommendations. The GDG did not think that their recommendations would represent a change in the current practice and therefore would not result in additional resource implications for the NHS.
London North West Healthcare NHS Trust	NICE	13	22	They suggest considering non-pharmaceutical treatments and cite acupuncture but meta analysis that include RCTs with sham treatment do not demonstrate efficacy.	Thank you for your comment. The systematic review on the treatment of short term symptoms included acupuncture as a comparator in the network meta-analysis, but the GDG did not find outcome data in line with the protocol. Given the absence of such data, the GDG did not make a recommendation for treatment with acupuncture, but said that information should be given to women about the various treatments.
Pfizer	NICE	13	22	In Section 1.3.21 the Committee state: *"For women with menopausal symptoms and contraindications to HRT:* • *provide information on non-hormonal and non-pharmaceutical treatments (for example, CBT, hypnosis, acupuncture and relaxation techniques) for the relief of menopausal symptoms* • *consider referral to a healthcare professional with expertise in menopause."* Pfizer believes that this recommendation is incomplete. An example of a contraindication to HRT includes women being unsuitable to use a progestogen containing HRT; therefore, the Committee should include in its	Thank you for your comment. The evidence review on the treatment of short term symptoms, which included a network meta-analysis of treatment options, did consider conjugated oestrogens plus bazedoxifene as a comparator. The recommendations relating to the outcome of this analysis are presented in this section of the guideline.

				recommendation that conjugated oestrogens with bazedoxifene (CE/BZA. 0.45mg/20mg) is a licensed, evidence-based alternative for these women unlike some of the suggested non-hormonal and non-pharmaceutical treatments included above.	
Pfizer	NICE	14	5	In Section 1.3.23 the Committee state: *"Explain to women with a uterus that unscheduled vaginal bleeding is a common side effect of HRT within the first 3 months of treatment but should be reported at review appointments."* Pfizer believe that this recommendation could potentially mislead HCPs. We agree that vaginal bleeding can be considered a common side effect of HRT; however, the above statement suggests that the likelihood of a woman experiencing vaginal bleeding is similar for all HRT, which is inaccurate. Unlike oestrogen plus progestogen HRT, conjugated oestrogens with bazedoxifene (CE/BZA, 0.45mg/20mg) has a similar rate of bleeding/spotting and amenorrhea to placebo [Mirkin 2013, Pinkerton 2013]. Therefore, this should be reflected in the guidance. References Mirkin S, Komm BS, Pan K, Chines AA. Effects of bazedoxifene/conjugated estrogens on endometrial safety and bone in postmenopausal women. Climacteric. 2013. 16(3), p.338-46 Pinkerton JV, Harvey JA, Lindsay R, et al. Effects of bazedoxifene/conjugated estrogens on the endometrium and bone: a randomized trial. The Journal of clinical endocrinology and metabolism. 2014. 99(2), e.189-98	Thank you for your comment. This recommendation focuses on the need to report unscheduled bleeding as a side effect of HRT as a class, rather than explaining the risks and benefits of individual treatments. Therefore the GDG believe that the wording should remain as it currently stands.
NCRI - Breast CSG	NIC	14	15	Reference is made to the NICE 2009 guidance on early breast cancer & management of menopausal symptoms, which provides only very limited advice for clinicians. We would like to highlight the practical supportive	Thank you for your comment. Women with breast cancer were included as part of the guideline population, and recommendations were made where

