Evidence-based Guideline:

Premature ovarian insufficiency

REVIEW REPORT

ESHRE, ASRM, CRE WHIRL and IMS Guideline Group on POI

September 2024

eshre SCIENCE MOVING PEOPLE MOVING SCIENCE
asrm American Society for Reproductive Medicine
CREWHiRL Centre for Research Excellence in Women's Health in Reproductive Life
International IMS Menopause Society Promoting education and research on midlife women's health

The draft of the guideline "Evidence-based guideline: Premature Ovarian Insufficiency." and an invitation to participate in the stakeholder review were published on the ESHRE website between 17 April and 27 May 2024. The invitation to contribute to the stakeholder review was circulated to all collaborating and partnering organisations.

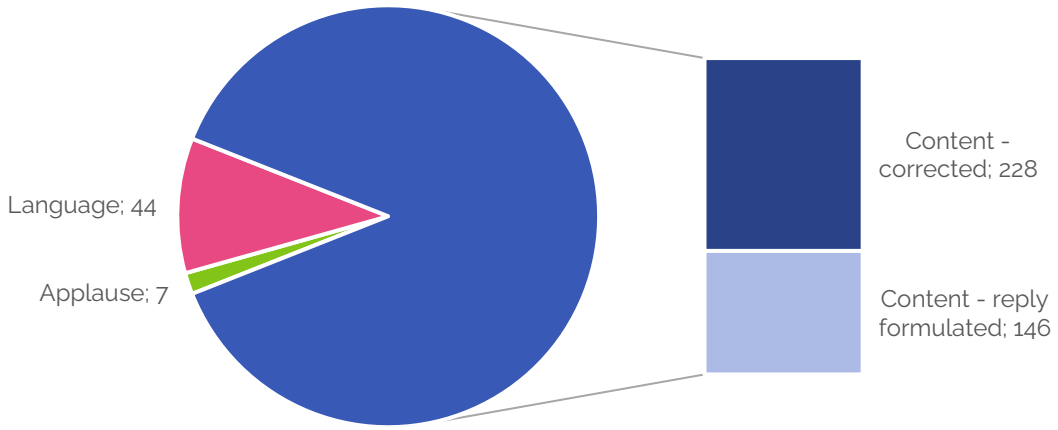
This report summarizes all reviewers, their comments and the reply of the guideline group and is published on the ESHRE website as an annex to the guideline.

During the stakeholder review, a total of 425 comments were received from 23 reviewers. Reviewers included professionals and representatives of other stakeholder groups, including patients.

The comments were focussed on the content of the guideline (374 comments), language and style (44 comments), or were remarks that did not require a reply (7 comments). All comments to the language and format were checked and corrected where relevant.

The comments to the content of the paper (n= 374) were assessed by the guideline group and where relevant, adaptations were made in the guideline (n=228; 61.0%). Adaptations included revisions and/or clarifications of the text, and amendments to the recommendations. For a number of comments, the guideline group considered them outside the scope of the guideline, or after discussion did not consider it appropriate or relevant to make a change to the text (n= 146; 39.0%). For these comments, a reply was formulated

Overview of comments per type of comment. For the comments to the content of the guideline, the graph indicated the proportion where a correction was made to the text



Experts that participated in the stakeholder review

The list of representatives of professional organization, and of individual experts that provided comments to the guideline are summarized below.

Representatives of professional organisations

Organisation	Country	Representative
CRE WHiRL	Australia	
Ragdolls UK Charity	United Kingdom	
British menopause society	United Kingdom	
Dutch Menopause Society	The Netherlands	Femi Janse
Menopause Services, Royal Women's Hospital, Victoria, Australia and on behalf of the Centre for Research Excellence in Women and Non-communicable Disease (CRE-WAND)	Australia	Martha Hickey
EMAS	NA	Angelica Lindén Hirschberg
ACOG	United States	Sigal Klipstein
RCOG	United Kingdom	
ASRM	United States	Jessica Goldstein
RANZCOG	Australia	Dr Kwik

Individual experts

Reviewer	Country
Elena Tucker	Australia
Brian M Cohen	United States
Elżbieta Zarychta	Poland
Sujoy Dasgupta	India
Claudia Bartolo Tabone	Malta
Marco Sbracia	Hungary
Adam Balen	United Kingdom
Carlos Calhaz-Jorge	Portugal
Stéphane Viville	France
Svetlana Dubrovina	Russia
Ahmed Samy Abdel-Azim Saad	Egypt
Jennifer Merrill	United States
Svetlana Dubrovina	Russia
Wendy Wolfman	Canada

Reviewer comments and replies

Reviewer	Page	Line	Comment	Action / Reply
Elena Tucker		Genetic diagnosis of POI	I have reviewed the discussion of the genetics of POI as this is my area of expertise. I agree that genetic testing can improve patient management and outcomes and should be offered where feasible. My overall concern, however, is that genetic testing has to be done in a clinically-approved manner with appropriate genetic counselling and accurate variant curation. This is contrary to the way it has been published in most research-based studies, that have poor variant curation and overstatement of diagnostic rate. If variant curation is performed in the manner of these published studies, patients are likely to receive wrong diagnoses or missed diagnoses and the opportunity to personalize patient care will be lost.	The reason why the studies are now separated according to their value. Studies with poor value should better be indicated in an appendix. Appropriate genetic counselling is discussed
Elena Tucker	39	664-685	There is considerable overlap between the genes involved in cancer predisposition and the genes involved in POI. Some of the patients being treated for cancer will have increased risk of POI irrespective of treatment and this might need to be considered as part of pretreatment counselling.	In the case of POI, biallelic DNA repair genes alteration is necessary. For patients with cancer and cancer gene predisposition a single allele is mutated and the other is normal. The impact on fertility is discussed. Indeed the heterozygous mothers of patients with POI and bialleic variants in DNA repair genes have no fertility problems.
Elena Tucker	41	759-772	Given the uncertainty of the association of XXX and POI, there seemed unbalanced discussion of this as a potential cause. In fact, the majority of 47,XXX individuals have normal ovarian function/fertility. The Baronchelli et al study identifies only one XXX individual and one XXX mosaic in their cohort of 269 women (0.7%). The Jiao et al study is based on only 3 XXX/mosaic individuals (0.6%). My concern about including this discussion in the guideline is that there is still uncertainty as to this being causal and diagnostic investigations could cease after 47,XXX karyotyping and true cause may be missed, limiting potential for personalized care.	The text has been supplemented to state the uncertainty regarding causality.
Elena Tucker	41	776	It is better to define DSD as "differences of sex development" as there is controversy in describing these conditions as disorders.	We agee and have changed this
Elena Tucker	41	799	The FMR1 gene name has been updated to Fragile X messenger ribonucleoprotein, https://www.fraxa.org/fmr1-renamed-to-fragile-xmessenger-ribonucleoprotein-1/	Thank you for pointing this out. The text has been updated accordingly.
Elena Tucker	42	812-817	This is not the leading theory of causation. POI is not associated with the full mutation, although this causes a loss of FMR1 protein. The difference is that the premutation causes increased FMR1 mRNA. Increased mRNA is known to be toxic to oocytes – see the cited Rosario et al 2022 paper	This was important information to be updated. Thank you! The text has been amended according to the suggestion.

Elena Tucker	42	847-852	Most of the cited studies fail to use strict criteria to establish causation and their claims of diagnostic yield are inflated. These research-based POI studies do not use clinically accredited curation and claim many variants of uncertain significance are diagnostic. For example: Eskenazi et al: No functional studies are performed. They state, "when no such tests had been done previously, we considered a missense variant as pathogenic when 2 of the 3 algorithms (SIFT, PolyPhen-2 and MutationTaster) gave identical results." This is completely insufficient to determine a variant is pathogenic as the prediction programs are imperfect. The genes analysed are also not validated POI genes. Heterozygous varaints are found in these genes but their functional consequence is not determined and even when a deleterious impact of the variant has previously been reported, the potential for autosomal dominant inheritance has not been validated. Franca et al: Again heterozygous missense variants without functional characterization are labelled pathogenic. The associated genes are either not well established human POI genes (eg. BMP8B, CPEB1, UBR2) or are autosomal recessive POI genes, so usually pathogenic variants are inherited from unaffected family members, so the identification of heterozygous variants does not explain cause (eg. MCM9) Vogt et al: Does not apply ACMG criteria rigorously. They report on "hot/warm" VUSs as "possibly pathogenic". Although the cited ACGS guidelines refer to hot/warm VUSs, these are still variants of uncertain significance, do not reflect identification of genetic cause and should not be reported except in "exceptional circumstances following MDT". Table 4 of the manuscript highlights their lack of rigor with their headings implying pathogenic variants are found, but clearly the majority remain VUSs as shown in the table text. Monoallelic variants in autosomal recessive POI genes can also not be considered causative because the inheritance pattern does not match that known to be associated with the gene. To achieve their diagnosis rate of 41%, it appears they have not only included "hot/warm" VUSs but even cold VUSs (as shown in the pie chart). Heddar et al: Again, heterozygous variants are considered causal without functional validation or established autosomal dominant inheritance of human POI related to the gene (eg. CENPE). Another example is CAV1 that the authors claim they have confirmed a causal role for, however CAV1 variants are a known cause of autosomal recessive lipodystrophy with fertility of parents carrying pathogenic variants. There is no evidence to support autosomal dominant CAV1 variants causing POI. Rossetti et al: Although this paper claims that "among the 43 patients screened for diagnostic purposes, we could identify at least one genetic variant in known POI genes in 11 of them, thus providing a genetic diagnosis in about 25% of POI patients through NGS.", most identified variants are heterozygous in autosomal recessive POI genes, have no functional validation and/or have benign predictions using online algorithms. These are not solved cases. Unfortunately, the over-statement of significance is a common feature of genomic studies of POI cohorts. I would consider it inappropriate to cite these references in the guideline as they will reinforce inaccurate curation of genetic variants. It is papers such as these that prompted our group's commentary, published in Biology of Reproduction: PMID: 35908231 DOI: 10.1093/biolre/ioac153	The articles have been now classified according to their values i. e. respect of international criteria for variant analysis in particular. Eskenazi et al and Franca et al do not follow ACMG criteria. Rossetti considered heterozygous variants and concluded to a possible oligogenic involvement in POI, still a research area. Vogt et al consider VUS variants cannot be used for genetic diagnosis. Heddar et al: It is now known that some genes may have different mode of transmission according to the phenotype: for example ERCC6, a DNA repair gene, has a monoallelic dominant mode of transmission in the case of POI and a biallelic recessive mode of transmission in the case of the Cockane syndrome. CENPE: transmission studies show a correlation with the phenotype, three affected sisters with POI have the identical truncating variant of CENPE (NM_001813.2: c.2023C>T; Gln675ter). This allowed to establish an association between the CENPE variant and the phenotype. CAV1: In fact CAV1 has already been shown to cause POI (Huang K et al Hum Reprod 2018). Hung et al reported a patient presenting POI and a heterozygous variant of CAV1 (c.142 G >C, c.Glu48Gln). The deleterious effect of this variant was demonstrated by functional studies in vitro. Hung et al stated that "CAV1 regulates primordial follicle formation via the Notch2 signalling pathway and is associated with POI in humans". https://doi.org/10.1093/humrep/dey299.

Elena Tucker	43	868 -875	The significance of the variants identified in POI patients remains uncertain. Rosetti et al 2021 merely reports on genetic variants identified in POI patients without any functional validation and including variants in unvalidated candidate genes. Ke et al 2023 is more balanced with some functional evidence supporting variant causation and a more modest diagnostic claim (~18.7%) than many other cohort genomic studies. Although they provide functional evidence to support deleterious impact of some variants in novel POI genes, whether heterozygous variants can be considered causal remains unknown.	Yes . All genes have to be validated to be included in a POI NGS panel either by functional validation or identification in several POI patients with the same mode of transmission. This is explained in the text.
Elena Tucker	43	878-882	Importantly, the data in Shekari et al also demonstrates that heterozygous variants in most "POI genes" are tolerated and not causal. This is in contrast to the many variants curated as causal by research genomic POI studies.	Yes because most POI genes are recessive and heterozygous variants in recessive POI genes are tolerated
Elena Tucker	44	903	The association of NFkB with human POI is not yet well established. It would be better to refer to AIRE in which variants are a well established cause of POI.	The gene NLRP11 involved in NF-kB signaling and regulation of inflammatory responses has been shown to cause POI in Heddar et al, 2022. A reference to POI and autoimmunity related to the AIRE gene can be added (Huhtaniemi et al 2018)

Elena Tucker	44	911-914	The cited paper very poorly identifies variants of significance with regard to co-morbidity. For example, the paper reports "Seven patients had genetic defects in POLG encoding the mitochondrial DNA polymerase, without associated neurological or ocular symptoms." Three of these variants, however, are clearly benign and not causal. For example, one (rs41549716) has 14 submissions in ClinVar agreeing that it is likely benign and it is found in 543 XX individuals in gnomAD. Another (rs61752783) has 8 ClinVar entries considering it likely benign and is found in 417 XX individuals. The cited paper continues that "In all these cases, a comprehensive evaluation of patients and their families was recommended with appropriate follow-up in a multidisciplinary team." This is part of the problem if curation is not done rigorously. These patients could be counselled that they are at risk of neurological or ocular symptoms and have unnecessary follow-up and stress	The bibliography concerning POLG and POI should be carefully read, without focusing only on so-called "reliable" sources. The two POLG variants described in Heddar et al, Y831C (rs41549716) and G517V (rs61752783), have been previously published as clearly pathogenic (see Horvath R Brain 2006, Barthélémy C Hum Genet 2002, Mancuso M Arch Neurol 2004). Heddar et al also performed segregation studies of the Y831C variant in a family (two affected sisters and their mother) and demonstrated segregation with POI. At least five studies have reported dominant variants of POLG, including Y831C, in isolated POI or in syndromic POI associating progressive external ophthalmoplegia with or without Parkinsonism (see Luoma P Lancet 2004, Pagnamenta AT et al Hum Reprod 2006, Blok MJ J Med Genet 2009). The Y831C variant was identified in a child with sensorineural deafness, ophthalmoplegia, epilepsy and permanent muscle weakness and his asymptomatic mother but the latter presented mitochondrial alterations in the muscle biopsy as her child (Barthélémy C et al Hum Genet 2002). This finding confirms the variable expressivity associated with POLG mutations. The Y955C variant was first identified in familial forms of dominant PEO with or without Parkinsonism and then in isolated POI by an independent team (Pagnamenta AT et al 2006). The use of sources as Clinvar to classify variants as benign or pathogenic is not recommended by the ACMG. Errors are possible, particularly in the control population, given the very broad profile of the syndromes associated with POLG mutations and the great variability in the expression and penetrance of POLG variants. At least 12 different phenotypes are associated with this gene. For instance, we are not sure that the control population used for the study of POLG and PEO or Parkinsonism does not have fertility problems. Care should be taken when such resources are used but also GnomAD databases especially in the field of infertility.

Elena Tucker	44	table	It is stated that the table is not exhaustive but other examples that could be added include MRPL50, MRPS7, PEX6, GGPS1, RMND1 as causes of Perrault syndrome. Other syndromes include 3-Methylglutaconic Aciduria due to CLPB variants (neurological signs, movement disorder, cataracts and neutropenia) and hypotonia syndrome due to PREPL variants, Leigh syndrome due to variants in LRPPRC.	Additional examples were added, as suggested
Elena Tucker	46	934	After listing the rationale for genetic testing, I feel the need for some discussion of the possible risks of genetic testing (eg see PMID: 35908231). For example, it is absolutely critical that curation be performed accurately. Another very important point that HCP need to be aware of and discuss with their patients before genetic testing is that sometimes POI can be the first sign of an evolving syndrome. For example, POI can precede cancer, neurodegerenation or hearing loss (eg PMID: 29706645, PMID: 36450801). The ovaries are very susceptible to damage and are impacted by many physiological processes, so it is not uncommon for them to manifest disease before other organs/tissues. It is very important that patients and their HCP are aware that genetic diagnosis can identify something with broader consequences to their health. I think this needs to be written into the guideline. This is different from "incidental findings" for which individuals are often given the opportunity to opt out from learning about. These genetic variants are related to the test question and would be reported back to the patient.	In rational for genetic testing it is stated in the guidelines that identifying the genetic cause of POI can be helpful for patients and families by enabling appropriate co-morbidity screening with involvement of multidisciplinary teams. In the cohort of Heddar et al, 44.8% of patients had, or were at risk to develop, associated comorbidities, requiring a comprehensive assessment by a multidisciplinary team. POI pathogenic variants of genes causing syndromic POI were identified in 8.5% of cases. Before genetic testing it is therefore important to inform the patients that sometimes POI can be the first sign of other related health conditions in a syndrome and that a comprehensive assessment by a multidisciplinary team may be necessary. This was added to the text.
Elena Tucker	46	940	As above, I think it should be reiterated that genetic testing for POI can identify other related health conditions that are currently subclinical/dormant. This should be discussed as part of pre-testgenetic counselling.	We agree and have addressed this comment
Elena Tucker	46	953	Chromosomal microarray is often used interchangeably with conventional karyotyping, rather than being restricted to investigation for smaller CNVs/breakpoints.	The text has been modified in an attempt to clearer demonstrate that CMA can be used interchangeably with karyotyping, but also has complementary properties. In addition. Of note it is important that karyotyping is generally more accessible and half the price of CMA.
Elena Tucker	48	1013	Heddar et al overstates significance of gene variants and diagnostic rate. Ke et al, claims 18.7% diagnosis which is more accurate but there remains some question of causality of identified variants	In a large international cohort of patients included consanguineous and familial POI a targeted NGS-POI panel comprising all known POI genes (88) allowed a high diagnostic yield of 29.3% (Heddar et al). But excluding the familial and consanguineous forms in the European population, the positivity is 26,3% very close to 23.5% positivity obtained by Ke et al in a large Chinese cohort of POI when novel genes are included with a very similar number of genes studied (95) (Ke et al.,).
Brian M Cohen		REC 4	Would not compulsive excess exercise with low BMI be an issue?Data suggests earlier loss of oocytes in these hypoestrogenic young women .Just a suggestion for review please.	Thank you for this comment. We did include a note on low BMI in the text, but data is not specific to POI and hence not discussed in further detail

Elżbieta Zarychta	179	5469/table XI	Suggested doses of progestogens administered sequentially seem to be TOO LOW to induce endometrial transformation and prevent hyperplasia. As for suggested doses of estrogens (2-4mg oral E2 or 100-200ug of transdermal E2, which are equivalent) the minimal progestogen doses to elicit changes equivalent to premenopausal secretory phase endometrium are: 200mg for micronized oral progesterone and 10mg for dydrogesterone (for 2mg of oral E2 or 100ug of transdermal E2) Schindler, A. E. (2009). Progestational effects of dydrogesterone in vitro, in vivo and on the human endometrium. Maturitas, 65, S3–S11. doi:10.1016/j.maturitas.2009 – Table 4, 5 and 6	The table pertains to Puberty Induction not HT. This was clarified in the caption of the table
Sujoy Dasgupta	23	175-177	Women with low ovarian reserve are at increased risk of POI. There is evidence that marker of ovarian reserve like anti-mullerian hormone (AMH) can predict the age of menopause. (Broer et al., 2011). One study found that poor response to ovarian stimulation may be linked to early onset of menopause (Lawson et al., 2003). In fact, the interval between decline in oocyte quality and age of menopause remains relatively "fixed" (Broekmans et al., 2009). Therefore, low ovarian reserve can be followed by POI. Reference: • Broekmans FJ, Soules MR, Fauser BC. Ovarian aging: mechanisms and clinical consequences. Endocr Rev. 2009 Aug;30(5):465-93. doi: 10.1210/er.2009-0006. Epub 2009 Jul 9. PMID: 19589949. • Broer SL, Eijkemans MJ, Scheffer GJ, van Rooij IA, de Vet A, Themmen AP, Laven JS, de Jong FH, Te Velde ER, Fauser BC, Broekmans FJ. Anti-mullerian hormone predicts menopause: a long-term follow-up study in normoovulatory women. J Clin Endocrinol Metab. 2011 Aug;96(8):2532-9. doi: 10.1210/jc.2010-2776. Epub 2011 May 25. PMID: 21613357. • Lawson R, El-Toukhy T, Kassab A, Taylor A, Braude P, Parsons J, Seed P. Poor response to ovulation induction is a stronger predictor of early menopause than elevated basal FSH: a life table analysis. Hum Reprod. 2003 Mar;18(3):527-33. doi: 10.1093/humrep/deg101. PMID: 12615819.	We acknowledge that AMH has some predictive value, but it is low (discussed fully in the Nelson et al systematic review). This is clearly stated in the text (eg in justification of the section on AMH)