Working Group on Symptom Management	E		23	information available to breast cancer patients from a number of charities e.g. Breast Cancer Care, Macmillan & CRUK, which many patients find helpful. If menopausal symptoms remain troublesome especially in the form of hot flushes, we would only then advise non-hormonal prescription medication, complimentary therapy strategies, menopause clinic referral or any combination of these options after discussion with the patient. We would emphasise caution regarding the use of HRT. We are in the process of developing a "clinician quick guide" for health care professionals treating breast cancer patients. We are aware that there is geographical variation across the UK regarding access to menopausal clinics or complimentary therapies.	evidence was available. A discussion of the risks and benefits of treatments is provided in the linking evidence to recommendation section of the full guideline. This comment has been forwarded to the NICE implementation support team to inform their support activities for this guideline.
Breast Cancer Now	NICE	14	15	It may be helpful to signpost patients and clinicians to information provided by patient groups as well as that provided by NICE. Breast Cancer Now's Best Treatment Guidelines provide information about breast cancer treatment and side effects that may be helpful to patients and clinicians. This is available at breastcancernow.org. Breast Cancer Care, Macmillan Cancer Care and Cancer Research UK also provide information that patients and clinicians may find useful.	Thank you for your comment. This has been forwarded to the NICE implementation support team to inform their support activities for this guideline.
Gransnet	NICE	14	16	Information on the risks of breast (and other types of) cancer need to be clearer and more consistent in the NHS. "I find it interesting that it is stated so clearly above that oestrogen only HRT is associated with little or no increase in the risk of breast cancer. My (very good) GP still tells me I am at risk and would prefer me to come off it. I am on the lowest dose oestrogen only patch and this keeps me almost sane and hot flush free." "However, how do these recommendations fit with findings that HRT increases uterine cancer risk?"	Thank you for your comment. Information about the risk of developing breast cancer associated with HRT use is presented in section 11.5 of the full guideline. The NICE implementation team will support the dissemination of this information throughout the NHS. The recommendations of this guideline fit with the well-established findings that for women with a uterus, the combination of oestrogen plus progestogen is the most appropriate type of

					hormonal treatment because progestogen is needed in women with a uterus to prevent the proliferation of the endometrium which could cause endometrial cancer if not controlled. This consideration fitted the design of the network meta-analysis (NMA) and the interpretation of results.
Mylan EPD (BGP Products Ltd)	NICE	14	16	In vitro results indicate that not all progestogens act equally on breast cancer cells. Some progestogens (medroxyprogesterone acetate (MPA), norethisterone acetate (NETA) and dienogest) alone or combined with estradiol (E2) stimulate proliferation of breast cancer cells, while others (dihydrodydrogesterone (DHD), the active metabolite of dydrogesterone, tibolone and progesterone (Prog)) alone or combined with estradiol induce apoptosis These results must be interpreted with caution and further investigations are required but it suggests a possible underlying explanation for the breast cancer incidence rates in the French and Finnish studies 1. Franke H.R. & Vermes I. Differential effects of progestogens on breast cancer cell lines Maturitas 2003; 46S1: S55-S58	Thank you for your comment. The systematic review of data for risk of breast cancer associated with HRT did not differentiate by type of HRT preparation (for example, progestogen), as agreed by the GDG at the time of developing the protocol. In the absence of such data, the GDG are unable to make a statement about any potential differences between preparations.
Mylan EPD (BGP Products Ltd)	NICEFul	14139911	21124444	Mylan agree that it is key that information on all available treatment options should be provided, this should also include differences between HRT preparations particularly progestogen risks	Thank you for your comment. The systematic review of data for risk of breast cancer associated with HRT did not differentiate by type of HRT preparation (for example, progesterone), as agreed by the GDG at the time of developing the protocol. In the absence of such data, the GDG are unable to make a statement about any potential differences.

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Mylan EPD (BGP Products Ltd)	NICEFullIFullI	1520241127	1639403539411	Mylan would like to highlight that the risk of VTE is not only associated with mode of delivery but also oestrogen dose and type of progestogen used. Low dose oestrogen is associated with a lower risk of VTE whilst micronized progestogen and pregnane derivatives such as Dydrogesterone appear to have an acceptable thrombotic risk profile. Oestrogen Dose A population based nested case-control study examined the risk of stroke in HRT. (Renoux C et al. BMJ 2010;340:c2519) The study involved about 400 general practices in the UK contributing to the General Practice Research Database. Data were analyzed from all women (regardless of whether they were on HRT) in the database aged 50–79 years between 1 January 1987 and 31 October 2006. Overall, there were 15,710 cases of stroke matched to 59,958 controls. The rate of stroke in the cohort was 2.85 per 1000 per year. Overall, the risk of stroke was increased with transdermal HRT compared with no use (adjusted rate ratio 0.95, 95% CI 0.75 to 1.20). However, when analyzed according to dose, the risk of stroke was not increased with low oestrogen dose patches vs. no use (adjusted rate ratio 0.81, 95% CI 0.62 to 1.05).	Thank you for your comment. The evidence review did not evaluate data on the dose of various preparations, so are the GDG are unable to comment. The review did, however, aim to consider the differences between progesterones, although data were mixed and firm conclusions could not be reached. The study mentioned here does not meet the protocol for inclusion in the review.

				High dose patches (>50ug) were associated with a higher risk (adjusted rate ratio 1.89, 95% CL 1.15 to 3.11). Low dose oestrogen 1mg oestradiol/0.3 CEE (adjusted rate ratio 1.25, 95% CI 1.12 to 1.40) 0.5mg oestradiol preparation was not available at time of study. High dose patches increase risk therefore route alone is not the determining factor Type of Progestogen ESTHER multicentre case-control study(1) looked at the impact of route of oestrogen administration and progestogen on the risk of venous thromboembolism (VTE) among postmenopausal women (aged 45–70 years) receiving HRT. The study included 271 consecutive cases with a first documented episode of idiopathic VTE and 610 controls matched for center, age, and admission date. Overall, users of oral oestrogen had an approximately 4-fold increased risk of VTE compared with non-users. This increased risk was not seen with transdermal estrogen (adjusted OR 0.9, 95% CI 0.4 to 2.1). There was no significant association of VTE with micronized progesterone or pregnane derivatives (which included dydrogesterone, medrogestone, chlormadinone acetate, cyproterone acetate, and MPA). Norpregnane derivatives (either nomegestrol acetate or promegestone) were also associated with an approximately 4-fold increased risk of VTE vs. no use. The results suggest that norpregnane derivatives may be thrombogenic, whereas micronized progesterone and pregnane derivatives (e.g. Dydrogesterone) appear to have an acceptable thrombotic risk profile.	

				A nested case control study of an analysis of the UK General Practice Database provided results consistent with the ESTHER study. Regarding venous thromboembolism, as compared to non-users of HRT, the adjusted relative risk estimates (odds ratios) for oestradiol/dydrogesterone users or users of other HRT were 0.84 (95% CI 0.37–1.92) and 1.42 (95% CI 1.10–1.82) respectively. Oestrogen +dydrogesterone was not associated with a statistically significant increased risk of VTE. 1. Canonico M. Hormone Therapy and Venous Thromboembolism Among Postmenopausal WomenCirculation 2007;115:840–5 2. Schneider C. et al. Risk of cardiovascular outcomes in users of estradiol/dydrogesterone or other HRT preparations Climacteric 2009; 12: 445-453	
London North West Healthcare NHS Trust	NICE	15	8	they suggest women with high-risk of VTE should be referred for assessment to an haematologist but do not include a specialist menopause clinic that also currently offers this expertise	Thank you for your comment. The GDG recommended the type of care that is needed, rather than where it might be available given that there may be differences in local commissioning.
Royal College of Nursing	NICE	15	8	The guidelines recommend that *women with high-risk of venous thromboembolsm (VTE) should be referred for assessment to a haematologist* but do not include referral to a specialist menopause clinic that also currently offers this expertise. Our members are concerned that haematology clinics could not cope with this influx of referrals and GPs may not want to fund it. Perhaps the recommendation should be re-worded to also allow referral to specialist menopause clinics (where available).	Thank you for your comment. The GDG recommended the type of care that is needed, rather than where it might be available given that there may be differences in local commissioning.

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Mylan EPD (BGP Products Ltd)	NICE	15	26	Differentiation between progestogens – Different progestogen have a different effect on the CV parameters and Lipid parameters Cieraad et al.(1) performed a clinical study comparing the effects of sequential hormone replacement therapy with oestradiol/dydrogesterone and conjugated equine oestrogen/norgestrel on lipids and symptoms. This double-blind study was conducted in 193 peri- and post-menopausal women randomised to receive six, 28-day cycles of oral sequential oestradiol 1 mg/dydrogesterone 10 mg or CEE 0.625 mg/norgestrel 0.15 mg. The authors concluded that oestradiol/dydrogesterone and CEE/norgestrel were equally effective in treating climacteric symptoms, but oestradiol/dydrogesterone showed some advantages in terms of lipid profile and incidence of bleeding. 1. Cieraad,D et al. Clinical study comparing the effects of 39 sequential hormone replacement therapy with oestradiol/dydrogesterone and conjugated 40 equine oestrogen/norgestrel on lipids and symptoms, Archives of Gynecology and 41 Obstetrics, 274, 74-80, 2006	Thank you for your comment. The GDG discussed this at the time of protocol development and subsequently agreed to review the evidence as a class. However, they acknowledge that there may be differences in efficacy according to the preparations but that making recommendations relating to this was not evaluated by the review.
London North West Healthcare NHS Trust	NICE	16	General	What constitutes low dose vaginal oestrogen? Is it 10 mcg twice weekly Vagifem or 50 mcg per week? Is the suggestion to consider increasing the dose a recommendation to exceed the recommended maximum dose (ie we sometimes target specific areas with ovestin as well as background Vagifem)	Thank you for your comment. The GDG considered this comment and agreed that the term "low-dose" was not universally agreed and often defined by the manufacturer. Therefore, this term has been removed from the recommendation. A preparation that is designed to treat local as opposed to systemic symptoms should be used.
Sheffield Teaching	NICE	17	2	clarify route of E2	Thank you for your comment. The route of administration was not always specified in the studies and the recommendation reflects this fact.