Sujoy Dasgupta	30	463	One section should be added on "Endometriosis- as a risk factor for POI" (Though it has been mentioned in page 39, lines 686-689 in the section B, it needs detailed description in the "risk factors for POI") The surgical treatment of endometriosis in the form of bilateral oophorectomy leads to POI (Malhas and Robinson, 2020; Ottolina et al., 2018). Even conservative surgeries (like cystectomy) can affect the ovarian reserve (Tan et al., 2023; Coccia et al., 2011). In particular, women who underwent bilateral ovarian cystectomy for endometrioms arre at risk of POI (Coccia et al., 2011). However, even without any surgical intervention, presence of endometrioma itself can adversely affect ovarian reserve by causing inflammation, fibrosis, abnormal angiogenesis, and oxidative stress, resulting in POI (Tan et al., 2023; Ottolina et al., 2018; Kasapoglu et al., 2018). In a large population-based cohort study conducted in 106,633 women, laparoscopically confirmed endometriosis increased the risk of early natural menopause by 50% (hazard ratio [HR], 1.51; 95% CI, 1.30-1.74) (Thombre Kulkarni et al., 2022). The increased risk persisted even after adjusting for variables like race, anthropometric and behavioral factors (Thombre Kulkarni et al., 2022). References: • Coccia ME, Rizzello F, Mariani G, Bulletti C, Palagiano A, Scarselli G. Ovarian surgery for bilateral endometriomas influences age at menopause. Hum Reprod. 2011 Nov;26(11):3000-7. doi: 10.1093/humrep/der286. Epub 2011 Aug 24. PMID: 21868401. • Kasapoglu I, Ata B, Uyaniklar O, Seyhan A, Orhan A, Yildiz Oguz S, Uncu G. Endometrioma-related reduction in ovarian reserve (ERROR): a prospective longitudinal study. Fertil Steril. 2018 Jul 1;110(1):122-127. doi: 10.1016/j.fertnstert.2018.03.015. Epub 2018 Jun 20. PMID: 29935810. • Malhas R, Robinson L. Induced menopause in women with endometriosis. Post Reprod Health. 2020 Sep;26(3):163-165. doi: 10.1177/2053369120911548. PMID: 32997588. • Ottolina J, Bartiromo L, Viganò P, Makieva S, Schimberni M, Candiani M. Does endometriosis influence the age of menopause? Minerva Ginecol. 2018 Apr;70(2):171-177. doi: 10.23736/S0026-4784.17.04125-9. Epub 2017 Sep 5. PMID: 28891281. • Tan Z, Gong X, Li Y, Hung SW, Huang J, Wang CC, Chung JPW. Impacts of endometrioma on ovarian aging from basic science to clinical management. Front Endocrinol (Lausanne). 2023 Jan 4;13:1073261. doi: 10.3389/fendo.2022.1073261. PMID: 36686440; PMCID: PMC9848590. • Thombre Kulkarni M, Shafrir A, Farland LV, Terry KL, Whitcomb BW, Eliassen AH, Bertone-Johnson ER, Missmer SA. Association Between Laparoscopically Confirmed Endometriosis and Risk of Early Natural Menopause. JAMA Netw Open. 2022 Jan 4;5(1):e2144391. doi: 10.1001/jamanetworkopen.2021.44391. PMID: 35061039; PMCID: PMC8783263.	We have addedsome detail to section on iatrogenic POI and referred to ESHRE guideline on endometriosis for further information on Endometriosis.
Sujoy Dasgupta	65	1474	While the guideline provides detailed explanation on hormone therapy and puberty induction in women with POI, it should also provide some highlights on possible "stimulation protocols" for women in POI who refuse oocyte donation and who wants to do IVF using their own oocytes. Therefore, such section should be considered.	The reviewer will be aware of the very limited evidence as to ovarian stimulation protocols in women with POI . However the possibility of ongoing ovarian activity is clearly highlighted, which in itself indicates the potential for attempting ovarian stimulation.

Claudia Bartolo Tabone		Inter sex wo men	The guidelines refer to women with Turner's Syndrome and, where genetic causes of POI are concerned, "Disorders of Sex Development/DSD." Aside from the fact that TS also falls under the umbrella of "DSD", the latter term is considered pejorative, stigmatizing, and controversial. The medical term accepted by most intersex advocacy groups nowadays is innate variations of sex characteristics (IVSC). POI is common in several presentations of IVSC and therefore it would be pertinent to address these guidelines to the intersex community as well.	There is no consensus regarding the prefered term but we agree the term "disorders" should not be used and have therefore changed the text to "Differences in sex development" as this will be best recognised by the broader medical community to whom this guideline is aimed. Turner syndrome is discussed as the commonest DSD causing POI and with the greatest underlying evidence base for management. Other DSD are referred to in the section regarding pubertal induction.
Claudia Bartolo Tabone			Taking also into consideration that some IVSC are not diagnosed in childhood (that is, when anatomical differences are not overt at birth), intersex women are often unaware of their intersex variation. The possibility of this, and therefore tests to investigate whether an IVSC is present, should be included in medical protocols on the management of POI.	We consider this is covered in the section on genetic testing, and have added a clarification in that section
Marco Sbracia			The Guideline group made an outstanding efforts in drafting these guidelines, that are really interesting and scientifically valid.	Thank you for this comment
Marco Sbracia	11	2	There is inconsistency in the definition, since before 40 years is POI after early menopause, without any clear motive and clinical validity. This should be re-considered and should be found only one clear cut-off for POI (according to the normal menopause, may be<42?)	The current comment pertains to the introduction which only briefly comments on the target population and definitions. We have not added information, as the reasoning behind the cut-of age of 40 years for POI is discussed in detail in section I.2. Definition of POI
Marco Sbracia	11	4	The PICO question is what the risk factors for POI are, but the recommendation does not answer to this, but include only generic recommendation that often should be done to other specialists, such as oncologists or others. This recommendation should be re-formulated, including in this the anamnestic findings of familiarity for POI or physical characteristics that may suggest the presence of recurrence in the family for POI (short height, familiarity for some gene etc.). Furthermore, another risk factor may be the presence of infertility with AMH levels very low.	We have amended the recommendation and we have slightly rephrased the justification. The value of AMH in a diagnosis of POI is discussed in the respective section.
Marco Sbracia	11	5	The HCP should put more effort in the prevention of POI or at least to diagnose it early, evaluating its risk factors and select people with higher risk.	We have amended the recommendation and we have slightly rephrased the justification..
Marco Sbracia	12	456 06	AMH should be considered as a test to find women at risk for POI in their 20s or 30s, and not a test for the diagnosis of POI These two recommendations may be re formulated?	There are no studies supporting screening of young women to predict later POI. While this may be an interesting question for further research, based on the currently available evidence, this is not a recommended approach.
Marco Sbracia	13	28-31	Female relatives should be strongly advised of the risk of developing POI, and in case of their reproductive age offer them always fertility preservation. This point should be particularly stressed since fertility preservation is often the only medical intervention in these patients as well as for women with low or very low AMH to procreate.	We highlight the issue of informing relatives about the risk of POI and that FP should be considered (line 1255).

Marco Sbracia	13	42	In this recommendation the real risk value with respect to normal women should be reposted since a generic affirmation of "they are to high risk" of pregnancy complication may be misleading, and generate a negative impact on the patient's counseling, considering that these guidelines are for gynecologist. For a right counseling, the real digits should be always reported and explained to patients.	We have provided information on risks in the text, but considered it not relevant to repeat them in the recommendation.
Marco Sbracia	14	50	It is too generic reports "in some women can be of such high-risk oocyte donation". The classes of patients in which the oocyte donation should be inappropriate need to be reported clearly for a correct adherence of HCP to the guidelines.	We consider the aortic root cut off is addressed in the text, but additional risk factors may be present, and considered it appropriate to personalise risk assessment rather than developing a general recommendation on this
Adam Balen			I congratulate the authors on an excellent and comprehensive guideline. I wonder if you would consider during the introduction making mention of the new FIGO classification of disorders of ovulation, which replaces the outdated WHO classification and presents a framework for the classification and diagnosis of all causes of POI as outlined in our recent review: Balen AH, Tamblyn J, Skorupskaite K, Munro M. A Comprehensive Review of The new FIGO Classification of Ovulatory Disorders. Human Reproduction Update, 2024; 30: 355-382. 10.1093/humupd/dmae003. This is the paper that first presented the FIGO classification in 2022: Munro MG*, Balen AH*, Cho S, Critchley HOD, Díaz I, Ferriani R, Henry L, Mocanu E, van der Spuy ZM; FIGO Committee on Menstrual Disorders and Related Health Impacts, and FIGO Committee on Reproductive Medicine, Endocrinology, and Infertility. The FIGO ovulatory disorders classification system. *Joint first authors. Simultaneous publication: Hum Reprod. 2022 Sep 30;37(10):2446-2464. doi: 10.1093/humrep/deac180. PMID: 35984284; PMCID: PMC9527465; Fertil Steril. 2022 Oct;118(4):768-786. doi: 10.1016/j.fertnstert.2022.07.009. Epub 2022 Aug 19. PMID: 35995633; Int J Gynaecol Obstet. 2022 Oct;159(1):1-20. doi: 10.1002/ijgo.14331. Epub 2022 Aug 19. PMID: 35983674.	Thank you for this comment
CRE-WHiRL	8	introduction	A definition and brief summary of what a GDG statement/ GPP/ Conditional and Strong recommendations are needed in the introduction section in addition to Appendix. Consider rewriting "GDG statements" as a GPP.	We have added a short section on terminology of the recommendations in the introduction. We have explained the difference between GDG statements and GPP, so we have not merged these.
CRE-WHiRL	11	diagnosis	Need to define what is meant by oligomenorrhoea (eg. no menses for >3 months in person with previous regular menses) or secondary amenorrhoea. Consider including in Table 1 Terminology (line 73) and repeating in the diagnosis section.	Oligomenorrhoea was removed from the text. Secondary amenorrhoea was explained at first use in the text.
CRE-WHiRL	11	Recommendation 2	Age at natural menopause is predominately determined by heredity especially mother's age at menopause. Should mother's age of menopause be considered when defining POI? For example, if mother's age at menopause is 56 years and daughter has menopause at age 45 years is this significantly earlier than would be expected and potentially pathological for this women? Consider including this as a research question, ie. "What are the implications of mother's age of menopause when defining POI or early menopause? "	We have added this as a research recommendation

CRE-WHiRL	11	Recommendation 4	There is conflicting evidence regarding the effect of increased BMI on ovarian reserve/ AMH levels in addition to evidence suggesting low BMI as possible risk factors for POI. Two recent systematic reviews which investigated the association between AMH/ ovarian reserve and BMI (below) which may be of relevance but would not have been included in the original search. 1. Moslehi et al 2018 identified 26 studies and sub-grouped them into non PCOS fertile, PCOS and infertile (possibly including some POI patients but not specified). Mean difference in AMH was lower in obese versus non-obese in the non-PCOS fertile and PCOS groups but not the infertile group. However, Fisher test indicated a negative correlation between AMH and BMI in infertile , non-PCOS fertile and PCOS groups. The same meta-analysis showed no significant relationship between FSH and BMI in the infertile group. (Moslehi, N., S. Shab-Bidar, F. Ramezani Tehrani, P. Mirmiran and F. Azizi (2018). "Is ovarian reserve associated with body mass index and obesity in reproductive aged women? A meta-analysis." Menopause 25(9): 1046-1055) 2. Werner et al. 2024 looked at 36 studies investigating the relation between AMH levels or AMH decline and BMI, of which 28 were cross-sectional, seven were prospective cohort studies and one was a retrospective cohort study. Twenty-two studies found an inverse association between AMH levels and BMI, three studies found a positive association and 11 studies found no significant association. In two of the prospective studies obese and overweight women had slower rates of AMH decline compared to women with a healthy weight. Overall, the relation of BMI with AMH appeared stronger or more apparent in women with PCOS in comparison with women who did not meet this classification; in some studies, the relation between BMI and AMH was only significant in women with PCOS. (Werner, L., Y. T. van der Schouw and A. C. de Kat (2024). "A systematic review of the association between modifiable lifestyle factors and circulating anti-Müllerian hormone." Human Reproduction Update 30(3): 262-308.) Therefore we suggest rewriting the recommendation as: "The guideline group recommends that in view of the long-term health consequences of POI, efforts should be made to reduce the risk of POI. Modifiable factors may include: - gynaecological surgical practice - lifestyle such as smoking or body mass index (BMI) - modified treatment regimens for malignant and chronic diseases". [GPP]	The suggestion of adding BMI to the recommendation as a modifiable risk factor was discussed in the guideline group, but it was decided not to include BMI as there is no evidence of a direct association between BMI and POI and adding it to the recommendation could have a negative impact on patients
CRE-WHiRL	11	Recommendation 5	In view of the changes to recommendation 4 above we suggest that recommendation 5 be rewritten as: "The guideline group recommends that women with risk factors for POI are counselled regarding the potential for prevention of POI, such as stopping smoking, maintaining a normal body weight/ BMI and fertility preservation." [GPP]	As no changes were made to the previous recommendation, we have also not include BMI in this recommendation.

CRE-WHiRL	31	Line 472	Rewrite research recommendations as: Further research is required to (i) identify and clarify risk factors for POI, in addition to those related to early menopause, especially the role of socio-economic factors, lifestyle (including the effect of BMI and diet) and environmental chemicals; and (ii) identify and quantify strategies that may mitigate modifiable risk factors.	We agree with the suggestion and have amended the research recommendation accordingly
CRE-WHiRL	11	Recommendations 6-9	Need to clarify what is meant by "oligomenorrhoea" and "amenorrhoea". Should the recommendations only state "amenorrhoea for at least 4 months"? For example, should someone who has amenorrhoea for 2 months then monthly menses for three months then amenorrhoea for 3 months be investigated for POI?	We have revised the recommendations on diagnosis to address this and other comments.
CRE-WHiRL	11	Recommendation 9	• We agree that only one elevated FSH level required for diagnosis in most women. We agree with the FSH threshold of 25IU • Consider removing sentence below or need to define "uncertainty" "FSH assessment should be repeated after > 4 weeks if there is diagnostic uncertainty". • Consider including "low estradiol" in diagnostic criteria (to differentiate elevated FSH from potential midcycle FSH rise) as estradiol test also included in diagnosis algorithm on page 37 • Consider adding LH<10 IU to diagnostic criteria especially if diagnostic uncertainty	We have revised the recommendations on diagnosis to address this and other comments.
CRE-WHiRL	37	Fig 6: Diagnosis algorithm	• Consider adding LH<10 IU to "Repeat FSH/ E2 test" box • Consider having "Consider AMH test" box as an "OR" situated next to instead of below "Repeat FSH/ E2 box" • Does the symptoms box need to include "infertility" as it is not mentioned in the diagnostic criteria? • Write the text in the symptom box as "Symptoms of estrogen deficiency AND/OR oligo/amenorrhoea before the age of 40 years"	We have revised the recommendations on diagnosis to address this and other comments.
CRE-WHiRL	13	Recommendation 33	• Instead of saying "at least until the usual age of menopause", should this be: "at least until age 50/51 years "? • Need to be careful of wording to indicate that continuing HT after the age of usual menopause should be considered for all women with POI. The wording of this principle should be consistent throughout the guideline when referred to. • Include a research recommendation about investigating the benefits/ risks of HT continuing for a further 5 years or more after the age of usual menopause	"Usual age of menopause" terminology has been extensively discussed in the GDG and agreed because the age of menopause varies depending on country/region being referred to. Using the term "at least" indicates that HT can be continued beyond this if appropriate. Inclusion of the suggested research recommendation was discussed in GDG meeting.
CRE-WHiRL	15	Recommendation 74	Wording is unclear suggest add "therefore" so recommendation would read: "The effect of other therapies, including testosterone, on muscle health in women with POI is uncertain and therefore they should not be offered."	We agree with this suggestion and have reworded the reommendation to: "The effect of other therapies, including testosterone, on muscle health in women with POI is uncertain and therefore they should not be offered."

CRE-WHiRL	16	Recommendation 79	Is there a better word than “control” in the sentence: “control future risk of cardiovascular disease”. For example, use “manage” or “reduce” instead.	We have revised the wording of the recommendation as suggested
CRE-WHiRL	17	Hormone therapy in POI-Principles and Indications	Consider adding an additional GPP regarding the timing of starting HRT. This is especially important in those women within the first year of diagnosis of POI who are more likely to have intermittent ovarian function and are desiring spontaneous pregnancy. Mention of this situation should also be included in the explanatory text. A potential GPP could be: “In women with POI with evidence of intermittent ovarian function desiring natural pregnancy, the guideline group recommends commencing HRT if estrogen deficiency symptoms are present OR no later than 12 months after POI diagnosis to avoid bone loss. Sequential HRT is suggested as any subsequent development of amenorrhoea may indicate pregnancy.”	We have a recommendation reading "Delayed initiation and non-adherence of estrogen therapy should be avoided." and one stating "In women with POI with evidence of intermittent ovarian function and desiring natural pregnancy, recommendations for hormone therapy remain unchanged and do not impact chances for natural conception. A sequential hormone therapy regimen is recommended."
CRE-WHiRL	17	Recommendation 103	See concerns about wording for recommendation 33	"Usual age of menopause" terminology has been extensively discussed in the GDG and agreed because the age of menopause varies depending on country/region being referred to. Using the term "at least" indicates that HT can be continued beyond this if appropriate. Inclusion of the suggested research recommendation was discussed in GDG meeting.
CRE-WHiRL	17	Recommendation 105	• This is a strong recommendation but contains the word “generally” Consider rewording as “ Women with POI should be informed that systemic hormone therapy is contraindicated in women with hormone/estrogen receptor positive breast cancer.” • Include as a research recommendation that research is needed into the risks of hormone therapy in women with hormone receptor negative breast cancer	The word "generally" was included by guideline group to indicate that there are exceptional circumstances where hormone therapy may be prescribed in breast cancer survivors. The recommendation has not been changed.