Hospitals NHS Foundation Trust					
Pfizer	NICE	18	1	In Section 1.4.9 the Committee state: *"Ensure that women with type 2 diabetes and all healthcare professionals involved in their care are aware that HRT is not associated with an adverse effect on blood glucose control."* Pfizer is concerned that this statement is inconsistent with the warnings and precautions section of the summary of product characteristics (SmPCs) of some HRT products, which include references to possible deterioration of diabetes control during treatment. For example, the SmPC for Premarin 1.25mg includes a statement that "A worsening of glucose tolerance may occur in patients taking estrogens and therefore diabetic patients should be carefully observed while receiving hormone replacement therapy"; therefore, the statement in Section 1.4.9 of the draft guideline is inaccurate.	Thank you for your comment. This recommendation was based on the best available evidence and GDG consensus and it has been amended in light of stakeholder consultation. However, they recognise that the evidence base on this topic had flaws and the generalisation of results should be interpreted with caution. The guideline assumes that prescribers will use a medicine's summary of product characteristics to inform decisions made with individual patients.
Gransnet	NICE	18	101 13	User observations that these two lines seem to be contradictory. Perhaps re-wording is needed?	Thank you for your comment. The first statement on mortality from breast cancer is now deleted after reconsidering the evidence included in this review.
Mylan EPD (BGP Products Ltd)	NICEFul	18 22 24 1	17 18 13 2	Although it is agreed that oestrogen and progestogen in combination can be associated with an increased risk of breast cancer it is important to highlight that there are different classes of progestogens available (see table in comment 1). Large epidemiological studies have shown that micronized progesterone or dydrogesterone used with oestradiol may be associated with a better risk profile for breast cancer than synthetic progestogens.	Thank you for your comment. The systematic review of data for risk of breast cancer associated with HRT did not differentiate by type of progesterone, as agreed by the GDG at the time of developing the protocol. In the absence of such data, the GDG are unable to make a statement about any perceived differences between the preparations. However, the

	Full	60	13 13 2 1 4 2 2	In the French E3N cohort study(1), 2,354 cases of invasive breast cancer occurred among 80,377 postmenopausal women during 8.1 years of follow-up. 1. Fournier A et al. Unequal risks for breast cancer associated with 9 different hormone replacement therapies: Results from the E3N cohort study, Breast Cancer 10 Research and Treatment, Breast Cancer Res Treat 2008;107:103–11 Compared with HRT never-use, use of E alone was associated with a significant 1.29-fold increased risk of breast cancer (95% CI 1.02–1.65). The risk for all breast cancers associated with combined HRT varied according to progestogen type 1.00 (0.83–1.22) for Oestrogen/progesterone 1.16 (0.94–1.43) for Oestrogen /Dydrogesterone 1.69 (1.50–1.91) for Oestrogen /other progestogens Overall 77.6% were ductal breast cancers vs. 22.3 lobular breast cancers The authors concluded that the findings suggest that choice of progestogen component for HRT may be an important factor regarding breast cancer risk. A registry study from Finland (2) also reported no increase in risk with dydrogesterone after at least 5 years of use compared to synthetic progestogens which were associated with a small increase in risk This study included all Finnish women aged >50 years using combined HRT for ≥6 months during 1994–2005 (n=221,551) identified from the national medical reimbursement registry and followed up for breast cancer diagnosis (n=6,211 cases) through the Finnish Cancer Registry.	GDG have added a paragraph to the linking evidence to recommendation section of the guideline (Section 11.5.8.5) that acknowledges that there may be different risks of developing breast cancer associated with different progestogens that they have not reviewed. Further research has been recommended (Section 1.4 of the short guideline) into the risk of developing breast cancer associated with different treatments, which could include a detailed review of the evidence for different types of progestogens.