CRE-WHiRL	156	Line 467 5	• Add a sentence regarding the use of hormone therapy in women with hormone receptor negative breast cancer. Eg data from LIBERATE study (Kenemans P, Bundred NJ, Foidart JM, Kubista E, von Schoultz B, Sismondi P, Vassilopoulou-Sellin R, Yip CH, Egberts J, Mol-Arts M, Mulder R, van Os S, Beckmann MW; LIBERATE Study Group. Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. Lancet Oncol. 2009 Feb;10(2):135-46. doi: 10.1016/S1470-2045(08)70341-3. Epub 2009 Jan 23. PMID: 19167925.)	LIBERATE studies (Kenemans, 2009) does mention that "Patients with oestrogen-receptor-negative tumours had no increased risk of recurrence (HR 1·15 [95% CI 0, 73-1, 80]; p=0·058) by contrast with patients with oestrogen-receptor-positive tumours (HR 1·56 [95% CI 1·22- 2·01]; p=0·0005).". We added this conclusion in the text. But researchers remain cautious about using hormone therapy in patients with receptor-negative breast cancer. They said in the discussion section, "On the basis of the present trial data, it is not possible to identify a specific subgroup of patients who could use tibolone without risk of increased breast-cancer recurrence." Therefore, hormone therapy for patients with receptor-negative breast cancer needs to consider the individual situation of the patient.
CRE-WHiRL	17	Rec om men dati on 109	Wording of the recommendation needs clarification as the current wording implies that combined estrogen plus progestogen does not need to be continued after usual age of menopause ie. it infers that the progestogen component could be stopped at age of usual menopause	We have rephrased this recocmmendation to avoid confusion
CRE-WHiRL	18	Rec om men dati on 122 and 123	Need clarification and consistent wording across these two recommendations in the use of the term “low risk”	We have modified the recommendation where needed
Carlos Calhaz-Jorge			Great work! Congratulations and thanks to all involved	Thank you for this comment
Carlos Calhaz-Jorge	14 (88)	rec 53 / 2282	Is this GPP needed? The same recommendation is already present in the previous PICO (as conditional)	We have removed recommendation 53
Carlos Calhaz-Jorge	16 (125)	rec 94 / 366 0	Is the wording correct? "The GDG recommends that laser … is not currently considered standard care…". Maybe “recommends” may be replaced by “considers” or similar	We have reformulated the recommendation for clarity. "The guideline group currently does not recommend applying laser or thermal energy as standard care for GSM due to the lack of clear benefit in RCTs "
Carlos Calhaz-Jorge	18 (159)	rec 127 /47 81	Maybe more clear if the word cancer is added in “… hormone therapy before cancer risk reducing bilateral…”	We have adapted the recommendation accordingly

Carlos Calhaz-Jorge	159	4782	Recommendation missing in the list of pages 11 to 19	These recommendations were mentioned in 2 sections of the guideline, but not duplicated in the list of recommendations. To avoid confusion, a comment/note will be added in this respect.
Carlos Calhaz-Jorge	159	4783	Recommendation missing in the list of pages 11 to 19	These recommendations were mentioned in 2 sections of the guideline, but not duplicated in the list of recommendations. To avoid confusion, a comment/note will be added in this respect.
Stéphane Viville			Some changes to be made to the Fragile X premutation section. The subject is much more controversial than presented in this text. Some people are seriously questioning the value of this test. This should be mentioned. It is clearly stated in the text that this is a risk and not a definite cause, but this is not developed. (See also unpublished data)	We have re-assessed the text in line with this comment. While the shared data are interesting, they are not published and hence are - per definition - not eligible for inclusion. We consider the text as it stands now is clearly stating that FMR1 premutation is a risk and not a cause of POI. It is also highlighted that genetic and environmental factors other than CGG repeats likely modify the risk of POI
Stéphane Viville			The Other genetic causes of POI section should be completely revised	We have revised this section.
Stéphane Viville			Make a distinction between syndromic and non-syndromic causes.	We have made a distinction between syndromic and non-syndromic causes.
Stéphane Viville			For syndromic causes, it should be added that they are generally treated by specialities other than reproductive medicine, and that their health, in the majority of cases, does not allow them to envisage a parental project.	It is stated that comprehensive assessment by a multidisciplinary team may be necessary. For metabolic diseases or syndromic diseases a parental project is possible (GALT). PGD may also be performed in other cases. It was considered not appropriate to make one conclusion for all cases, but rather we reenforce that genetic counseling must be adapted to specific cases.
Stéphane Viville			The table with the genes can be removed, or a table added for non-syndromic genes	A table with non syndromic genes cannot be added as it increases rapidly with time and will not be updated.
Stéphane Viville			There should be a reference to the OMIM (Online Mendelian Inheritance in Man) database, which is the reference genetics database for genes involved in human pathologies. OMIM classifies POIs under three headings: "premature ovarian insufficiency" (28 entries); "premature ovarian failure" (116 entries) and "ovarian dysgenesis" (200 entries). Not all of these relate directly to POI. Some are syndromic, others non-syndromic. Some are also associated with spermatogenic failure. This needs to be analysed in more detail and mentioned. I enclose the corresponding tables.	OMIM references are heterogeneous with very confusing POI names. This chapter does not includet all genetic databases.
Stéphane Viville			There is also little or no mention of the genes involved in both POI and male infertility.	We have added that some genes may be shared with azoospermia genes: in particular genes involved in meiosis/DNA repair or gonadal development (NR5A1)

Stéphane Viville			I think the section "clinical steps in identifying a genetic cause" should be entitled "Genetic management of POI". the "Genetic studies" section should be entitled "Genetic diagnosis"; the "Specific gene variant testing" section, "Monogenetic analysis". It should be discussed whether FMR1 analysis should be carried out first, before starting the analysis of monogenic causes.	The headings were changed. Obviously the positivity of NGS is much higher than FMR1 study. Both genetic studies have to be performed in parallel and not one after the other. A single blood sample should be obtained from the patient and not two.
Stéphane Viville	46	930	cites an article by Huhtaniemi et al, and the more recent article by Verpoest et al should also be cited	We have included the reference for Verpoast 2023
Ragdolls UK Charity		Diagnosis	Referral to relevant patient charities should be standard at diagnosis, including during pregnancy for parents who are carrying a foetus with TS.	We have addressed referral to patient support groups this in the section "Care for women with POI at diagnosis". We don't think it is relevant for the current document to be more specific on this, but it can be considered in the information for patients to be deeveloped,
Ragdolls UK Charity		Diagnosis	Information should be available in plain language so that accurate information about the condition can be shared with the wider members of the family, pre-empting misunderstandings and difficult questions.	Thank you for this comment. The current version of the guideline is aimed at professionals, but will be complemented with resources for patients in appropriate language.
Ragdolls UK Charity		General	It is vital to continue efforts to describe the condition and its associated signs in plain language, particularly when the patient/parents are distressed.	This version of the guideline is aimed at professionals, but it will be complemented with further versions for patients in appropriate language
Ragdolls UK Charity	68	1618	The guideline group recommends that fertility preservation is discussed with women at risk of POI. Research is continuing on ovarian tissue preservation for girls with Turner Syndrome. Although only a small number of girls will be eligible for this treatment, there is wider interest in this technology from families of girls with TS. In this context, ovarian tissue preservation is a treatment for prepubertal girls rather than adults. Similarly, girls with TS who are eligible for egg freezing will most likely be under 18. We suggest amending this guideline. Where possible, information about eligibility criteria for fertility preservation should be made available to the wider TS community, to set expectations. Parents should be able to access informed guidance on their daughter's eligibility, on her behalf. Children should have access to age-appropriate information and counselling if needed. Coelen, S.V.D., Schleedoorn, M., Nadesapillai, S., Peek, R., Braat, D., Velden, J.V.D., Fleischer, K. and Oerlemans, A., 2021. O-185 Evaluation of the decision-making process of girls with Turner syndrome and their parents considering ovarian tissue cryopreservation. Human Reproduction, 36(Supplement_1), pp.deab127-086. Fearon, K., 2023. What do families affected by Turner Syndrome think of ovarian tissue freezing in childhood?. Human Fertility, 26(2), pp.355-364.	Thank you for this comment, we agree that ovarian tissue cryopreservation is a potential approach for some girls as well as women with ovarian disorders such as TS and have amended to text to include this.

Ragdolls UK Charity	68	1618	Further questions arise on the implications of reproductive preservation, and it would be useful to have a professional consensus on them. • It needs to be clear what happens in the event that the eggs or ovarian tissue are unused - would they be destroyed, or could they be donated? • What are the considerations around genetic screening of eggs for TS or other conditions, should technology support this in the future? • There is a small risk that TS is heritable in some women with mosaic TS. Would a woman with TS using embryos created from her own frozen eggs be required to have PGT? Eg, see: Portnoï, M. F., Chantot-Bastaraud, S., Christin-Maitre, S.,Carbonne, B., Beaujard, M. P., Keren, B., Levy, J., Dommergues, M., Cabrol, S., Hyon, C., & Siffroi, J. P.(2012). Familial Turner syndrome with an X;Y translocation mosaicism: Implications for genetic counseling. European Journal of Medical Genetics, 55	In the chapter, we highlight the experimental nature of fertility preservation In TS (and related conditions). While these are relevant considerations, they are more appropriate for documents focussing on the details of fertility preservation.
Ragdolls UK Charity	71	1743	It is appropriate to conduct pre-pregnancy checks; however in conditions causing POI in childhood, these discussions need to take place before pregnancy becomes an issue. This is because girls/families are often considering their options early on, and and it is important to set expectations, especially about the risks and care needed. Also, because the amount of fertility tourism means that IVF is not always taking place in countries where rigorous pre-pregnancy checks for POI are the norm. In addition, there is a real need for more representative sex education in schools that reflects that some pupils are likely to not menstruate/go through puberty in synch with peers and a significant number of people (1/6 couples) will experience infertility during the usual childbearing years. This may not be relevant to the work of this guideline group but nevertheless it is important.	We agree on the importance of fertility awareness and education, but agree with the reviewer this is not necessarily something to be addressed in the guideline on POI
Ragdolls UK Charity	77	1881	Guideline on pre-pregnancy counselling - Guidance is also needed that risk factors change throughout life. Girls (and their families) who know from a young age that they are infertile are often thinking about their reproductive options early on. Plans that seem feasible when young might have to change based on information found during pre-pregnancy checks. Environment of family could also have an effect. Such things as diet and general lifestyle choices could alter the effectiveness of reproductive options over the years.	We agree on the importance of fertility awareness and education, but discussion of these issues was outside the scope of the current guideline on POI
Ragdolls UK Charity	112	3127	Personalised care, including psychological support, should be accessible to women with POI This is a point where peer support and family support have a role to play and it would be useful for clinicians to be able to refer to patient support groups if needed.	We thank for the comments but we prefer to stay general mentioning psychological support in the reccomendation. We mention supportive relationships in the justification
Ragdolls UK Charity	116	3272	The guideline group recommends that HCPs routinely enquire about sexual wellbeing and sexual function in women with POI. If an enquiry elicits a need or request for care, there needs to be a clear pathway of referral if a woman needs additional medical or psychosocial support.	Absolutely right and we include a possible pathway in figure 12

Ragdolls UK Charity	178	5443	What preparations, mode of delivery and doses of estrogen should be used? It is good to see there is a consensus on the preferred medication for pubertal induction. We agree that if puberty is not in synch with peers, it can be very stigmatizing. We ask clinicians to note that transdermal patches are visible ways of delivering medication and it is not always possible to conceal them, as it is with pills. Patches that are visible, eg during school swimming and sports lessons, are likely to need explanation to peers and teachers, which can prompt sharing information that a girl might wish to keep private. It is important to offer support for the girl and her family and the opportunity to normalize her experience of puberty within a peer group of girls with TS.	All types of estrogen can be used, but, if avalaible, it is recommende to use transdermal estrogen for induction of puberty. During adulthood, both oral and transdermal applications can be used.
British menopause society			Include reference to HRT not being contraceptive and to offering advice on this to women with POI who are trying to conceive naturally	We agree with the reviewer and have added a recommendation as suggested.
British menopause society			The guidance uses the term 'usual age of the menopause'. Assuming this is referring to the average age of menopause, consider clarifying in the early part of the document when first used.	The introduction of the guideline includes a section "terminology" which clarifies the term "usual age menopause"
British menopause society	222		Consider adding: Research on the role of AMH in diagnosis of POI / prediction of menopause.	This is a good suggestion and we have now added it as a research recommendation.
British menopause society	223		Consider adding research on other effects (other than libido related) of testosterone.	We thank for the comment and have added a research recommendation reading "Studies should evaluate the efficacy and safety of testosterone treatment on several domains of health in women with POI."
British menopause society			In women who have had BSO when they talk about HT they really should include testosterone replacement in these women as a major source of androgens has been removed	We thank for the comment and have tried to state this more clearly
British menopause society	23	170	The term 'ovarian reserve' encompasses both the quantity and quality of primordial follicles. Women 170 with low ovarian reserve often respond poorly to ovarian stimulation resulting in retrieval of fewer 171 oocytes, producing poorer quality embryos and reduced implantation rates and pregnancy rates. 172 Incidence of poor ovarian response over all assisted conception cycles ranges from 5 to 35% (173) Consider re-phrasing to indicate that the term ovarian reserve mainly reflects oocyte quantity as a number of studies suggest age is the main reflection of oocyte quality with pregnancy probabilities in women with low ovarian reserve (both with natural conception and assisted conception) correlating more with age. This is also supported by studies showing that the risk of miscarriage in women with POI appears similar to age matched controls with normal ovarian function.	We have addressed this comment in the text.

Svetlana Dubrovina	14	rec 60	This definition has to be published with caution, COC could be recommended for women with POI who do not want to get pregnancy but for bone protection it is not a good option, because COCs do not save bone mineral density according some results («Compared with participants who never used oral contraceptive pills, those who did use oral contraceptive pills had a lower lumbar BMD» Zhang H, Ma K, Li RM, Li JN, Gao SF, Ma LN. Association between testosterone levels and bone mineral density in females aged 40-60 years from NHANES 2011-2016. Sci Rep. 2022;12(1):16426. Published 2022 Sep 30. doi:10.1038/s41598-022-21008-7. «Compared with participants who never used oral contraceptive pills, those who did use oral contraceptive pills had a lower lumbar BMD.»	The studies indicating decreased BMD with COC are with non-continuous COC use. Observational study indicates that bone density is maintained with continuous COC use but not usual (ie non-continuous) COC use. The study quoted does not specifically involve a POI population and the pattern of use of COC is not defined. The recommendation says that the COC should be used continuously if it is used but has been amended to provide greater clarity
Svetlana Dubrovina	16	rec 89	It is necessary to determine the duration of «short term treatment»	We have not added a clarification as data vary, but this is discussed in the text
Svetlana Dubrovina	66	1539	Investigators are uncertain of the effect of an oral or vaginal administration route on uterine volume and endometrial thickness 14 or 21 days of administration (1 RCT, N = 20; very low-certainty evidence). The study reported no other relevant outcomes (including adverse events). Investigators are uncertain of the effect of conjugated oral oestrogens compared to transdermal 17ß-oestradiol (mean deference (MD) -18.2 (mL), 95% confidence interval (CI) -23.18 to -13.22; 1 RCT, N = 12; very low-certainty evidence) on uterine volume, measured 12 months of treatment. The study reported no other relevant outcomes (including adverse events). Craciunas L, Zdoukopoulos N, Vinayagam S, Mohiyiddeen L. Hormone therapy for uterine and endometrial development in women with premature ovarian insufficiency. Cochrane Database Syst Rev. 2022 Oct 6;10(10):CD008209. doi: 10.1002/14651858.CD008209.pub2. PMID: 36200708; PMCID: PMC9536017.	Thank you for this, we have now included this review in the text.
Svetlana Dubrovina	84	2118 - table	HRT and ORC are appropriate… Counterargument: RCT of 36 women with POI has shown MHT (oral) superior to COC increase in BMD in lumbar spine after 2 years of treatment (+0.050 g/cm2; 95% confidence interval 0.007–0.092; P=0.025). Cartwright B, Robinson J, Seed PT, Fogelman I, Rymer J. Hormone Replacement Therapy Versus the Combined Oral Contraceptive Pill in Premature Ovarian Failure: A Randomized Controlled Trial of the Effects on Bone Mineral Density. J Clin Endocrinol Metab. 2016 Sep;101(9):3497-505. doi: 10.1210/jc.2015-4063. Epub 2016 Jun 24. PMID: 27340881.	Figure 11 algorithm has been revised. Cyclic COC was used in this study which may contribute to the lower effect on BMD. Continuous COC use was associated with increased BMD as examined in the Costa systematic review. We agree that HRT has a greater effect on BMD in women with POI and should be used preferentially. However, some women with POI may choose to use the COC hence the recommendation that it be used continuously. Non-use of estrogen is associated with bone loss.
Svetlana Dubrovina	86	2204 - table	HRT and ORC are appropriate… Counterargument: RCT of 36 women with POI has shown MHT superior to COC increase in BMD in lumbar spine after 2 years of treatment (+0.050 g/cm2; 95% confidence interval 0.007–0.092; P=0.025). Cartwright B, Robinson J, Seed PT, Fogelman I, Rymer J. Hormone Replacement Therapy Versus the Combined Oral Contraceptive Pill in Premature Ovarian Failure: A Randomized Controlled Trial of the Effects on Bone Mineral Density. J Clin Endocrinol Metab. 2016 Sep;101(9):3497-505. doi: 10.1210/jc.2015-4063. Epub 2016 Jun 24. PMID: 27340881.	Figure 11 algorithm has been revised. Cyclic COC was used in this study which may contribute to the lower effect on BMD. Continuous COC use was associated with increased BMD as examined in the Costa systematic review. We agree that HRT has a greater effect on BMD in women with POI and should be used preferentially. However, some women with POI may choose to use the COC hence the recommendation that it be used continuously. Non-use of estrogen is associated with bone loss.

Svetlana Dubrovina	132	3921	Oral CEE, oral E2, and transdermal estradiol have shown similar GIE risk after all adjustments. (SEE TABLE) Crandall CJ, Hovey KM, Andrews C, Cauley JA, Stefanick M, Shufelt C, Prentice RL, Kaunitz AM, Eaton C, Wactawski-Wende J, Manson JE. Comparison of clinical outcomes among users of oral and transdermal estrogen therapy in the Women's Health Initiative Observational Study. Menopause. 2017 Oct;24(10):1145-1153. doi: 10.1097/GME.0000000000000899. PMID: 28697036; PMCID: PMC5607093.	The principle refers specifically to first pass hepatic effects/VTE, not the global index event (GIE), Therefore, we did not change the text.
Svetlana Dubrovina	135	402 4	In the French E3N cohort study, 2354 cases of invasive breast cancer occurred among 80 377 post-menopausal women during 8.1 years of follow-up.1 Compared with MHT 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).1 Compared with MHT never-use, the risk for all breast cancers associated with combined MHT varied according to progestogen type:1 • 1.00 (0.83–1.22) for E/progesterone • 1.16 (0.94–1.43) for E/Dydrogesterone • 1.69 (1.50–1.91) for E/other progestogens. Incidence of breast cancer subtypes with use of MHT was assessed in 80 391 post-menopausal women, in which 2265 invasive cases of breast cancer occurred.2 Overall, 68.9% of cancers were ductal and 19.8% lobular.2 Compared with never-use of MHT, Estradiol/Dydrogesterone was associated with a significant increase in risk of lobular carcinoma (relative risk [RR] 1.7; 95% CI 1.1, 2.6), with increased risk with longer duration of treatment.2 E/other progestogens was associated with significant increases in risk of ductal (RR 1.6; 95% CI 1.3, 1.8) and lobular (RR 2.0; 95% CI 1.5, 2.7) carcinomas compared with never-use of MHT.2 The authors concluded that the findings suggest that choice of progestogen component for MHT may be an important factor regarding breast cancer risk. References 1. Fournier A, et al. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. Breast Cancer Res Treat. 2008;107:103-111. 2. Fournier A, et al. Use of different postmenopausal hormone therapies and risk of histology- and hormone receptor-defined invasive breast cancer. J Clin Oncol. 2008;26:1260-1268. Finnish cohort study – 20093 estradiol/dydrogesterone was not associated with a significant increase in risk of breast cancer vs no MHT (incidence ratio 1.13, 95% CI 0.49, 2.22) after 5 years treatment 3. Lyytinen H, Pukkala E, Ylikorkala O. Breast cancer risk in postmenopausal women using estradiol–progestogen therapy. Obstet Gynecol. 2009;113:65–73.	We have added the reference to the text.