				After 5 years of use, E/D was not associated with a significant increase in risk of breast cancer vs. no HRT (incidence ratio 1.13, 95% CI 0.49 to 2.22). The use of other combinations was associated with increased risk vs. no HRT: Oestrogen / Medroxyprogesterone, 1.64 (95% CI 1.49 to 1.79) Oestrogen /NETA, 2.03 (95% CI 1.88 to 2.18) Oestrogen /other progestogens, 2.07 (95% CI, 1.76-2.04) Overall, HRT products containing norethisterone (NETA) were associated with higher elevations in the risk for breast cancer than products containing MPA or D. In line with the results of the French E3N study, these results suggest that elevated breast cancer risk may not be the same for all progestogens. 2.Lyytinen H et al. Obst Gyn Breast Cancer Risk in Postmenopausal Women Using Estradiol–Progestogen Therapy 2009;113:65–73	
Cornwall Menopause Referral Service	NICE	22	General	The menopause clinic In Cornwall is to be decommissioned by the CCG to save money (communication 24th June) – we are going to struggle to implement the expert advice elements of the guideline – could a more robust recommendation about having an expert or specialist service be included	Thank you for your comment. The recommendations include referral to a healthcare professional with expertise in menopause, recognising that the person most suited to delivering the care may vary depending on regional pathways. The guideline did not evaluate evidence on service delivery and therefore cannot make a recommendation on service provision.
Cornwall Menopause	NICE	22	Gener	We think that stating the risks clearly will be useful for counselling and to allow fears but dissemination of this information to both women and their HCPs will be a challenge	Thank you for your comment. This has been forwarded to the NICE implementation support team to inform their support activities for this guideline.

Referral Service			al		
London North West Healthcare NHS Trust	NICE	22	13	We have no NHS facility for AMH testing. Question 2 . we have an arrangement with a local private laboratory which undertakes testing on our patients for a very low fee,	Thank you for your comment. This has been forwarded to the NICE implementation support team to inform their support activities for this guideline.
London North West Healthcare NHS Trust	NICE	22	158	In this section there should be mention of ongoing support not just annual treatment review. Such support shdoul include psychological support as the psycho-social needs of the women with POI will alter as she gets older.	Thank you for your comment. The GDG recognises the importance of including psychological support to women with premature ovarian syndrome and have made this explicit by adding it to a recommendation.
British Menopause Society	NICE	22	13	We have no NHS facility for AMH testing. Question 2 . we have an arrangement with a local private laboratory which undertakes testing on our patients for a very low fee,	Thank you for your comment. This has been forwarded to the NICE implementation support team to inform their support activities for this guideline.
British Menopause Society	NICE	22	13	There is no currently NHS provision for AMH testing within most areas of the NHS.This recommendation cannot currently easily be implemented	Thank you for your comment. This has been forwarded to the NICE implementation support team to inform their support activities for this guideline.
Royal College of Nursing	NICE	22	13	Our members have reported that there is currently no NHS provision for Anti-Müllerian Hormone (AMH) testing. This might present difficulties in the implementation of this recommendation.	Thank you for your comment. This has been forwarded to the NICE implementation support team to inform their support activities for this guideline.
London	N	2	G	Include here that research also needed into effects of HRT on patients with	Thank you for your comment. The guideline did not

North West Healthcare NHS Trust	ICE	3	general	other hormone dependent cancers, in particular endometrial cancer. There are one or two studies, showing no increased risk of recurrence in 1A endometrial cancers but gynae oncologists will always recommend their patients avoid HRT. (We have seen fairly young patients , below 50 , with these problems) There is no reference to HRT use and ovarian cancer risk ., but there have been meta analyses this year .	search for evidence relating to endometrial and ovarian cancer risk and therefore cannot make a research recommendation as they are unaware of what is currently available.
London North West Healthcare NHS Trust	NICE	23	General	Research and consensus needed into use of local oestrogen in patients on aromatase inhibitors. Oncologist views vary.	Thank you for your comment. The GDG believe that this is already covered by research recommendation number 3.1 in the short guideline.
British Menopause Society	NICE	23	General	Include here that research also needed into effects of HRT on patients with other hormone dependent cancers, in particular endometrial cancer. There are one or two studies, showing no increased risk of recurrence in 1A endometrial cancers but gynae oncologists often recommend their patients avoid HRT. There is no reference to HRT use and ovarian cancer risk ., but there have been meta analyses this year .Understand that this was not in the scope and so not addressed.	Thank you for your comment. The guideline did not search for evidence relating to endometrial and ovarian cancer risk and therefore cannot make a research recommendation as they are unaware of what is currently available.
Royal College of Nursing	NICE	23	General	Our members consider that research and consensus is needed into the use of local oestrogen in patients on aromatase inhibitors. Oncologist views vary. Current practice is mixed and this guideline does not clarify the issue.	Thank you for your comment. The GDG believe that this is already covered by research recommendation number 3.1 in the short guideline.
Gransnet	NI	23	16	Support for this. One user says “I applaud this, three friends with breast cancer have suffered appalling menopausal symptoms with no suggestion	Thank you for this comment.

	CE			from their respective GP's that they can alleviate these symptoms in any way."	
Mylan EPD (BGP Products Ltd)	NICE	23	23 25282829	Although Mylan welcome further studies in order to assess efficacy and safety of treatments in women who have had treatment for, or are at risk of, breast cancer Mylan would like to highlight that the findings from the Lyytinen H et al. Obst Gyn 2009;113:65–73 described above was not included in this guideline.	Thank you for your comment. This study was considered for inclusion in the systematic review about the risk of developing breast cancer associated with HRT. However, it was excluded because the population included women aged greater than 65 years. Please refer to the excluded studies list in Appendix G for details.
Breast Cancer Now	NICE	116	38 40	While we are pleased to see this guideline highlight the importance of the NHS Breast Screening Programme, there is a lot of public debate about the benefits of breast screening. Therefore, it is important that all women are provided with sufficient information about the benefits and risks of breast screening to make an informed choice about whether or not to attend. Breast Cancer Now's interactive guide to breast screening provides women with information about the benefits and risks of breast screening to allow women to make an informed choice. This is available at breastscreeningfacts.org.	Thank you for your comment. While the guideline stresses the importance of keeping up with breast screening, the provision of specific information about the benefits and risks is beyond the scope.
UK Clinical Pharmacy Association	Other	General	General	Is there any evidence base for the use of Angeliq HRT in postmenopausal group of women with hypertension? Angeliq contains Drospirenone as the progestogen component and mediates its pharmacological action via the aldosterone antagonist pathway. Data from preliminary work undertaken by Prof P Collins at Royal Bromptom indicated that this product may be of use in PM hypertension? The NICE guidance considers CVD / CHD and so this is an important consideration.	Thank you for your comment. The systematic review of data for treatment of short term symptoms did not differentiate by type of progestogen and their individual risk/benefit profiles, as agreed by the GDG at the time of developing the protocol. In the absence of such data, the GDG are unable to make a statement about any perceived differences between preparations.
UK	O	G	G	Work presented at the NOS conference in 2014 by Prof David Reid on the	Thank you for this comment. While the GDG are

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Clinical Pharmacy Association	ther	general	general	evaluation of an osteoporosis screening service in Scotland provided data for use of HRT as a cost effective treatment option for osteoporosis and fragility fracture risk reduction. If the final dataset has been published, then these may be helpful for the guidelines group to consider.	aware of this data, they understand that it is not yet published and as such it is not eligible for inclusion criteria in the review.
British Menopause Society	Short	4	5	You state 5 years here but the recommendations are not universally restricted to 5 years. I think you could shorten this to 'HRT Use' only.	Thank you for your comment. This has been amended as suggested.
British Menopause Society	Short	10	General	Fatigue and sleep disturbance which are major menopause symptoms is not mentioned (whereas low mood is)	Thank you for your comment. These outcomes were not prioritised for inclusion in the review as they often arise as the result of vasomotor symptoms such as night sweats (which was included in the review), see the protocols in Appendix D.
British Menopause Society	Short	16	General	What constitutes low dose vaginal oestrogen? Is it 10 mcg twice weekly Vagifem or 50 mcg per week? Is the suggestion to consider increasing the dose a recommendation to exceed the recommended maximum dose (ie we sometimes target specific areas with ovestin as well as background Vagifem)	Thank you for your comment. The GDG considered this comment and agreed that the term "low-dose" was not universally agreed and often defined by the manufacturer. Therefore, this term has been removed from the recommendation. A preparation that is designed to treat local as opposed to systemic symptoms should be used.
British Menopause Society	Short	23	General	Research and consensus needed into use of local oestrogen in patients on aromatase inhibitors. Oncologist views vary.	Thank you for your comment. The GDG believe that this is already covered by research recommendation number 3.1 in the short guideline.
Menopa	F	1	2	From our experience women want to know where they are within the process	Thank you for your response. The scope of the