Svetlana Dubrovina	136	4050	A follow-up study with a nested case-control analysis conducted using the UK General Practice Research Data (GPRD).1 Three study groups were considered: (1) women below 70 years of age who had received at least one prescription of any Estradiol/Dydrogesterone dosage (n = 4658); (2) frequency-matched women (matched on year of first MHT prescription and age) who received at least one prescription for other MHT (n = 30 048); (3) women who had never received MHT, matched on age at start of follow-up (n = 34 706). Women were followed up until they developed a first-time diagnosis of a gynecological cancer of interest, died, left the practice or reached the end of follow-up in the database. Estradiol/dydrogesterone combination therapy was associated with lower breast, ovarian and cervical cancer risks compared with other MHT formulations or non-users. Estradiol/dydrogesterone use was associated with a lower risk of breast cancer compared with users of other MHT medications, even after 6 years of use. Schneider C, Jick SS, Meier CR. Risk of gynecological cancers in users of estradiol/dydrogesterone or other HRT preparations. Climacteric. 2009;12:514–524	We have added the reference to the text.
Svetlana Dubrovina	140	4158	For women with BRCA1/2 mutations after RRBSO, without a personal history of breast cancer oral estradiol + neutral progestogens (dydrogesterone, MVP) can be also proposed. 1. Fournier A, et al. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. Breast Cancer Res Treat. 2008;107:103-111. 2. Fournier A, et al. Use of different postmenopausal hormone therapies and risk of histology- and hormone receptor-defined invasive breast cancer. J Clin Oncol. 2008;26:1260-1268. 3. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of breast cancer: nested case-control studies using the QResearch and CPRD databases. BMJ. 2020 Oct 28;371:m3873. doi: 10.1136/bmj.m3873. PMID: 33115755; PMCID: PMC7592147.	We agree that dydrogesterone can be an option in these women and have amended the text accordingly

Svetlana Dubrovina	140	4158	For women with hypertension as a risk factor to VTE or CVD event oral estradiol+dydrogesterone\MVP could be proposed. According to E3N Data estradiol + dydrogesterone/progesterone are not associated with risk of hypertension development. Madika AL, MacDonald CJ, Fournier A, Mounier-Vehier C, Béraud G, Boutron-Ruault MC. Menopausal hormone therapy and risk of incident hypertension: role of the route of estrogen administration and progestogens in the E3N cohort. Menopause. 2021;28(11):1204-1208. Published 2021 Sep 27. doi:10.1097/GME.0000000000001839 For women with Diabetus Mellitus Oral Estradiol + Dydrogesterone could be preferred. 1. Salpeter SR, Walsh JM, Ormiston TM, Greyber E, Buckley NS, Salpeter EE. Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women. Diabetes Obes Metab. 2006 Sep;8(5):538-54. doi: 10.1111/j.1463-1326.2005.00545.x. PMID: 16918589. 2. Slopien R. et al. Menopause and diabetes: EMAS clinical guide. Maturitas 117 (2018) 6–10 A recent publication from South Korea (a retrospective cohort study based on national health insurance data and cancer screening data from 2002 to 2019), included postmenopausal women older than 40 years (330,771 women in the MHT group and 798,550 women in the control group), and evaluate use of MHT and the risk of type 2 diabetes mellitus. There was an increased risk of type 2 diabetes mellitus in the groups that used tibolone, estrogen only (either topical or oral), estrogen + progestogen combined by the physician, but not with manufactured combinations of estrogen + progestogen. (SEE PROVIDED HR chart AND TABLE) As main conclusion, the authors highlight that "MHT, including tibolone, which is currently the most prescribed agent, increased the risk of T2DM; however, CEPM (combined estrogen plus progestin by the manufacturer) did not increase the risk of T2DM. Only tibolone increased the risk of T2DM in participants older than 70 years." Reference: Yuk JS, Kim JM. Menopausal hormone therapy and the risk of type 2 diabetes mellitus: Health Insurance Database in South Korea-based retrospective cohort study. Menopause. 2023 May 1;30(5):497-505. doi: 10.1097/GME.0000000000002170. Epub 2023 Mar 12. PMID: 36917757	We agree that dydrogesterone can be an option in these women and have amended the text accordingly
Femi Janse			Thank you for this excellent update of the POI guideline!	Thank you for this comment
Femi Janse	44	907	Table II is mentioned; this should be Table III	We have corrected and double-checked the labelling of all tables and figures in the final version.
Femi Janse	46	935	Genetic counselling. I agree with the GDG that this should be performed in which implications and limitations of genetic testing should be explained. By whom should this be performed? Clinicians may not always be trained in such way that they can provide this information well enough. This holds especially true for counselling regarding the implications of NGS testing. Should a woman be referred to a clinical geneticist?	Pretest information's before genetic testing can be given by the clinician just as for FMR1 gene studies. If the NGS or FMR1 study is positive genetic counselling should be performed by a geneticist. This has been added to the text.

Femi Janse	47	974	Specific gene variant testing. Could the GDG perhaps advice for which women with POI NGS POI gene panels should be investigated? For example: - younger age at diagnosis of POI - multiple affected family members?	The NGS panel should be proposed for all unexplained POI, together with FMR1 studies. This was added to the text.
Femi Janse	47	992-997	Why does the GDG not advice to follow (or adopt) the French position statement?	The French position is possible as there is a French Plan Genomic Plan supported by the French Ministry. It might be adopted as soon as other countries have and adequate access to NGS.
Femi Janse	50	1103 - 1117	How about incorporate anti-TPO testing at baseline; if it is negative; I would assume 5-yearly TSH screening seems to be avoidable.	There is consensus that TSH is a better predictor of thyroid dysfunction, while TPO antibodies provide confirmation of thyroid autoimmunity. TPO antibodies should also be considered in patients with subclinical hypothyroidism as it can provide information on rate of progression to treatment-requiring hypothyroidism. Of patients with subclinical hypothyroidism (with elevated TSH), 4–5% per year with pos TPOAb progress to overt hypothyroidism compared with 2–3% per year for patients without TPOAb. These patients are however identified by elevated TSH levels. The serum concentration of TPOAb may change over time but repeated measurements are generally not recomended. 1. Dwivedi SN, Kalaria T, Buch H. Thyroid autoantibodies. J Clin Pathol. 2023;76(1):19-28. doi:10.1136/jcp-2022-208290 2. Jonklaas, J., et al., Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement. Thyroid, 2014. 24(12): p. 1670-751 3. Garber, J.R., et al., Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Thyroid, 2012. 22(12): p. 1200-35

Femi Janse	84	2117 Fig 11	Blood test: UEC, CMP, LFT, TSH, 25hydroxy vit D: Please comment on this in text further on. I don't see any evidence in the guideline to support testing all of the above. As the GDG notes page 85 lines 2142-2167: lifestyle/ dietary advise for vitamin D and calcium; this does not support regular blood tests.	The investigations cited form part of the "Initial bone health evaluation" in the algorithm and only require repeat testing based on individual assessment. The investigations form part of screening for osteoporosis risk factors. LFTs, UEC, TSH are also part of the initial assessment to determine presence of co-morbidities and choice of hormone therapy. Additional investigations listed are suggested to screen for secondary causes of osteoposis if low bone density identified on DXA scanning. The figure has been amended.
Femi Janse	89	2288	Daily dose at least 2 mg oral estradiol or 100 mcg transdermal estradiol to optimize bone density. I wonder, did the GDG identify any evidence to support lower estradiol dosages in women in whom BMD at baseline is normal and who do not need to increase BMD but rather keep it within normal ranges?	The study of Gazarra 2020 (DOI 10.1097/gme.0000000000001592) observed that use of 1mg estradiol or 0.625mg CEE was associated with decreased BMD over 2 year time period in women with POI with normal BMD at baseline (z scores all>-2.0). The prospective study of Jiang in women post RRBSO also with normal BMD at baseline indicated that HT at usual doses (1mg oral or 50mcg TE) did not prevent bone loss at the LS at 24 months follow-up although the magnitude of change was small (-2.3%). It is important to remember that many women with POI may not have acheived peak bone mass and therefore an increase in BMD is desired. Further research is required to confirm the optimal dose and determine if estrogen dosing should change across the life course.
Femi Janse	102	2736	Why should lipid and glucose levels be monitored annually? I don't see any papers cited to provide evidence to support this laboratory testing nor at this frequency; as the GDG itself states further on, there is no supporting evidence. Please try to provide any background how the GDG decided to recommend this annual testing. There are no validated tools for screening CVD risk in women with POI or Turner Syndrome. Conventional screening tools are not suitable for women with POI as they are at increased relative risk for cardiovascular disease as compared to age-matched healthy women. Estrogen deficiency at young age adds to the 'lifetime' risk for CVD. However, screening for cardiovascular risk factors at diagnosis may be indicated as lifestyle measures during pre-menopause improve health in later years.	We have reformulated the recommendation, now stating; The guideline group recommends that all women with POI should have a lipid profile and diabetes screening at diagnosis. Thereafter, frequency of measurement should be based on the presence of hyperlipidaemia, hyperglycemia and additional risk factors or global cardiovascular risk.
Femi Janse	146	4399-4404	Why does the GDG comment on doses of NETA and MPA while evidence was also provided earlier on (p143 4252-5254) that these prescriptions are associated with increased breast cancer risk? May I suggest to remove these prescriptions (also from table VIII)	NETA / MPA are included in the guideline because in some countries other progestogens may not be available.
Ahmed Samy Abdel-Azim Saad	23	178	We have subgroups of patients with regular menses or polymenorrhea (short menstrual cycles) presented with POI. Also we have groups with low AFC & low AMH with normal gonadotropins. So, these should be included as clinically speaking they are POI patients.	We have expanded the justification to clarify this point

Ahmed Samy Abdel-Azim Saad	35	563	Clinically, polymenorrhea may be added. Any change in the normal menstrual cycle of the patient (menstrual irregularity) should be investigated. Ultrasound, if have low AFC of great significance more than the lab. testing	We added a sentence to the justification that women with POI may have low ovarian volume or low AFC but ultrasound not needed to make diagnosis. It might be good if we have a few more references to support the low volume / low AFC statement. I found one but can keep looking.
Ahmed Samy Abdel-Azim Saad	36	623	Low AMH levels can occur even before the high gonadotropins and is indicative of POI that already existed if induction of ovulation is warranted.	We agree that low AMH can occur without a high FSH level, and we discuss that the clinical presentation can be fluctuant (line 570) and that AMH testing may be indicated under those circumstances.
Ahmed Samy Abdel-Azim Saad	51	1143	We cannot depend on TSH alone in cases of total thyroidectomy. So, in such cases we need to measure also Free T3 & T4	There are medical conditions where testing/monitoring thyroid function by TSH is not functional, such as in pituitary failure. These are however very rare cases. The guideline is ment to be clinically relevant and applicable to the general POI population. In order to be clear we have to make general recomendations.
Ahmed Samy Abdel-Azim Saad	88	2285	Vit. K should be added for any form of calcium & vit. D supplementation for better metabolism of the calcium and deposition in the bone itself not in the arteries	No evidence regarding Vitamin K use in women with POI was found in the systematic literature search. The section on non-pharmacological approaches has been amended to include Vitamin K. Furthermore, the research recommendations have been ameded to include Vitamin K
Ahmed Samy Abdel-Azim Saad	95	2470	Vit. K should be added for any form of calcium & vit. D supplementation for better metabolism of the calcium and deposition in the bone itself not in the arteries	No evidence regarding Vitamin K use in women with POI was found in the systematic literature search. The section on non-pharmacological approaches has been amended to include Vitamin K. Furthermore, the research recommendations have been ameded to include Vitamin K
Ahmed Samy Abdel-Azim Saad	125	3659	This is a conditional recommendation and the use of any lubricants and moisturizers are still lacking evidence so we should also include other devices which have some evidence or at least in the context of research as use of phytoestrogens,PRP injecetion in the submucosa of the vagina or HIFU or laser devices all with the same principle is to induce breaking then reformation and regeneration of collagen synthesis in the submucosa of the vagina	We thank for the comments. We include this concept in the research recommendations under the umbrella of other non-hormonal approaches.
Jennifer Merrill			Thank you for writing this guideline to bring attention to POI and attempt to improve care for this patient population. The literature review is thoughtful and detailed. It is a significant improvement from other guidelines I have read on the topic.	Thank you for this comment
Jennifer Merrill			Many of the topics (bone health, cardiovascular risk, etc) addressed in these guidelines may not be addressed by reproductive endocrinologists in clinical practice. It would be great to have buy-in from the Endocrine Society and/or other parties who care for these patients across the lifespan.	The guideline group has actively sought endorsement for the guideline from other organisations representing professionals caring for women with POI prior to the start of the work, and we will continue to do so after the finalisation.

Jennifer Merrill	9	58	Do you mean both primary and secondary amenorrhea? Although Europe has decided to call it premature ovarian insufficiency, elsewhere P stands for Primary. Primary, secondary, tertiary are used throughout endocrine nomenclature when the hypothalamus/pituitary is involved. I really appreciate that you have otherwise de-emphasized what the P stands for to center focus on the disease.	The guideline group, including American representatives, agreed to use the term "premature ovarian insufficiency". However, to improve uptake, we have used the abbreviation "POI" as much as possible throughout the guideline
Jennifer Merrill	12	rec 14	I would suggest that genetic counseling should be offered before karyotype and FMR1 testing. If there is potential for genetic discrimination in any form, this should be discussed with the patient before the testing is ordered (Eg. US physicians may use this guideline and US law does not prohibit genetic discrimination for some important types of insurance). The patient's decision to decline this testing should not affect their ability to access the rest of POI care.	The karyotype is first performed with prior pretest information. If abnormal no other genetic testing will be performed. Specific genetic counseling for FMR1 and NGS genetic studies should be performed before the corresponding blood sample informing the patient of the nature of the tests, their implications and possible associated comorbidities. It is clear that the patient's refusal is possible and in no way affects access to other care as with any genetic study.
Jennifer Merrill	12	23	Most primary care physicians can diagnose and treat hypothyroidism. There is a great shortage of medical endocrinologists in some countries, so I would suggest that endocrine referral is not needed for this unless the referring physician is not planning to assume care for POI or there are other endocrine concerns.	The guideline group agrees with this comment and the text and recommendation have been changed accordingly.
Jennifer Merrill	23	166	Please clarify the difference between diminished ovarian reserve and biochemical POI. Are you just describing AMH and AFC as the markers of diminished ovarian reserve? Is it a clinical diagnosis? References: 1. Nelson LM. Clinical practice. Primary ovarian insufficiency. N Engl J Med 2009; 360:606.	Diminished ovarian reserve is a clinical term, which is not discussed in detail here as it is not the topic of this guideline. For more information on DOR, the reader is referred to the ESHRE guideline on Ovarian Stimulation.
Jennifer Merrill	27	306	Thank you for your detailed discussion of risk factors for POI. I was interested to see nulliparity as a risk factor. I wonder if there is concern for confounding, since many women with POI may have suffered from infertility prior to diagnosis.	We have added a sentence stating "However, POI is associated with infertility or subfertility which may have a confounding role in the findings of parity and age of menopause" to address this comment
Jennifer Merrill	32	493-499	Thank you for including this discussion of the wide variety of symptoms that may be experienced by women with POI. Many of these symptoms are nonspecific and experienced frequently in the population. Could you clarify the rate of these symptoms in the general female population? For other endocrinopathies, it is well known that symptoms do not correlate strongly with the presence or severity of disease. (see Canaris et al, 2000 - https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/415184).	We have added the findings from a study comparing premature menopause and controls. Line 618 "Menopausal symptom subscale domain scores, including psychological, somatic vasomotor and sexual symptoms, were higher (indicating greater "bother") in women with premature menopause compared to premenopausal controls in a cross-sectional study {Gibson –Helm, 2014}. Difficulty sleeping, loss of interest in most things, vasomotor symptoms, feeling unhappy, crying spells, irritability and loss of interest in sex were the individual symptoms more prevalent in women with premature menopause compared to controls {Gibson-Helm, 2014}"

Jennifer Merrill	34	531	This may be a discrepancy between American and European English, but favor the word "elevated" gonadotropins, rather than "raised"	We have adapted this
Jennifer Merrill	34	547	For Goldenberg 1973 study, please clarify the kind of ovarian biopsies. Were they oophorectomy, FNA, core needle? This has important implications for women with POI seeking fertility. This study is not open access so I was unable to verify. This is important due to the multiple case reports of women with much higher FSH values who conceived with their own egg.	We have added further information to the text.
Jennifer Merrill	40	751	It seems more accurate to state that most rather than all women with 45XO Turner's syndrome have streak gonads and primary amenorrhea. There are quite a few reports of non mosaic 45XO women having spontaneous puberty and conceiving their own offspring. A sampling of studies with spontaneous pregnancy occurring in 45XO: Bernard, V, Donadille, B, Zenaty, D, et al, Spontaneous fertility and pregnancy outcomes amongst 480 women with Turner syndrome, Human Reproduction, Volume 31, Issue 4, April 2016, Pages 782–788, https://doi.org/10.1093/humrep/dew012 Taylor, A. E., Adams, J. M., Mulder, J. E., et al (1996). A randomized, controlled trial of estradiol replacement therapy in women with hypergonadotropic amenorrhea. The Journal of clinical endocrinology and metabolism, 81(10), 3615–3621. https://doi.org/10.1210/jcem.81.10.8855811 Hadnott, TN, Gould, HN, Gharib, AM, Bondy, CA. 2011. Outcomes of spontaneous and assisted pregnancies in Turner syndrome: the U.S. National Institutes of Health experience, Fertility and Sterility; 95 (7): 2251-2256. https://www.sciencedirect.com/science/article/pii/S0015028211005152	Thank you so much for the references. The text has been modified and the references added.
Jennifer Merrill	44	919	I suggest pseudohypoparathyroidism type 1A be listed together in one line with pseudohypoparathyroidism, which is one word.	We have adapted this in the table

Jennifer Merrill	46	921	I think this is likely mentioned in other guidelines elsewhere, but I would suggest that it is equally important to mention the significant drawbacks of genetic testing and harm that it can cause the individuals diagnosed with a genetic disease. Careful counseling should be undertaken before this testing is recommended as the harm may outweigh the benefit and is permanent. This should be mentioned early and often in the guideline, rather than deep in the text, so that patients are not harmed by genetic testing without full nderstanding. Some harms/risks include: - Risk of genetic discrimination - Cannot predict whether a person will develop a condition, but can cause increased anxiety related to uncertainty - Patient may feel defective or broken - Change in family dynamics and relationship with spouse - For many diseases, the relationship between genotype and phenotype is still unclear, and this may unnecessarily increase the cost of and delay care for the patient. Genetic testing should only occur after extensive genetic counseling and in people who deeply want to know and not be categorized as "idiopathic". This can vary from person to person based on their personality. Genetic Alliance; The New England Public Health Genetics Education Collaborative. Understanding Genetics: A New England Guide for Patients and Health Professionals. Washington (DC): Genetic Alliance; 2010 Feb 17. Chapter 7, Psychological & Social Implications. Available from: https://www.ncbi.nlm.nih.gov/books/NBK132186/ Donohue KE, Gooch C, Katz A, Wakelee J, Slavotinek A, Korf BR. Pitfalls and challenges in genetic test interpretation: An exploration of genetic professionals experience with interpretation of results. Clin Genet. 2021 May;99(5):638-649. doi: 10.1111/cge.13917. PMID: 33818754; PMCID:PMC8489659. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8489659/	We are here in a monogenic disease and all the genes studied are indeed involved in POI. Thorough genetic counseling is recommended before FMR1 and NGS genetic study. The signed consent of the patient is necessary to perform the test which will only be performed after information and agreement of the patient and eventual family members. In the Donohue et al. article, interpretation pitfalls are due to misclassifications of variants (variants of unknown significance), lack of genetic counseling, unclear reporting wording, and suboptimal communication between providers. Communication between clinicians, specialists, the molecular geneticist and the geneticist are indeed essential in this process.
Jennifer Merrill	47	998	I would suggest that not enough is known about the clinical significance of low-level mosaicism for this to be a strong recommendation. Women should have the right to reject this testing. Newer data suggests that women with low level mosaicism likely have no phenotypic differences other than POI, so identifying mosaicism may delay their care and increase expense unnecessarily. Snyder, E. A., San Roman, A. K., Piña-Aguilar, R. E., Steeves, M. A., McNamara, E. A., Souter, I., Hayes, F. J., Levitsky, L. L., & Lin, A. E. (2021). Genetic counseling for women with 45,X/46,XX mosaicism: Towards more personalized management. European journal of medical genetics, 64(3), 104140. https://doi.org/10.1016/j.ejmg.2021.104140 Tuke, M.A., Ruth, K.S., Wood, A.R. et al. Mosaic Turner syndrome shows reduced penetrance in an adult population study. Genet Med 21, 877–886 (2019). https://doi.org/10.1038/s41436-018-0271-6	We agree with the reviewers that these are essential considerations and we have adapted the text accordingly

Jennifer Merrill	47	1000	If not restricting karyotyping based on age, I suggest discussing that that age related x chromosome loss in peripheral lymphocytes is a fairly common finding. Russell, L. M., Strike, P., Browne, C. E., & Jacobs, P. A. (2007). X chromosome loss and ageing. Cytogenetic and genome research, 116(3), 181–185. https://doi.org/10.1159/000098184	We agree with the reviewers that these are essential considerations and we have adapted the text accordingly
Jennifer Merrill	50	1101	Is lab testing for CYP450CC autoantibodies commercially available in Europe? This search term yielded no results when I searched the major reference labs in US – Mayo, Quest, Labcorp. If making this recommendation, please provide information on how this test can be obtained.	For now SCC antibody testing in not comercially available but it is done in research laboratories in some European countries (for example Norway, Sweeden, Italy). This confirmatory test applies to very few of the POI women (only for autoimmune POI in women with Addison's disease). These patients should follow guidelines and recommendations for Addison's disease and therefore not too many details were included in the POI guideline about this. Still, the text has been amended to clarify that the test is for now only available in selected research laboriatories.
Jennifer Merrill	51	1162	Thank you for discussing adrenal testing. I was wondering why testing aldosterone levels is not recommended. I typically interpret renin, aldosterone (and potassium) together, and aldosterone is secreted by the adrenal	Thank you for pointing this out. The text has been supplemented based on updated recommended screening guidelines for Addison. We have added "Furthermore, low aldosterone and high renin and low dehydroepiandrosterone sulphate concentrations are also helpful indications of adrenal insufficiency."
Jennifer Merrill	53	Figure 7; line 1180	Informed consent should occur before genetic test	We have amended the figure to include Informed consent prior to genetic testing
Jennifer Merrill	57	1252	"They should watch for symptoms and signs of POI…"	We have adapted the sentence in line with the comment
Jennifer Merrill	60	1325 - 1371	Thank you for this detailed discussion of the research to date. It would be helpful to specify that these cohort studies did not evaluate whether the women had hormone replacement therapy.	We have added this information to the text.
Jennifer Merrill	61	1373 - 1384	Huan et al excludes women on estrogen therapy. I was unable to access full text for the other studies, but I do think it is important to mention whether women in these studies were on estrogen replacement or not. Failing to mention this could unnecessarily scare women who develop POI who are taking estrogen replacement about their risk of early mortality and cause health care providers to give them incorrect information about the disease. Line 1402 alludes to this, but I think it would be important to include in the description of the studies.	We have added a comment to the respective study in the text.
Jennifer Merrill	67	1561	Yaron et al does not mention how the women with TS were diagnosed, but given the time when it was done, the women included likely had phenotypic TS, rather than the low-level mosaicism in healthy adults with POI that developed later in life that are often detected today.	The Yaron study is based on a karyotypic diagnosis rather than purely phenotypic.

Jennifer Merrill	67	1565	Thank you for recognizing that egg donation is the most effective way to help these women conceive and can save time and money. However, it is important for the guideline to be sensitive to the fact that oocyte donation may not be an acceptable cure for many women for personal reasons. Although this should be recommended as a reliable way to achieve pregnancy, it is important to continue to provide assistance to women who would want assistance achieving a pregnancy with their own egg, as long as they are counseled that this may not (probably will not) be possible, and given accurate statistics about this. Additionally it seems odd for a European body to recommend a treatment that is not legal in several European countries. Ghelich-Khani, S., Kazemi, A., Fereidooni-Moghadam, M. et al. Psycho-social experience of oocyte recipient women: a qualitative study. BMC Women's Health 21, 406 (2021). https://doi.org/10.1186/s12905-021-01562-4 https://bmcwomenshealth.biomedcentral.com/articles/10.1186/s12905-021-01562-4 https://bioethics.hms.harvard.edu/journal/donor-technology	Thank you, we recognise this and discuss in detail the evidence regarding the prevalence of ongoing ovarian activity and the chance of pregnancy (eg section from line 1445)
Jennifer Merrill	68	1618	Women with POI who value own-oocyte conception already experience difficulty accessing care for their reproductive goals. This guideline will make it even more difficult for them to access care, and encourages reproductive endocrinologists to abandon this patient population.	We do not see that this guideline will encourage reproductive endocrinologists to abandon such women, but it is important that both doctors and their patients are aware of the evidence.
Jennifer Merrill	68	1624	There are multiple case reports of women undergoing monitoring for oocytes that are able to achieve pregnancy. Here is an example: https://www.frontiersin.org/journals/genetics/articles/10.3389/fgene.2021.676262/full For this individual woman, pursuing monitoring and achieving a pregnancy with her own oocyte was worth it, despite the poor odds based on evidence. Please consider clarifying the statement that the follicle pool is exhausted, since some authors have found follicles in these patients. Nelson, L. M., Anasti, J. N., Kimzey, L. M., Defensor, R. A., Lipetz, K. J., White, B. J., et al. (1994). Development of luteinized graafian follicles in patients with karyotypically normal spontaneous premature ovarian failure. J. Clin. Endocrinol. Metab. 79, 1470–1475. doi: 10.1210/jcem.79.5.7962345 Hubayter, Z. R., Popat, V., Vanderhoof, V. H., Ndubizu, O., Johnson, D., Mao, E., et al. (2010). A prospective evaluation of antral follicle function in women with 46,XX spontaneous primary ovarian insufficiency. Fertil. Steril. 94, 1769–1774. doi: 10.1016/j.fertnstert.2009.10.023	We highlihgt the potential for intermittent ovarian activity and achieving pregnancy using a woman's own eggs.
Jennifer Merrill	74	1762	Thank you for suggesting that earlier studies may overestimate cardiac risk in pregnancy for women with Turner Syndrome. It may be helpful to include the only multicenter study of this which showed no mortality in 65 pregnancies. Grewal, J., Valente, A. M., Egbe, A. C., Wu, F. M., Krieger, E. V., Sybert, V. P., van Hagen, I. M., Beauchesne, L. M., Rodriguez, F. H., Broberg, C. S., John, A., Bradley, E. A., Roos-Hesselink, J. W., & AARCC Investigators (2021). Cardiovascular outcomes of pregnancy in Turner syndrome. Heart (British Cardiac Society), 107(1), 61–66. https://doi.org/10.1136/heartjnl-2020-316719	We have added this reference to the text

Jennifer Merrill	76	1832	All genetic analysis should only follow genetic counseling. Studies of TS have significant sampling bias and likely overestimate risk to a woman without clinical features of TS.	We have indeed recommended genetic counselling to all women with non-iatrogenic POI prior to genetic testing, in the respective chapter, and have further clarified this. On the comment on sampling bias, we are not aware of any literature in this respect
Jennifer Merrill	78	1898	Karyotype after genetic counseling	We have indeed recommended genetic counselling to all women with non-iatrogenic POI prior to genetic testing, in the respective chapter, and have further clarified this.
Jennifer Merrill	80	1969	I am only able to access the abstract of the Costa, et al Systematic review, but the abstract says it analyzed 16 rather than 8 studies.	Only 8 studies compared BMD in women with POI to controls
Jennifer Merrill	92	2390	I am unable to access the full text of Divaris et al., 2023, but it would be helpful to include whether the women in this meta-analysis were treated with hormone therapy.	4/6 studies included in the meta-analysis provided information on MHT use. Past/current MHT use was reported in 30%, 33% and 38% of particpants in 3 studies of Europenan/American women and 16% in one Korean study. There was no analysis between MHT users and non-users. The text has been amended.
Jennifer Merrill	93	2404	Thank you for including the Freitas et al., 2021 study, which showed no sarcopenia compared to controls in women who had been on HRT for a year. For this section it may be helpful to further delineate if the women in the studies were on HRT where possible. Women with POI will be most interested in interventions to modify their risk.	This section has been amended to provide details regarding hormone therapy use in the studies.
Jennifer Merrill	94	2465	Please consider removing the Bonnet et al., 2019 study since postmenopausal women are a different patient population than POI. Additionally, denosumab discontinuation is associated with increased fracture risk. There are only 10 years of safety data for this medication, making it a poor choice for lifelong therapy for women under 40. Anastasilakis AD, Makras P, Yavropoulou MP, Tabacco G, Naciu AM, Palermo A. Denosumab Discontinuation and the Rebound Phenomenon: A Narrative Review. J Clin Med. 2021 Jan 4;10(1):152. doi: 10.3390/jcm10010152. PMID: 33406802; PMCID: PMC7796169.	We have removed the sentence as suggested by the reviewer.
Jennifer Merrill	98	2595	Thank you for including the Bruschi et al., 1996 study. It may also be helpful to include this small study in the following section about estrogen being cardioprotective, since the women in this study who were treated with estrogen had subsequent improvement in their lipid profiles.	We have added the reference to the section regarding cardioprotection and amended to include Burgos systematic review.
Jennifer Merrill	100	2649	"...menopausal transition are associated with greater atherosclerotic changes."	This language error was corrected
Jennifer Merrill	100	2679	"estrogen decreases insulin resistance"	This language error was corrected

Jennifer Merrill	104	2797	Thank you for considering the psychological wellbeing of women in this guideline. In terms of psychosocial health, please do not conflate POI with menopause, since POI is clearly a disease state and not a natural transition. POI is much more distressing to women because of the age at which it occurs. Groff AA, Covington SN, Halverson LR, Fitzgerald OR, Vanderhoof V, Calis K, Nelson LM. Assessing the emotional needs of women with spontaneous premature ovarian failure. Fertil Steril. 2005;83(6):1734.	We refer to menopause to introduce the topic of QoL in the first paragraph. In the following paragraph we address your point, and we have included the reference mentioned. POI is not a homogenous and fixed state, and most importantly is not natural because, even when a specific cause is not identified, it occurs early in the life course and assumes the characteristics of a chronic health problem requiring long-term care.
Jennifer Merrill	107	2914	Please consider the following as potentially more sensitive language "a sample of 31435 women who had not had a hysterectomy over age 45"	Thank you now we have replaced the sentence
Jennifer Merrill	107	2938-40	Thank you for recognizing the unique trauma of POI. It would be wonderful if this point could be highlighted earlier in the paragraph/section	We thank you for the comments and have adapted the text accordingly
Jennifer Merrill	111	3083	"Involvement of the partner can help in understanding and communication."	We have rephrased thus sentence
Jennifer Merrill	112	3110	Suggest omitting "The author reported that on the whole.."	We have adapted the sentence in line with the comment
Martha Hickey			PURPOSE: The authors highlight the critical gap between the (previous) guidelines recommendation and implementation in clinical practice. Why doesn't this guideline then focus on implementation?	Implementation of the guideline will be addressed in a second step, after the finalisation of the recommendations
Martha Hickey			TRANSPARENCY. Authorship: Only the names of the guideline group are listed with no affiliations or COI. Please add affiliations (public and private). Also, for transparency, please indicate how the committee were selected and what specific skills each person brings.	The affiliation will be added in the final version. The text already includes a statement on the different expertise within the group
Martha Hickey			METHODOLOGY. There did not seem to be a methodology section or even a search strategy. Developing an evidence-based guideline requires a clear methodology indicating the research questions, how evidence was gathered, how evidence quality was graded and how the data were analysed (and by whom). This seems like a very basic omission for a clinical guideline.	The methodology is described in an annex of the guideline, and further in depth information in available in the manual for guideline devlopment and the literature report which will be published with the guideline
Martha Hickey			SEARCH STRATEGY. This was not stated. This is worrying because key papers were overlooked. Worse, when we looked up some of the references, we found that some were incorrectly reported. We did not check all the references (of course) but when we looked up references supporting unexpected statements, several were inaccurately reported. We think an independent person should have searched for the evidence (using a transparent strategy) and checked for accurate reporting	The search strategies will be included in the literature report which will be published with the guideline, We have meanwhile performed another check of the references and made a few corrections
Martha Hickey			Despite the PICO questions, the evidence presented often strayed from the question. For example, including basic and animal data alongside human evidence without clear differentiation and justification. This was confusing and often appeared selective. For example, describing data from primate models of surgical menopause as being clinical data.	The data of animal studies were removed from the guideline

Martha Hickey			EVIDENCE QUALITY: Unfortunately, almost all the evidence pertaining to clinical care after POI is low or very low quality. In many places, low-quality evidence (cross sectional or retrospective studies) is reported alongside higher quality evidence with no critical analysis of evidence quality. This lack of assessment of evidence quality undermines the content. Whilst there are few RCT, evidence from prospective observational studies is reported alongside retrospective and cross-sectional data as if they were equal quality. The guidelines state that the GRADE system was used. However, GRADE considers issues such as risk of bias, imprecision, inconsistency, indirectness and publication bias, but these are not mentioned in the guidance. Worryingly, "strong recommendations" are made based on very low-quality evidence. Despite the statement on page 225 (partly obscured by the figure) the guidelines do not seem to reflect GRADE recommendations. Throughout there was a lack of critical appraisal of the evidence and accurate allocation of evidence quality.	The reviewer is correct that in many sections the evidence is limited observational data only. Data from RCTs have been highlighted where needed, but based on often small sample sizes, there quality does not always seem to be ranked higher than observational data. This is an agreement with the GRADE approach. Formulating "strong recommendations" based on very low-quality evidence is also in agreement with the grade approach
Martha Hickey			More worryingly, there is an apparent persistent bias towards recommending (high dose) HT without sufficient supportive evidence. The potential benefits of HT are emphasized throughout without any consideration of potential risks, especially when high doses are recommended.	The comments on the bias to HT have been addressed in the HT chapter.
Martha Hickey			We were puzzled by the evidence grading system used. This was stated to be GRADE but was not. Based on Fig 16, the basis for a "strong recommendation" was described as "most people in your circumstances would want the recommended course of action". What does this mean? Who are "most people"? Does "most people" apply to clinicians or to patients? How does the committee know what "most people" want?	The statement refers to patients, which were represented in the guideline group, and who's opinion was very much considered throughout the different recommendations
Martha Hickey			We wonder if different sections of the guidance were written by different people? That might account for the variation in style and evidence appraisal throughout.	We ackknowledge difference in style across chapters, as well as in the amount in background information. While uniformity was a goal, it is considered more important to tailor the content to the audience
Martha Hickey			Overall, we felt that combining and conflating data from women with TS with those experiencing POI for other indications was clinically unhelpful and potentially inaccurate. We would favour separate guidance for TS. We note that an international TS guideline was published in 2024. Why do we need an additional TS guideline?	The great majority of data concerning pubertal induction stems from Turner syndrome research and therefore it is currently necessary to extrapolate from this body of data to other types of primary POI when issuing guidance concerning pubertal induction in these groups of patients. Admittetly, it would be great if specific sets of data was available for all separate groups of primary POI, but for now we need to rely on data from Turner syndrome. Many more aspects of Turner syndrome than just pubertal induction and treatment with estrogens are addressed in the new guidelines on Turner syndrome which are not addressed here. So we still need a separate guideline on Turner syndrome, apart from the current guideline.

Martha Hickey			The guidelines don't specifically indicate who should manage POI. Should this be a specialist or can the GP manage this? Surely clear guidelines would support ongoing management of POI in primary care.	The guideline includes a section on target users (in the introduction) reading: "The guideline covers the care provided by health care providers who have direct contact with, and make decisions concerning the care of, women with POI. ESHRE guidelines are mainly focussed on gynaecologists. However, women with POI suffer health problems that require multi-disciplinary care and are not limited to the field of gynaecology. Therefore, this guideline is also targeted at health care providers of other disciplines (e.g. general practitioners, endocrinologists, oncologists, geneticists, paediatricians, internists). "
Martha Hickey			The conclusions are inconsistent with other recent evidence-based guidelines such as the draft 2024 NICE guidelines on menopause. This is worrying since NICE has a transparent search strategy, systematic reviews and grading process. For example, NICE did not identify any long-term health benefits for HT in early menopause. We are not saying there are no health benefits, there is just no high (or even moderate) quality evidence demonstrating benefits. Yet, these ESHRE guidelines recommend high dose HT until age 50 years for the prevention of chronic disease. What is the evidence base for this recommendation? Also, since the average age at menopause is lower than 50 in many racial/ethnic groups, what is the reasoning for recommending HT until age 50 for them?	Unfortunately, we did not have access to the final versoin of the NICE guieline, even not when requested. We do want to point out that there are differences in POI and Menopause, which is why a specific POI guideline was initiated. Furthermoire, the work of NICE, while excellent methodological quality, is targeted at the UK context and not necessarily transferable to other settings. The comment on "high dose HT until age 50 years" is replied to elsewhere.
Martha Hickey	Clinical need	2	A justification for this update is poor uptake of the previous guideline. The long and unwieldy nature of this update may lead to a similar fate. Similarly, when recommendations are not based on strong evidence, clinicians and patients are less likely to follow them. A clear flow chart would help here. You could draw on the one we produced for our Lancet early menopause paper recently.	We have revised this section. The justification for the update is the outdated evidence, while the justfication for involving several societies was drawn from the low uptake. The Study from Richardson was maintained, but it was clarified that it highlights difficulties of uniformity when the care is spread across departments, rather than implementation of the ESHRE guideline in the UK.
Martha Hickey	Scope	32	Spelling mistake of Turner	Thank uou, this was corrected
Martha Hickey	PATIENT POPULATION	61	We thought early menopause was 40-44 years and menopause age 45 or above was considered normal. This is how NICE have defined early menopause. Both 40-45 and 40-44 years are used to define early menopause in this.	This is addressed in the text. We have defined early menopasue as menopause at age 40-44, consistent with other documents, but we also acknwoledge sometimes a cut off of 45 years is used
Martha Hickey	PATIENT POPULATION	61	It would be helpful to define whether the POI population includes those with spontaneous POI and iatrogenic POI at this point. Bearing in mind that short and long-term outcomes may differ. This is mentioned under terminology but for clarity should be in the patient population section. Throughout the Recs I was unclear whether they were aimed at all women with POI or just non-iatrogenic	We have added a sentence above the list of recommendations on this topic
Martha Hickey		73	International terminology is RRSO not RRBSO. BRCA1/2 has self-corrected to BRCA half.	We agree and have made appropriate changes.