use Self Care (MSC) CIC	ull	8	1	of the menopausal transition. Just knowing relieves anxiety and worry. As we are learning more about ageing and there's more access to medical research on the internet women in any part of the transition would find it helpful to know their FSH levels as they move through the menopausal years. There is a study entitled "Follicle Stimulating Hormone and Its Rate of Change in Defining Menopause Transition Changes" (Clin Endocrinol Metab. 2008 Oct; 93 (10): 3958-3964 Published online 2008 Jul 22. Doi:10.1210/jc.2008-0482) that describes 8 transitional phases of menopausal years changes correlating with rising FSH levels with the most change happening after age 45. Repeated FSH tests would be of help to women in self care and selfmanagement and could be cost-effective for the NHS as well as women as patients become more educated.	guideline did not include an evaluation of the cost-effectiveness of repeated FSH tests to define the transition of a woman's menopause. As such, the GDG are unable to comment on its perceived usefulness in the clinical setting.
Menopause Self Care (MSC) CIC	Full	58	27	From our experience women want to know where they are within the process of the menopausal transition. Just knowing relieves anxiety and worry. As we are learning more about ageing and there's more access to medical research on the internet women in any part of the transition would find it helpful to know their FSH levels. There is a study entitled "Follicle Stimulating Hormone and Its Rate of Change in Defining Menopause Transition Changes" (Clin Endocrinol Metab. 2008 Oct; 93 (10): 3958-3964 Published online 2008 Jul 22. Doi:10.1210/jc.2008-0482) that describes 8 transitional phases of menopausal years changes correlating with rising FSH levels with the most change happening after age 45. Repeated FSH tests would be of help to women as would more information and education about their own blood tests and biochemical changes throughout the menopausal years. Lifestyle changes impacts and medicines adherence 'success' could be seen in the blood tests as well as'felt' in the women. In this way women would be encouraged to be more pro-active in their own health and wellbeing choices as they age. This would be better for women as individuals and better for positive health outcomes in the short and long run.	Thank you for your response. The scope of the guideline did not include an evaluation of the cost-effectiveness of repeated FSH tests to define the transition of a woman's menopause. As such, the GDG are unable to comment on its perceived usefulness in the clinical setting.

Menopause

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Menopause Self Care (MSC) CIC	Full	67	29	We are very glad to see these recommendations. We are a social enterprise and have experience in delivering a peer support program for women in 'the Change'. Menopause Self Care (MSC) CIC customers are businesses, charities, Cornwall Council, the DWP, Peninsula Community Health, and Cornwall College. We would be willing to share our experiences on the peer support approach and how women value talking about their experiences and having a frame of reference to understand the many physical, emotional and mental challenges and opportunities inherent in ageing. We have developed accredited and non-accredited courses. Founded in May 2010 Menopause Self Care (MSC) CIC is based on the belief that how we live and what we choose in our forties and fifties directly impacts our quality of life for the rest of our life. The Menopause Self Care Learning Series offers different formats, accredited and non-accredited, for learning 'conscious selfcare'. The MSC courses offer selfcare & selftrust skills to enable women to discover resources and information for them to be pro-active, to understand the territory of ageing and to consider and discern what medical,dietary, lifestyle and complementary resources could be for them and their well-being. People can then create their own self-care plan with the advice of their GP and other health professionals. Women tell us they want a more open relationship with their GP. Women want more menopause specialists and GPs who are willing to address their concerns. Women in mid-life comprise a big part of the 'caring core' of society. Women are more stressed than ever with life changes, work stresses, raising children and caring for elders. How we navigate the ageing years is very important for women and for society. Raising consciousness will lead to better outcomes and lower costs in the long run. It is our opinion that the recommendations for increased information and guidance support women.	Thank you for your comment. This has been forwarded to the NICE implementation support team to inform their support activities for this guideline.

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