Martha Hickey	LIST OF ALL RECOMMENDATIONS	78	The terminology used to describe the level of evidence was unusual. The definition of "strong" and "conditional" evidence is not presented with the recommendations which makes it hard to interpret. Did you consider using the standardized numbered levels of evidence or the GRADE system?	We have added a section to the introduction of the guideline explaining the strength of the recommendations and the grades
Martha Hickey		Rec 5	Stopping smoking and FP have not been shown to prevent POI.	The recommendation has been revised and rewritten
Martha Hickey		Rec 9	"although proper diagnostic accuracy in POI is lacking" What does this mean? If you cannot diagnose a condition how can you have a guideline on how to manage it? This suggested diagnostic criteria does not mention whether the amenorrhoea/oligo men is spontaneous.	We have revised the recommendations on diagnosis to address this and other comments.
Martha Hickey		Rec 10	Why should AMH testing be considered in the diagnosis of POI? What specifically is the diagnostic uncertainty and what threshold of AMH should be considered diagnostic?	We only recommend consideration of AMH testing where there is diagnostic uncertainty. We clearly state that AMH is not of value under most circumstances.
Martha Hickey		Rec 28	Re counselling relatives – what exactly should they be told? What is their risk of POI? This is important because Rec 31 suggests they should consider FP. This will be costly so the justification needs to be clear.	The recommendations evolve around providing information to women at risk of POI that have concerns about it. It states Some relatives may wish to consider family planning and fertility preservation options. This does not mean a general implementation of FP for all relatives of women with POI.
Martha Hickey		Ref 32	Given the low quality evidence (particularly around HRT and life expectancy after POI), I do not understand why this statement is considered "strong". The statement on page 62, line 1402 is "there are no clinical trials examining the long-term effects of HT on mortality after POI".	The low quality evidence is represented by the GRADE of the recommendation (++00). The strength of the recommendation relates to it station women "should" be informed, which is based on the evidence, but also other factors such as patient values.
Martha Hickey		Rec 33	We question the strength of evidence for recommending MHT until the "usual age at menopause" after POI. We did not read any evidence in this guideline demonstrating benefit for HRT until age 50 years. We are very concerned about this recommendation since it also conflicts with the systematic evidence search by NICE that found no benefit for HRT beyond age 44 years (and a small increase in BC risk vs non-users). The rec even says "at least" implying that longer use of HRT (beyond 50) is beneficial after POI. What is this based on?	We have slightly adapted the recommendations in reply to this comment
Martha Hickey		Rec 34	Regarding prevention of CVD, rec says "in addition to HRT…". This suggests that HRT prevents CVD after POI but evidence is not provided to support this.	The evidence for CVD and HT is provided in the cardiovascular health chapter. We don't consider this recommendation is in conflict with the evidence provided in that section.
Martha Hickey		Rec 41	We were surprised by the "strong evidence" classification that pregnancies after POI are low risk. Strong evidence is not presented for this statement. Does this include POI following uterine radiation (e.g. cervical cancer) when maternal and infant risks are high? This Ref conflicts with rec 44	The recommendation is a strong recommendation for reassuring women with POI, it does not reflect strong evidence. The evidence level was graded as low

Martha Hickey		Rec 52	Bizarre that there is insufficient evidence to demonstrate that POI increases fracture risk but that (high dose) HRT is recommended to prevent fracture!	Recently published data (Jones et al 2024) from the Australian Longitudinal Study on Women's Health indicates that women with POI/ EM (mean age 38 years) had an increased risk of osteoporosis and fracture (doi.org/10.1093/humrep/deae037). This finding has been added to the text and the recommendation was amended.
Martha Hickey		Rec 58	The language around bone is confusing. At different points terms like bone health" "bone density" "osteopenia/porosis and "fracture" are the end points. Surely the critical end point is fracture? Flicking between biomarkers and clinical end points is confusing because (of course) not all those with low bone density or even osteoporosis will develop a fracture. Also, cancer patients particularly will have other reasons (apart from POI) to explain biomarkers and even fracture. This issue is critical because it directs clinical practice. Specifically, use of high dose estrogens after POI. For many this will also require high dose progestogens. What is the justification for use of high dose estrogen? This appears to be based on "conditional" evidence. Presumably this is evidence for bone benefit. What about evidence for risk?	We agree that the terminology can be confusing but this reflects the published literature. Osteoporosis is defined as a T score<-2.5 or the presence of a fragility fracture therefore both outcomes are vaild to include. The preferred term of low bone mass (z score< -2.0) is especially relevant in younger individuals who have not yet attained peak bone mass. In postmenopausal women, two thirds of those who develop a fragility fracture have BMD in the osteopenic range. Bone density is an independent risk factor for fracture and interventions which increase bone density reduce fracture risk. As outlined in the section of HRT, prescribing should be personalised and the risks of HRT are included in this section.
Martha Hickey		Rec 58	What is an osteoporosis specialist and how accessible is this advice?	"Osteoporosis specialist" changed to endocrinologist to assist with applicability
Martha Hickey		Rec 64	How often should DXA be repeated for a woman not taking HRT?	There is no data which defines the optimal timing of bone density scans in women with POI but more scans should be performed more frequently in women not taking HT compared to women taking HT as bone loss is more likely and especilally if other risk factors for bone loss are present (for example aromatase inhibitor use). The section has been amended to include the International Society for Clinical Densitometry position statement (Kendler et al 2019) which concluded that "repeat BMD measurement should be considered sooner among those where the rate of bone loss is expected to be greater and for those whose baseline BMD is lower" with an interval of 1-3 years.The wording of recommendation 64 has been clarified.
Martha Hickey		Rec 66	Given the paucity of evidence it seems unhelpful to suggest that BTM "can be considered" without giving advice on what to measure and how to modify practice depending on the results.	Recommendation has been removed
Martha Hickey		Rec 73	Is the panel recommending that HRT should be offered for "reduced muscle mass" after POI? Does this have any supportive evidence?	The GDG is not recommending HRT for reduced muscle mass after POI and the recommendation dose not state this.

Martha Hickey		Rec 79	Guidelines state that "despite lack of evidence from RCT…". Are any of the guideline recommendations based on RCT evidence? More strange language here "HT is recommended to control future risk of CVD". What does this mean exactly? If you are saying that taking HRT after POI reduces the risk of CVD, this evidence is very scanty and specific to POI in specific circumstances. Please clarify where benefit is demonstrated.	Recommendation wording amended. There are no RCTs assessing the effects of HRT on specific CVD outcomes but do exist for surrogate markers including lipids profile, glucose metabolism and endotherial function. However, observational studies indicate an increased risk of CVD in non users of HRT both in spontaneous and surgical menopause. We have added a paragraph to the text.
Martha Hickey		Rec 67	Evidence on POI and muscle mass. Is this prospective or cross sectional? If cross sectional, how can it be classed as "strong"? Strong evidence would require prospective measures.	Consideration of muscle health is a new section in this guideline necessitating an introduction explaining the concepts of muscle health and sarcopenia to the reader unfamiliar with these concepts and references of internationally accepted guidelines provided. These conditions are recognised in the older population. The initial paragraph has been rewritten for clarity. The strength of the respective recommendation relates to the systematic review, additional cross-sectional studies and case control including those in Turner syndrome. We acknowledge the only prospective study did not show a diffence in lean body mass between women with POI/ early menopause. We have changed the recommendation to reflect the uncertainty of the evidence
Martha Hickey		Rec 79	Similarly, given the very limited evidence on HT and CVD after POI, what is the basis for recommending HT "at least until the average age at menopause"?	We acknowledged the limited evidence and have further revised the recommendation
Martha Hickey		Rec 89	Is the "strong evidence" for the safety of testosterone derived from women with POI?	This is a strong recommendation for awareness on the available/unavailable safety data for testosterone. The ++00 indicate that the data itself are observational only (low quality)
Martha Hickey		Rec 95	The statement "earlier menopause is associated with an increased risk of dementia" is bizarre. Earlier than what? We think the "strong evidence" of POI and dementia is neither "strong evidence" – largely based on a retrospective cohort study – and is based on surgical menopause rather than POI generally. This rec is not evidence based.	The recommendation was rewritten to focus on POI. The asssociation of POI with increased risk of dementia is observational but strong because consistent across many observational studies. The +ooo label indicates that the evidence is of very low quality only, but still enough to support a string recommendation for awareness
Martha Hickey		Rec 96	What are the "preventive actions" for dementia that are recommended?	We rewrote the recommendation to refer to general preventive actions for dementia.
Martha Hickey		Rec 98	What is the "strong evidence" that HT reduces the risk of dementia after POI? NICE has identified no evidence for benefits from HT after early menopause and this is a research rec. Statements like "strong evidence" should be based on high quality research – preferably RCT but at least large observational studies. These are not available for POI.	There is no mentioning of strong evidence. The recommendation is strong for offering HT based on the evidence but also benefits vs harms, patient values etc. The evidence is clearly labelled as "low quality", through the ++00 label

Martha Hickey		Rec 101	We also question the "strong evidence" that HT preserves bone health, CV and brain health. What is this derived from?	Strength of GRADE recommendations depends on a number of factors and given the evidence for risks of untreated POI and evidence derived from short term RCTs, observational data and extrapolated from the postmenopausal population it was deemed by the guideline group that a strong recommendation could be made.
Martha Hickey		Rec 103	We cannot see any evidence presented to demonstrate the benefits vs harms of continuing HRT until the average age at menopause. What is the "strong evidence" to support this recommendation?	Strength of GRADE recommendations depends on a number of factors and given the evidence for risks of untreated POI and evidence derived from short term RCTs, observational data it was deemed by the GDG that a strong recommendation could be made.
Martha Hickey		Rec 104	We are not aware of substantive evidence on breast cancer risk in women under age 40 years (POI) who take HT. The 2019 Lancet meta-analysis that showed increased risk of breast cancer in HT users from 40+ vs non users. This recommendation is not evidence based.	This is a conditional recommendation based on the principle that HT aims to restore the physiological hormonal environment in this age group. The Lancet analysis used age-matched women not on HRT as the comparator who have a lower risk of breast cancer than premenopausal women in the same age group, Other observational data in women > 40 with EM using HRT have not shown an increased risk of breast cancer.
Martha Hickey		Rec 108	The evidence that unopposed estrogen increases endometrial cancer risk is strong. Why is this rec only "suggesting" increasing progestogen dose with higher estrogen dose?	Many women experience progestogenic side effects with higher doses of progestogen and there are few data for higher doses of progestogen giving adequate endometrial protection. As such, this was only a conditional recommendation to give the opportunity for individualisation of therapy where progestogen intolerance exists where endometrial surveillance can be instituted. Upon further discussion, it was agreed to rephrase the recommendation as a GPP to be able to recommend this more strongly in the absence of data
Martha Hickey		Rec 109	Why recommend combined HT after hysterectomy and endometriosis? Potential harm and insufficient evidence of benefit	This recommendation is derived from another ESHRE Guideline, but has now been further clarified. The benefits and harms were considered in formulating the recommendation and could be consulted in the ESHRE Endometriosis guideline, as stated
Martha Hickey		Rec 113	Are the committee recommending compounded HT when nothing else is available? What evidence supports this?	The lack of evidence is visualised to the reader by formulating this as a GPP, and outlined in the recommendation. The guideline group argued that where conventional types of HT are not available the benefits for compounded HT may outweigh the risks in the POI population. It is clearly stated that in other cases compounded HT should not be used.

Martha Hickey		Rec 118	We did not see any evidence presented for the safety and efficacy of testosterone in POI. How was this "strong evidence". Compared (for example) where the evidence for non-hormonals on VMS in POI is described as "conditional". There have been no studies of testosterone or non-hormonals in POI so the evidence grading is inconsistent	We believe a strong recommendation is appropriate based on the evidence that in these women low androgens are documented and therefore there is a biological plausability that testosterone can be an option and we have data suggesting that it is safe on short term. The quality of the evidence is labelled as ++00 (low quality), being transparent that the recommendation is based on observational data only.
Martha Hickey	25	Line 240	Whilst it is helpful to consider both iatrogenic and non-iatrogenic POI, it cannot be assumed that the short and long-term consequences are the same. Throughout the guideline, the distinction between iatrogenic and non-iatrogenic POI is made inconsistently. This makes it hard to determine whether "POI" refers to iatrogenic, non-iatrogenic or both (e.g. the section "What are the risk factors for POI?"	We have clarified at the start of the guideline that POI pertains to all women with POI, unless there is a specification of iatrogenic or non-iatrogenic POI
Martha Hickey		Line 124	The guidelines are very long. We did not find the section around terminology (POI) to be helpful. We think this terminology issue was addressed in the last guideline.	While we understand the comment on the terminology, it was discussed and considered relevant to also update this section. Several stakeholder comments referring to the definitions and terminology further support the relevance of this section.
Martha Hickey	32	509	Disappointing to see the unsubstantiated statement. "In contrast, women experiencing surgical menopause usually have severe and persistent symptoms". Our large prospective controlled study of surgical menopause did not find this. Whilst 80% had VMS, most (>80%) described these symptoms as mild. Our findings are consistent with other prospective studies of surgical menopause More research is needed but please don't make statements like these based on cross sectional or no data! We think all the evidence here on symptoms is based on cross sectional data. The limitations of this should be mentioned	We have updated the text accordingly.
Martha Hickey	33	514-fig 5	We feel very uncomfortable about this figure. To our understanding, these "symptoms of POI" are not based on prospective evidence, and it is unclear what evidence they are derived from, most likely limited cross sectional data. Things like "melancholia" (whatever that is) and "joint clicking" and "mental fog" will not have been measured or defined. Is this a helpful message for those with POI? Perhaps consider "identifying the nature and severity of symptoms after POI" as a research recommendation?	We have amended the figure and clarified the data are based on retrospective studies.
Martha Hickey	37	633-fig 6	Why does the figure indicate "consider AMH" testing when the evidence presented above indicates no value in measuring AMH beyond FSH?	We have removed Figure 6 from the guideline.
Martha Hickey	39	696	Presume this refers to "non-iatrogenic POI?"	Indeed, the study of Silven 2023 excluded women with iatrogenic POI. This was clarified in the text
Martha Hickey	53	1180 - Fig 7	Idiopathic POI – Helpful diagram but bit concerned by the "risk factors may be able explain the etiology" comment. Risk factors are risk factors	We have removed the box on risk factors

Martha Hickey	58	1289	The mention of egg freezing for the relatives of those with POI may be alarming. We have recently developed and evaluated (using an RCT) a Decision Aid for elective egg freezing. The RCT showing the benefit of the DA has recently been accepted by Human Reproduction (Sandhu et al, 2024). Following publication, we plan to make the decision aid freely available. You may want to add a link to it here?	We have added the reference, but could not add the link to the decision-aid as it is not available (we emailed the authors of the paper)
Martha Hickey	58	1293 - Fig 10	The exclamation marks around "watch out for POI" are alarming and it's unclear how these may help patients.	We have adapted the figure
Martha Hickey	60	1323	POI and life expectancy – given the major limitations of the data, it is a bit disappointing that the life expectancy section fails to mention that women undergoing surgical menopause have multiple baseline risk factors for chronic disease and lower life expectancy. Those carrying BRCA1/2 PV's also have risk factors for cancer despite RRSO. Hence, it is inaccurate to report that chronic disease/mortality is fully attributable to surgical menopause. This may explain why.	We have added a paragraph in the text on risk factors or conditions that were present before the time of bilateral oophorectomy that could impact mortality.
Martha Hickey	61	1349	The section on mortality after surgical menopause is an example of the lack of consideration of evidence quality. Having indicated the large differences between cohorts, line 1336 on page 60 states "In any event, 7/8 studies confirmed that BSO at a younger (?) age was associated with increased mortality"? A large study (WHI) that did not show increased mortality after BSO was dismissed ". Therefore, the cardiovascular risk factors and conditions were most likely mediating events in the chain of causality between the original oophorectomy and mortality, and they should not have been included in the model". Where did this come from? The methodological limitations of other studies (e.g., Mayo study classing women up to age 56 years as premenopausal) are not mentioned.	We have considered this comment and the corresponding section. Apart from a few, minor clarifications, we did not consider amendments were appropriate to the text in line with this comment,
Martha Hickey	61	1361	It is difficult to plough through "a 2023 study" and "another study from Norway" when the evidence quality is not critically reviewed. Overall, our take home from this BSO and mortality section is that the data are mixed and the evidence quality is generally poor. Not sufficient to draw a "strong conclusion" from.	The evidence grading reflects that the recommendations are based on (very) low quality evidence. The strenght of the recommendations is based on evidence, but also patient values, harms and benefits, feasibility, resource implications. The annex with the literature report should help the reviewer in terms of the details of the study.
Martha Hickey	61	1372	Noting that the effect sizes of mortality after POI are very small and one reported as "marginal significance" is actually not significant. From line 1385 the HR and CI are no longer reported in the text. This makes the statements and quality of evidence hard to determine. There should be consistency.	We have added the HR and 95% CI as suggested.
Martha Hickey	61	1385	Throughout the guidance the language around evidence is sometimes inappropriate. For example, "confirmed the association" when describing studies with conflicting findings.	We took note of the comment, but the GDG agreed no adaptations were needed
Martha Hickey	62	1401	As the text states "there are no long-term trials of HT and mortality after POI". In the light of this, how can there be "strong evidence" that HT should be continued until (at least) the usual age at menopause?	The evidence grading reflects that the recommendations are based on (very) low quality evidence. The strenght of the recommendations is based on evidence, but also patient values, harms and benefits, feasibility, resource implications.

Martha Hickey	62	1402	As stated, much of the evidence comes from the Mayo (Rocca) data, some of which was a retrospective records linkage project. Please consider the strength of evidence on which the HT "strong" recommendations are based.	The evidence grading reflects that the recommendations are based on (very) low quality evidence. The strenght of the recommendations is based on evidence, but also patient values, harms and benefits, feasibility, resource implications.
Martha Hickey	63	1422	What is the basis for stating "the evidence is adequate to support a recommendation for HT"? I am not saying HT should not be offered, just that the evidence does not actually seem adequate. This section also fails to clarity that the optimum duration of treatment is actually unknown. Stating that "some authors suggest treating women up to the usual age of menopause" is not evidence, just opinion. We were mystified by the recommendation here – it seems entirely opinion based	We have clarified that the data are limited to observational evidence, and that there is no evidence on optimal dose. We still conisder a recommendation appropriate in this area to support clinical practice. The recommendation for offering HT was retained with the limitations clearly outlined in the text, the jsutification and the recommendation (which is based on very low quality evidence, as indicated by the +ooo label)
Martha Hickey	68	1586	If the section on FP is already covered elsewhere, suggest just linking. Guidance is already very long	The section indeed refers to the fertility preservation guideline (2018) and states that only a short summary is provided, combined with newer data. We have not adapted this.
Martha Hickey	69	1626	We found this section confusing. It is most relevant for cancer patients who have had FP and particularly following radiation. Rather than just list some potential complications, it would be helpful to have some specific guidance on whether pregnancy should be attempted after pelvic radiation and when? This is a very live clinical issue for many, particularly after cervical cancer.	We do discuss higher risk < 1 year after chemotherapy and < 2 years after radiation. For more in depth information, readers are referred to the guideline on fertility preservation.
Martha Hickey	74	1778	Why was a case report on PPD after POI included in the guideline? Estrogen is not a recommended treatment for PPD	It was decided to leave this sentence in the guideline. We're not stating estrogen as a treatment for PPD - but rather in this unique group with no endogenous estrogen
Martha Hickey	75	1818	There is a lot of detail about pregnancy in TS. Could the TS information potentially go into a separate guideline since it is specific to this group? Particularly since the European Endocrine Society have recently published a TS guideline which was a collaboration with ESHRE	Given TS is one of the most common causes of non-iatrogenic for POI and the highest risk for pregnancy, we consider it important to keep the information on TS in the guideline, but we have referred to the recent TS guideline for further details and guidance
Martha Hickey	75	1805	Have the NICE guidelines on PET been updated since 2010?	We have updated the reference.
Martha Hickey	75	1810	Conflicting figures are given for MM in Turner syndrome	We have updated the text accordingly.
Martha Hickey	79	1900	The quoted evidence that natural menopause leads to an accelerated decline in muscle mass that is due to "estrogen deficiency" quotes a review article and does not provide any evidence for this statement. The comments about bone loss and menopause appear to refer to usual age menopause – this limitation should be added.	Sentence clarified to state usual age menopause. Data from the SWAN study has been added indicating a decrease in lean mass during the menopause transition.

Martha Hickey	79	1914	Statements like "estrogen is important for muscle mass and function" appear opinion driven and are not backed up by evidence. What exactly does this mean? This systematic review in 2019 showed no effect for HT on lean body mass. The section on molecular effects of estrogen on muscle and bone is interesting but not relevant for a clinical guideline.	Consideration of muscle health is a new section in this guideline necessitating an introduction explaining the concepts of muscle health and sarcopenia to the reader unfamiliar with these concepts and references of internationally accepted guidleines provided. The initial paragraph has been rewritten to prvide greater clarity.
Martha Hickey	79	1940	The lead statement is misleading "the effects of POI on skeletal and bone health is the among the most clearly established ….". The reference is not to skeletal and bone health after POI but to patients concerns about this. Not the same thing. The section then goes on to discuss the evidence around POI and bone density, which is scanty and conflicting, including the influence of multiple other factors contributing to low bone density in this population. Throughout this section relative and absolute risk are used (apparently) randomly. The findings are almost impossible to follow	The lead sentence has been revised. The paragraph provides an overall summary of the data. The use of relative and absolute risks reflects the published data.
Martha Hickey	82 - Fracture	2053	It is a well-recognized knowledge gap around fracture risk after POI or EM. This section includes studies measuring fracture and "calculated hip fracture" (whatever that is). See Minakovic 2023. It also includes EM not just POI. The guidelines should be clear that the association between POI and fracture is not known.	FRAX is a validated online fracture risk tool widely used internationally by clinicans and recommended in osteoprosis guidelines and was used in the study by Minkovic et al 2023 to calculate hip fracture risk. The first sentence in this sentence recognises the uncertainty of the data. The GDG agreed that where relevant, findings regarding early menopause would be provided in the text. This is in response to the initial scoping review and recognition that early menopause and POI are likely to consitute a continuum and the age definition of POI set by convention.
Martha Hickey	84	2117	The algorithm on bone health seems to have been taken unaltered from an article based on other CPG. Suggest that this be critically appraised in the light of new evidence for this ESHRE guideline. Management (low-mod quality evidence) is for HRT or OCP for all, unless CI. No mention here about high dose (100 mcg) preps, as recommended in the text. Also, the figure does not recommend BTM though these are suggested in the recommendations.	Figure 11 algorithm has been revised. Recommendation regarding BTM has been removed.
Martha Hickey	85	2131	Recommendation language again – inform women with POI that they may have an increased fracture risk though this has not be adequately demonstrated. What on earth should patients make of that?	The recommendation has been revised to provide greater clarity
Martha Hickey		2136	Again, the mixing up of "surveys" with RCT and "observational study" (cross sectional/prospective/retrospective) and a SR on a different population! No critical evidence synthesis.	This reflects the lack of evidence in a POI specific population.
Martha Hickey		2168	The guidelines recommend HT (see varying terminology, HRT here) for the treatment of osteoporosis. Despite the "low to moderate" evidence statement in the figure, the guidelines state "an extensive evidence base and guideline exist". We have no idea what that means.	The statement "an extensive evidence base and guidelines exist" relates to postmenopausal women with usual age menopause.The sentence has been revised to provide greater clarity. As explained in Table 1 Terminology, hormone therapy is a term used to encompass both HRT and the combined oral contraceptive pill

Martha Hickey	86	2168	We were particularly keen to understand the evidence for using high dose estrogen in POI patients. We understand that the HT vs OCP question is being addressed in POISE. The evidence on estrogen dose was largely derived from the excellent Costa et al SR. They only identified three prospective studies of 366 women plus on blinded RCT of 30. No studies compared estrogen doses. Based on this limited evidence they report that higher dose estrogen (2mg oral) may confer benefit for bone but follow up only 2/3 years. No benefits for TD found. The authors identify limitations of this study and did not conclude that higher dose estrogen was superior to average dose for bone. Is this SR the basis for recommending high dose estrogen in POI? If so, does the strength of the evidence justify this recommendation? It has major implications for practice and will (of course) require higher dose progestogen for those with a uterus. These have safety implications which are not discussed.	The recommendation is conditional and strength of evidence is one plus so reflects evidence. All studies are short term and there is an urgent High dose transdermal estrogen was associated with BMD gains in both the Crofton and Popat studies as noted in the Costa SR. It is important to remember that many women with POI may not have acheived peak bone mass and therefore an increase in BMD is desired. Further research is required to confirm the optimal dose and determine if estrogen dosing should change across the life course.
Martha Hickey		2282	Recommendation for high dose estradiol based on bone data but not discussion of potential risk of higher dose E and P	We have added a reference to the respective section in the HT chapter where the risks of HT are discussed
Martha Hickey	90	2334	This section on BTM reflected many other sections. We are advised that BTM are "useful for the prediction of fractures" and monitoring treatment but then higher quality evidence is presented showing that they do not reflect clinical outcomes. Since the totality of the evidence suggests no clinical role for BTM, why don't the guidelines critically appraise the evidence to give a clear recommendation?	This sentence relates to postmenopausal women in general and not POI specifically. The recommendation regarding BTM has been removed
Martha Hickey	91	2358	The important information I need as a clinician is 1. How often to repeat DXA after POI on HT? 2. How often to repeat DXA after POI not on HT? We found the guidelines woolly on this.	There is no data which defines the optimal interval for monitoring of bone density either in women with POI or postmenopausal women in general. The wording of recommendation 64 has been amended and accompanying text clarified
Martha Hickey	92 - Muscle health	2369	In an evidence-based guideline it is bizarre to see opinion statements like "POI is likely to affect muscle mass although this remains under researched". The statement about sarcopenia in older women seems unrelated and also poorly evidence based. What is the point of this section? The evidence from POI seems to be all cross sectional, although described as "observational". This should be corrected. Only one prospective study included (Price et al 2023) which showed no difference. However (strangely) the recommendation states that "women with POI.. should be aware that POI is associated with lower muscle mass, strength and performance" which is apparently based on "strong" evidence. There is certainly no strong evidence presented in the literature review to justify this Rec.	Consideration of muscle health is a new section in this guideline necessitating an introduction explaining the concepts of muscle health and sarcopenia to the reader unfamiliar with these concepts and citations of internationally accepted guidleines provided. The initial paragraph has been rewritten for clarity and additional evidence provided. The strength of the recommendation relates to the systematic review, additional cross-sectional studies and case control including those in Turner syndrome. We acknowledge the only prospective study did not show a diffence in lean body mass between women with POI/ early menopause. However, the authors (Price 2023) acknowledge as a limitation that power calculations in WHAM were based on change in sexual function rather than weight or body composition. The body composition study include 135 participants instead the total 194 particpants. Recommendation 67 has been revised to reflect the uncertainity of the evidence

Martha Hickey	94	2440	We found the "muscle protection and improvement" section strange. The evidence in POI is very limited. We conducted a prospective controlled study of weight and body composition after RRSO. The findings are (again) misrepresented here, stating that our study was about muscle mass. The (negative) findings were then dismissed as due to "small sample size". This was a prospective controlled study where almost all the published evidence is cross sectional. A lack of understanding of evidence quality comes across again. The recommendation then states that HT may improve muscle mass. I did not see evidence presented to justify this	The Price 2023 study referred to whole body lean mass (not appendicular lean mass which is a better assessment of skeletal muscle mass) and this has been clarified. The authors (Price 2023) acknowledge as a limitation that power calculations in WHAM were based on change in sexual function rather than weight or body composition. The body composition study include 135 participants instead the total 194 particpants. The recommendation does not state that HRT may improve muscle mass. However, the recommednation has been rephrased to provide greater clarity.
Martha Hickey	95	2474	Similarly, since there is no evidence that HT makes a difference, why does the rec say "treatment may be of benefit and can be offered"?	There is evidence in postmenopausal women that HRT may imporve muscle parameters and conflicting data regarding an effect of HRT in POI. The recommendation has been rewritten to improve clarity
Martha Hickey	98	2582	The evidence listed here does not refer to RRSO. It refers to BSO at the time of hysterectomy. Consider adding that women undergoing BSO at hysterectomy have markedly increased baseline risk factors for CVD – more likely to be obese, smokers, low SES and non-white. Hence, CVD may be influenced by these factors in addition to BSO. It is alarming that Tom Clarkson's data – in monkeys – is listed with clinical studies. Suggest a lack of critical attention to evidence quality	We have removed "risk-reducing", and have revised the references to this sentence
Martha Hickey		2593	Prospective data on surgical menopause and CVD and metabolic risk are very limited. From WHAM we published a relatively large prospective controlled study on CVD risk after surgical menopause. This was not included and overall we were unclear whether the data and recommendations were based on systematic reviews or narrative reviews. Perhaps not systematic with (loaded) PICO questions like "is estrogen replacement cardioprotective?"! There seems to be a strong assumption that the answer is "yes", largely based on opinions. For this section particularly it would be nice to see findings considered by cause of POI. For example, does surgical menopause confer greater risk of CVD compared to natural POI? Does HT show a different CV outcome with surgical vs natural menopause? Bearing in mind that those with surgical menopause will generally get estrogen alone. We found this section difficult to read since it flicks in and out of preclinical, animal and human evidence. Arguably only the human evidence is relevant to a clinical guideline. This is particularly important for HT and CVD since the preclinical/animal data showing benefits of HT are not reflected in human evidence.	The WHAM study refers to RRBSO. We have removed the animal data and checked the text for readibility
Martha Hickey	100	2649	Missing words?	We have corrected the sentence, thank you for pointing this out.
Martha Hickey	100	2669	Since the 2006 Lookkegard study was published, we have published on CVD and oophorectomy in >25,000 nurses from the Danish Nurse study. Perhaps this was overlooked because there was not a systematic literature search? We think this is the largest prospective study of CVD after oophorectomy. We found no significant increase in CV mortality after oophorectomy. We only had baseline HT use so could not comment on this.	The Olesen 2022 study referred to was not included as the age at which bilateral oophorectomy occurred was not provided and thus relevance to POI uncertain.

Martha Hickey	100	2677	Throughout the guideline the evidence presented flicked between clinical end points and biomarkers. This was confusing and detracted from the important clinical questions. Due to the sheer volume of evidence, at NICE we made a decision to only focus on clinical outcomes. Why did ESHRE etc include clinical and nonclinical outcomes and how does this improve the clarity of guidance?	While we aim to focus on clinical outcomes, we also consider it important to educate and inform practititioners on other aspects and outcomes. We will consider this comment in ESHREs strategy for future guidelines.
Martha Hickey	101	2685	We found it alarming that the "timing hypothesis" which is (after all) only a hypothesis is integrated into this guideline as if it were an established fact. The authors will be aware that clinical trials to test this hypothesis have not demonstrated proof of theory. Again, this section throws in animal data with human data as if they were interchangeable.	We have removed the animal data from the text and adapted the section.
Martha Hickey	102	2730	Similarly, the Mehta and Manson 2024 review does not contain any new data showing that starting HT soon after POI diagnosis improves the CVD. It is a review that includes the studies already mentioned. For a CPG of this nature, we would expect original, clinical data to be used to support clinical recommendations, not reviews. It is also alarming that where original data are cited they sometimes have been misquoted. We obviously have not checked this detail but it is concerning.	The strategy for the literature is to refer to high quality reviews where available and only resort to original studies where high quality reviews are nit available, outdated, or where additional details from original studies is needed. We have kept the reviews in this section.
Martha Hickey	101	2696	We would like to see the evidence summarized (including quality) for treating POI with high dose estrogen. A study including 25 women. However, on reading this article (Ostberg et al 2007), 23 of these women had either TS or GD and the dose findings were not even significant! We are astonished that this kind of evidence is being (apparently) inaccurately reported and used to justify high dose estrogen in POI generally	Information regarding dose is provided in the text. However, we acknowledge that there is limited data regarding estrogen dose and CVD outcomes in women with POI and therefore there is no recommendation regarding this.It is clearly stated that the finding refers to a small study.
Martha Hickey	101	2696	Unless we are missing something, the only evidence presented for CVD benefits in POI is a 2007 study (Ostberg et al), of n=25 women of whom 23 had TS or gonadal dysgenesis. The CVD biomarker (CIMT) improved on estrogen. The authors do not interpret this as evidence for a cardioprotective effect and (of course) this cannot be generalized to other POI patients. Given this (almost) complete lack of evidence, astonishingly the rec says "HT with early initiation should be recommended in POI"! What is the clinical evidence to justify this? In addition, the guidelines completely fail to mention the possibility of reverse causality for CVD and POI/EM. This includes evidence from MR and large cohort studies showing that risk factors for CV predate POI/EM, suggesting a common underlying mechanisms. This evidence is presented in the Merha and Manson Nature paper (top of page 207).	The common underlying mechanism may be the reduced levels of AMH, but we agree there is need for more evidence, and have added a sentence in that respect.

Martha Hickey	102	2733	We were puzzled by the statement "Clinical data has shown that hormone therapy reduces the risk for CAD, and stroke and improves insulin sensitivity and lowers glucose levels, thus decreasing the risk for type 2 diabetes in postmenopausal women (Mehta and Manson, 2024)". We are unclear what "clinical data" means but the reference is a review. Scouring this review we cannot find evidence to support the statement in the guidance. This is very concerning if papers are being mis-quoted. The Manson paper does say "MHT might have cardioprotective benefits for women aged <60 who are within 10 years of menopause but should not be used for the express purpose of CV risk reduction". Bizarrely, the guidelines statement seems to have been extracted from the estrogen only section of WHI trials in older women. Wherever it came from, it was not referring to POI/EM and hence is not relevant for this guidance. For interest, the draft 2024 NICE guidelines did not find evidence for a "therapeutic window" for MHT and neither did USPTF (2022) – the two guidelines where the data are systematically reviewed. The authors should beware of conflating a hypothesis with fact.	We have revised the sentence and the section
Martha Hickey	104	2774	Regarding mental health, we think it's important to differentiate surgical menopause as RRSO from surgical menopause. They tend to be a different population. For example, cancer worry may decrease after RRSO. We have found in WHAM that the depression and anxiety seen at 12 months has gone by 24 months (Hickey et al, in prep). From a mental health perspective, we wonder whether there is sufficient evidence to infer commonality between those with POI since the causes e.g. cancer treatment, risk reducing BSO, spontaneous are so different? For example, the "silent grief" around fertility and POI is unlikely to be similar for RRSO where indications include having completed your family. It would be helpful to know how the prevalence of POI is split between non-iatrogenic and iatrogenic? It's likely that iatrogenic is now more common we believe. Overall this section was highly speculative and jumped around between different POI types and mental health – using terms like "mental health difficulties" that are vague an unquantified.	We thank the reviewer for this comment, but consider it had already been addressed in the text.
Martha Hickey	105	2852	Another example (and there are many!) is the Zilski et al 2023 study quoted about QoL and mental health after RRSO. This is a small, cross sectional study. We have published a larger prospective controlled study measuring QoL and mental health, using validated instruments (Hickey et al). The fact that the Zilski study was cross sectional was not clear from the abstract – we had to look it up. This scenario will happen if there is no systematic literature search and evaluation of evidence quality.	We have clarified that the data are derived from a cross-sectional study, but the study has a long follow-up, a high response rate, and the existence of a control group, which is why we consider it appropriate to be included. The reference by Hickey is also mentioned in the text

Martha Hickey	106	2869	We also have concerns about the Rocca et al 2008 study of depression after BSO. This was a retrospective study using a non-standardised questionnaire to measure depressive symptoms. It does not seem to have been used by other authors. The timing of depression or anxiety (i.e link with surgical menopause) was more than 14 years after BSO. The study design is complex and we cannot evaluate the evidence quality here – apart from retrospective design. We note the author was (rightly) part of the committee but it is the committee's responsibility to evaluate evidence quality.	The significant findings for depression came from depressive symptoms that were diagnosed by a physician. The women (or their proxy responders) reported having received a diagnosis by a physician during a structured telephone interview. For anxiety, the results were significant both using anxiety symptoms reported by the women (or their proxy responders) and by using only diagnoses confirmed by a physician. Even though the study did not use a standardized depression scale or an anxiety scale,we think that the evidence is of adequate quality.
Martha Hickey	107	2908	What on earth Is an "opportunistic descriptive study"?	We have adapted the sentence in line with the comment, now using cross-sectional survey
Martha Hickey	107	2931	Similarly, this section demonstrated no recognition that the experience of POI may vary between women. Specifically, RRSO may reduce cancer worry and does not necessarily lead to worse (or any) symptoms. It's hard to see this as similar to someone with TS for example.	We agree, but had already included a general sentence at the start of the chapter commenting on the diversity of these women
Martha Hickey	109	3009	The evidence review strays from POI into EM in a number of places. Whilst these are (of course) on a continuum, it's not necessarily the case that physical or mental health issues around POI are similar to those in EM. This is particularly important for those from ethnic minority groups where the average age at menopause is considerably younger. Hence, a high proportion of women would be labelled with early menopause.	We agree that in some cases it is difficult to distinguish women with POI from EM but we clearly stated in the text throughout the guideline, so the readers are aware this is indirect data.
Martha Hickey	110	3023	For clinical practice, we are trying to understand the reasoning behind giving high dose estrogen to women with POI. The SR by Kotz et al (2006) is provided as evidence that "physiological" levels of estrogen may improve wellbeing after surgical menopause. However, this paper does not compare different estrogen doses so does not provide evidence for higher estrogen dose.	The guideline group has revised this comment, but did not consider it necessary to add or change information.
Martha Hickey	110	3023	We found this section on testosterone hard to follow. Is testosterone helpful after POI and if so, for whom? The "safety" data for one year was a bit concerning, since these younger women are likely to request much longer treatment if they find testosterone helpful.	We included the studies in which testosterone was used in different groups of women with POI describing the results. The importance of safety and the need for further long-term research is reported in research recommendations on testosterone
Martha Hickey	110	3053	One of the few times that evidence quality is explicitly stated. Comment about limitations of cross-sectional studies. However, a very large number of the included studies are cross sectional, and this limitation is not consistently mentioned or reflected in the recommendations.	We agree that unfortunately many of the data are not based of controlled longitudinal data. We have clarified throughout the section that further research is needed.
Martha Hickey	110	3057	Talks about the effect of VMS on quality of life after POI. However, does not mention our prospective data from WHAM showing that MHT reduces but does not resolve VMS, also that MHT has a limited effect on quality of life. The prospective TUBA study found the same thing. Patients should be aware that MHT may have limited efficacy in reducing VMS after surgical menopause.	The WHAM study has been included in the guideline, and particularly the HT section.

Martha Hickey	111	3062	Whilst NK3R antagonists have not been tested in POI, they have been tested in other symptomatic women. Suggest this section is updated to show efficacy data – as with the other non-hormonals listed.	We considered the current sentence on NK3R antagonists is sufficient as is. "At present, there is some hope from the possible use of a new class of drugs (NK3R antagonists) that target the hypothalamic neuroendocrine mechanisms generating vasomotor symptoms [Menown, 2021 #2651], but no data on their efficacy and safety are available in women with POI."
Martha Hickey	111	3072	The statement about when psychological wellbeing might be particularly compromised in POI does not appear to be based on any evidence	This concept emerges from the reading of McDonald's review but we have rephrased this.
Martha Hickey	111	3104	We were surprised that care models for infertility in POI did not mention egg or embryo donation. This section talks at length about psychological approaches but these have not been tested in POI. What is the clinical message here?	Thank you for the comment, we have added a sentence on embryo/egg donation.
Martha Hickey	113	3155	Given the (stated) lack of high quality evidence about POI and sexual function, I was surprised that our prospective data on sexual function and distress after RRSO was not mentioned, also the TUBA sexual function data – these are the only prospective studies. Like many other prospective studies of sexual function, we found high rates of dysfunction prior to RRSO. For some reason this is only mentioned in the "systemic estrogen" section. However, cross-sectional studies are very limited for drawing conclusions about sexual function in POI. Because there was no systematic approach to the literature, important studies can be overlooked. Not all the women in these studies were <40 so perhaps that is why they were not included? Lara Terra's study is included which is great. However, this is mostly women >40 and is cross sectional. Throughout there is very patchy assessment of evidence quality. Study design is sometimes mentioned and sometimes not. Makes it different to evaluate the totality of the evidence	We agree that cross-sectional data offer limited evidence and in here we were focusing not on surgical. We referred in general to the importance of surgery for sexuality (Kingsberg) and then we mention prospective studies in the treatment section. In addtion, we included some information as suggested in the psychological section.
Martha Hickey	114	3205	What is sexual performance? The guidance is littered with statements like "rebuilding feminine identity"	Thank you for the comment, we have amended this to the term sexual function and influencing female identity
Martha Hickey	115	3232	Another example of variable reporting of evidence is "non-significant trend". This is a null result and should be reported as such. Overall, we found the sexual function section hard to follow. Choppy, poorly structured and lacking a clear evaluation of the evidence and its quality	We report the data available in the literature and when available reviews and meta-analyses, and we stated in the introduction the limitations of the present literature
Martha Hickey	117		The entire section was very heteronormative	The text is based on the study and data rather than aimed to be heteronormative. We have added a sentence in the introduction.

Martha Hickey	117	3320	We found this section hard to read. What we wanted to know was "does systemic HRT improve GU symptoms?" and "how does systemic HRT compare to vaginal estrogen for GU symptoms?". The global consensus core outcome set (COMMA) has recently concluded that measures such as vaginal pH and VMI do not correlate with symptoms and are not relevant to patients and clinicians. These measures are mixed in with clinical ones, makes this hard to follow. The recent systematic review (Meziou) concluded that "HT may slightly improve sexual function" and the guidelines should reflect this uncertainty about any efficacy. Subsequently (3475) there is an assumption that systemic HRT is effective for GU symptoms. In 3536 it states "Systemic hormone therapy (HT) relieves VVA/GSM symptoms in many postmenopausal women but not all" This is directly contradictory to the systematic review quoted earlier	We thank the reviewer for the comments and have rephrased the sentence to clarify that we want to say the same things.
Martha Hickey	117	3341	What is "vaginal trophism"? also COMMA concluded that vaginal pH and VHI were not relevant for either clinicians or patients and did not equate to symptoms. It would be nice to see this acknowledged here	We are aware of the disconnection between objective and subjective signs and symptoms but when describing the studies that have tried to investigate the issue we have reported what it was found by the authors. We have removed the word "trophism"
Martha Hickey	117	3349	Perineal stimulation?? Is this being recommended on the basis of strong evidence? If not, why is it mentioned?	We believe it is important to report the studies we have on POI and this is a study comparing a phisical therapy with LET. This does not translate into a recommendation
Martha Hickey	117	3350	Throughout the guidance there is a strong bias towards recommending HT. Note that the systematic review of HT and sexual function (Meziou et al 2023) concluded that "Hormone therapy may slightly improve sexual functioning". The ESHRE guidelines claim "evidence of a small benefit on sexual function". This is not what the SR said	While there was no intention to be biased, we have amended to use the exact phrasing as in the review.
Martha Hickey	117	3374	Suggest stating that the RCT of testosterone were all pharma funded.	We had already pointed out the different limitations of the trials, but have added another note to refer to them being company sponsored
Martha Hickey	118	3391	Given that pregnancy occurs in POI, alarming to see the potential adverse effects of exogenous testosterone on the fetus dismissed as "only occurring in a high hyperandrogenic state", referenced to a pilot study in PCOS (by one of the panel)!. Surely this is one of the "prescribing practices which may cause harm" (Davis et al 2019)	We include a review reference but have now replaced it with the original manuscript by Braunstein 2007 which explains well the theory on placental physiology, which is not something we have dismissed.
Martha Hickey	118	3379	We found the terms "estrogen replete and non-replete" quite offensive. Suggests that any low estrogen state is pathological and needs replacement.	We have used the terminology as it was done in the studies, but have now changed the wording.
Martha Hickey	121	3496	What are "genital-urinary symptoms"? The COMMA (and NICE and AHRQ) terminology "genitourinary symptoms associated with menopause"	We have amended the terminology
Martha Hickey	121	3502	Just to say, the "multiple signs and symptoms" of GSM have not been shown in any prospective studies to be attributable to menopause	We have adapted the text
Martha Hickey	121	3503	Some more bizarre statements with no clinical evidence to support them "Even the decline of androgens plays a role given the presence of androgen receptors in the urogenital sinus and vaginal canal (Simon et al., 2018b).	We have amended the sentence reporting however that androgen receptors are present in there

Martha Hickey	121	3505	COMMA has achieved global consensus about how GU symptoms associated with menopause should be measured and what tools should be used. Note that there is currently no consensus about what GSM is and not tools to measure it. Hence, the prevalence of GSM cannot be measured.	We have amended the text to include the COMMA consensus, but it had not been published before.
Martha Hickey	122	3535	The guidelines included the Christmas et al SR on urinary symptoms and menopause (no association found). However, the SR also reported (based on 10 RCT) that systemic HT causes or worsens urinary incontinence. This was "translated" in the guidance to say "systemic HT does not seems to improve urinary incontinence". This completely misrepresents the findings of the SR. We are concerned about who did the evidence checking here. When this level 1 evidence is put beside a "secondary analysis of a cross sectional study" without any apparent consideration of evidence quality, that is very worrying.	We have rephrased but we want to clarify that the reason why we reported also smaller studies is not because we believe they have the same relevance but because we want to describe also papers that have specifically tried to investigate POI women. We included the results of the nurses' health study because we want to mention foecal incontinence.
Martha Hickey	122	3567	What is the evidence that the osmolality of vaginal products is clinically relevant?	We have removed "in pH, osmolality, and additives" from the introductory sentence to avoid confusion
Martha Hickey	122	3574	Similarly, the RCT evidence that lubricants increase sexual satisfaction has no control group! One of the authors is a lubricant manufacturer. Once again, there is a real failure to address evidence quality. Similarly, we did not see any clinical evidence that moisturizers are beneficial. This section read like a pharma advert. The topical lidocaine reference should be Faubion but to Martha Goesch's data	We have revised the section and the incorrect reference. However, we never claimed there was any high quality evidence to support lubricants or moisterizers.
Martha Hickey	124	3628	Clinical trials of vaginal laser require a sham laser arm. This is equivalent to a placebo arm in medical therapies and essential when evaluating devices. The evidence review needs to critically assess which trials include a sham and what they found. What exactly does "laser therapy cannot be recommended as a standard of practice" mean?	We have rephrased the sentence and the recommendation
Martha Hickey	124	3647	Again, this section lacks critical appraisal of evidence quality. A pilot study of n=20 is quoted as evidence and the "injection of growth factors" does not refer to any evidence at all! Bear in mind that quoting these "studies" in ESHRE guidelines gives them validity and exposure. Also, "women are waiting for bioengineering techniques in regenerative medicine.". For goodness sake. Who exactly is waiting? This "systematic review" does not contain any evidence of these interventions in a clinical setting.	For completeness and to open the door for further research, we aimed at reporting the experiences with other treatments. We have now clarified that these are experimental options and not to be applied in clinical practice.
Martha Hickey	124	3657	Since systemic HRT confers no/minimal benefit for GU symptoms, why only offer vaginal estrogen after systemic HRT for GU symptoms?	The guideline group recommends HT for women with POI for bone function and management of other sequelae. For GU symptoms, it is suggested to add local estrogens if needed. We have checked the information in the guideline, but consider this is sufficiently clear.
Martha Hickey	126	3678	A very strange definition which includes cognitive decline, dementia, Parkinson's and restless legs! Subsequently biomarkers of dementia risk such as tau protein are included though these were not in the scope.	We clarified that these are neurological conditions for which a possible association with POI was studied.

Martha Hickey	126	3688	In this section TS is considered separately from other causes of POI but not in other sections. Why?	This was already explained in the introduction, where it reads "This chapter is not addressing neurological function in women who experience POI in the context of a genetic disorder because it remains unclear whether the neurological manifestations observed are related to the premature deprivation of ovarian hormones (POI per se) or to the underlying chromosomal or genetic condition. "
Martha Hickey	127	3745	In considering the potential association between BSO and dementia, the authors should consider the elevated risk factors for chronic disease (including dementia) in women undergoing surgical menopause (see Rocca paper above).	We added a comment about possible confounding.
Martha Hickey	127	3745	The evidence on cognitive impairment and dementia after iatrogenic POI is clearly mixed and inconclusive. It is confusing to include outcomes such as tau protein which is neither cognitive impairment or dementia. Suggest sticking with dementia in this confusing area.	The guideline group has revised the section and does not consider the evidence to be inconclusive. Tau is an imaging biomarker of Alzheimer's disease. In recent years, studies of biomarkers have been published to address the long lag time between POI and onset of clinically detectable dementia. We consider this relevant information for the reader and decided not to remove it.
Martha Hickey	128	3767	For reasons we cannot understand, retrospective studies of oophorectomy and dementia are painstakingly reported and a prospective study of >25,000 Danish nurses (3770) is dismissed as having "limited power". This Danish study did have limited power, but so did all the studies listed! This was a larger and more powerful study than Mayo studies. Again reflects a lack of critical assessment of the literature. Despite mixed findings the summary states that "BSO before age 45 years is associated with cognitive decline, MCI and dementia.	As it is agreed the Danish study was underpowered, we have not significantly amended the text.
Martha Hickey	128	3782	The evidence is clearly scanty and inconclusive – as stated in the 2022 Rocca paper. The evidence is certainly not reasonably strong" (undefined). This should be amended. A further concerning lack of critical evaluation of the data. Ibrahim et al 2022 was a small retrospective Egyptian study where they interviewed women with PD about previous hysterectomy and BSO. Clearly this is very poor-quality data. The Pesce study almost 20% had surgical menopause and associations were reported with PD. Larger study with superior methodology but both studies are reported in the same way in these guidelines.	Our conclusions are aligned with the Rocca et al, JAMA Open paper. We did addd some details about the Egyptian study and the French study.
Martha Hickey	129	3819	What are the "preventive actions" being recommended. HT has not been shown to prevent dementia in any population. The guidelines could reference the Lancet series on dementia prevention here.	We refer to general preventive actions for dementia.

Martha Hickey	129	3833	Several studies are quoted where use of HT after surgical menopause was associated with superior cognitive outcomes. Unfortunately, this section comes across as very skewed towards putative benefits of HT and insufficient consideration of the papers studied. For example, the Rocca et al 2007 study where no statistically significant reduction in dementia was seen in HT users but "clinically significant". We could not access the paper to understand what this means but id it not in the abstract. If this was a comment from a committee member that was not in the publication (peer reviewed) this should be transparent. Although the guidance states "this protected effect of ERT was confirmed 7 years later by another US study" – Bove et a (2014), This study does not actually show a significant effect of HT on global cognition and no association with AD pathology. The recommendations seem to reflect a lack of critical analysis of the actual findings from these studies. Many included studies did not differentiate between POI/EM. Using a systematic review approach, The 2024 draft NICE guidelines found no evidence for the benefit of HRT in women age 40-44 years. This conflicts with the evidence presented here showing dementia benefits for POI and EM and suggests some selective reporting. To claim that these findings support the timing hypothesis seems like a very big jump. Bearing in mind that the timing hypothesis remains a hypothesis without substantive human clinical evidence for CVD or other outcomes.(USPTF 2022).	We have made some small clarifications to the text in line with this comment. The comment about clinical significance for the Rocca et al, Neurology 2007 paper was removed. However, we consider the study by Bove et al, Neurology 2014 is quoted correctly. The timing hypothesis is presented as an hypothesis not as a fact.
Martha Hickey	130	3877	Based on these conflicting and limited findings we cannot see the evidence base to recommend HT to prevent dementia/Parkinson's and "other neurological diseases" until the usual age of menopause. Exactly what strong evidence demonstrates that HT taken after POI until age 50 is preventive of neurological disease?	The evidence is not labeled as strong, but as "low quality", indicated by the ++OO label. The strong recommendation for HT is based on the evidence, but also other factors such as benefits vs harms, patient values and feasibility. We have slightly rephrased the recommendation.
Martha Hickey	130		Similarly, "HRT may be recommended for neurological function even in the absence of symptoms". What does this mean? Does is mean prevention or treatment or neurological disease? Considering the evidence is mixed about whether those who take HT after POI have better neurological outcomes or not. Also, the safety of HT in this population is basically unknown.	We have clarfied in the recommendation that HT may be recommended to protect neurological function. The safety was considered as a factor in all recommendations.
Martha Hickey	131	3881	There is a strong thread of bias towards HT throughout these guidelines. It is worrying that study not showing the "correct" association between HT and cognitive outcomes are dismissed on methodological grounds. Particularly when the analysis of trial methodology is patchy at best throughout the guidelines.	We consider this is a comment to HT in general and consider this is covered in replying to other comments
Martha Hickey	131	3891	Suggestion that HT is beneficial for cognition after early menopause is contradictory to the evidence review findings in NICE which found no evidence for benefit. Recommending HT in those without VMS is particularly worrying when there is no demonstrated basis for this, in the context of neurology at least.	We state that "HT could reduce the possible risk of cognitive impairment and dementia", which Is not as the reviewer states "HT is beneficial for cognition". In these recommendations, it is considered that women with POI are recommended to use HT for other issues, such as bine health, and in that case, the treatment may also reduce the risk of cognitive impairment

Martha Hickey	131	3903	The inherent assumptions behind the research recommendations are alarming: "further research is needed to confirm the beneficial effects of HRT following POI". The basic questions about benefit/harm remain unanswered	We have removed "beneficial" in the research recommendations, as indeed further research will show whether the effects are beneficial or not.
Martha Hickey	132	3922	The basic concept that younger women should be given higher doses of HT requires further clear evidence of moderate or high quality for justification. This is not presented.	Evidence from POI bone density studies indicates that higher doses of HT are required to maintain /improve BMD - this alone should be sufficient evidence to recommend higher doses of HT in this population, but clinical practice also demonstrates that younger women with severe symptoms also require higher doses of HT to control their symptoms.
Martha Hickey	132	3918	Why is the "principal of HT to approximate physiological replacement" and what exactly does this mean? If it means achieving circulating levels similar to premenopausal women (in postmenopausal women), what is the evidence that this optimizes physical or mental health or long-term health? It seems naïve just to assume estrogen concentrations should approximate premenopausal levels. After all, this is not what happens with postmenopausal HT which achieves supraphysiological levels.	We know from various studies of spontaneous and iatrogenic POI that if sub-physiological doses of HT are used, this can result in suboptimal bone mineral density and increased cardiometabolic risk.
Martha Hickey	132	3925	These "principals" – unsupported by evidence – are then used to justify clinical recommendations!	Most of these principles are supported by evidence. The evidence shows that if the uterus is present progestogen is required otherwise the risk of endometrial cancer is increased; according to many studies non-oral estrogen does not increase the risk of VTE; the increase in BMD is dose dependent. The evidence for these statements has been detailed in the respective sections and was not repeated.
Martha Hickey	132	3938	The guidelines definitely do not provide sufficient strong evidence presented here to justify the statement to recommend women with POI that HRT will protect their bones, heart and brain. Particularly if they are not symptomatic. Similarly, continuing until age 50 is not justified. If NICE cannot identify evidence for the benefit of HT in early menopause. How can use until 50 be evidence based?	The risks of POI are greater than those of EM due to the longer duration of a hypoestrogenic state from an earlier age. Many of these women have lost significant bone density already by the time they present to the HCP due to the delay in diagnosis. As such, it is plausible that these women need to continue on MHT longer in order to give achieve primary prevention benefits.
Martha Hickey	133 - Table Vi	3942	GU symptoms. Should make it clear that systemic MT increases the risk of urinary incontinence.	The increased risk of incontinence has not been demonstrated in a POI population. The suggested review by Christmas is included in the Genito-urinary symptoms section
Martha Hickey	133	3942	Where is the evidence for increased life expectancy?	The table provides a summary of the respective sections of the guideline, the reader is referred to the specific sections for the details
Martha Hickey	133	3942	Where is the evidence for prevention of CVD?	The table provides a summary of the respective sections of the guideline, the reader is referred to the specific sections for the details

Martha Hickey	133	3942	Sexual function. What does "ameliorate sexual function" mean and where is the evidence? The Cochrane review cited above does not confirm this	The table provides a summary of the respective sections of the guideline, the reader is referred to the specific sections for the details
Martha Hickey	133	3942	Evidence is not presented to justify taking HT until age 50 to prevent dementia, PD and "other neurological diseases"	The table provides a summary of the respective sections of the guideline, the reader is referred to the specific sections for the details
Martha Hickey	134	3947	There is high quality evidence that earlier menopause is associated with lower breast cancer risk. Strange this was not identified – potentially reflecting the poor search strategy.	We have quoted the data from the Collaborative Group on Hormonal Factors in Breast Cancer and from Wu, 2014 indicating that earlier menopause is associated with a lower risk of breast cancer.
Martha Hickey	134	3956	What is the evidence supporting the statement that breast density is less of a risk factor for breast cancer than BRCA1/2? Doesn't this depend on the gene mutation and patient age?	The text states that increased breast density due to HT is not as significant as familial/genetically predetermined breast density. We did not state that breast density is less of a risk factor than BRCA.
Martha Hickey	134	3965	The studies of breast density in POI women taking HT are tiny – far too small to base a recommendation on.	Breast density is reviewed in the text but there is no specific recommendation linked to the breast density data.
Martha Hickey	134	3977	This section read oddly, as if the authors were trying to dismiss the limited evidence on breast cancer and HT in younger women. Note that NICE reported an increased BC risk after EM, but similar to that of women with ongoing ovarian function.	The text is reporting on the findings of the study and not dismissing them. It would have been useful to have compared the risk of breast cancer in women using HRT in EM to the risk in age matched women with normal ovarian function.
Martha Hickey	134	3985	In this section on "risk of BC in women with POI" the authors bizarrely include a Danish cohort study from 2005 (Ewertz) that was not in POI/EM and reported that HT reduced BC risk in women age 40-44 years. However, this observation was not significant and is in stark contrast to the much larger Lancet meta analysis data (2019) – showing an increased risk. The Lancet results are then rather dismissed. This all reads like selective reporting.	Both studies are reported upon as per the systematic reviews - as far as the Lancet data are concerned please see comments in 304. The text was modified to indicate that in the Danish study these women did not have proven EM.
Martha Hickey	134	3995	Whether or not RRSO reduces BC risk in BRCA1/2 is uncertain. We were astonished to see that "a recent expert narrative review" was the basis of a recommendation on HT in BRCA users. A scoping review (like a systematic review but without ROB) and international consensus on management of BRCA PV carriers after RRSO. Using a systematic approach this scoping review found that safety evidence was limited to 4 years of HT in this population. The statement about breast irradiation was also alarming. Breast irradiation increases BC risk to a similar extent as BRCA1/2. It seems rash to suggest that they can take HT without increased risk or at least screening.	Thank you for these comments. The BRCA section will be modified and radiation section removed.
Martha Hickey	135	4015	It seems odd that the evidence quoted for HT increasing BC risk is based on observational studies. A very large RCT (WHI) has confirmed that combined HT increases BC risk. Observational data (CGHFBC) suggest that estrogen alone also increases BC risk, though WHI did not find this.	Observational study contains data on breast cancer risk with HT in early menopause hence included - women in WHI had an average age of 63 yrs using only CEE/MPA; caution should therefore be exercised in extrapolating these data to a POI population using mainly BI varieties of HT these days.
Martha Hickey	135		Surprisingly the recommendation is that HT does not increase BC risk after POI, despite no evidence presented to back this up!	Following discussion, the recommendation was reworded

Martha Hickey	136	4034	We found this statement very odd "the evidence in terms of risk of HT in relation to BC are reassuring for all women apart from BC survivors". How is the RCT, biologically plausible, supported by observational studies evidence "reassuring"? Do they mean in POI? In which case there is insufficient evidence to be reassuring.	Following discussion, the recommendation was reworded
Martha Hickey	136	4055	Given the strong evidence around unopposed estrogen and endometrial hyperplasia/cancer, why is the recommendation about giving adequate dose and duration of progestogen with high dose estrogen so tentative?	The recommendation has been changed accordingly. Thank you.
Martha Hickey	137	4060	What exactly is "progestogen intolerance"? what are the diagnostic criteria and how should progesterone intolerant women on estrogen be managed?	These are typically PMS - type side effects the most distressing of which are low mood, cognitive probelems and even suicidal ideation. Women who can only manage small amounts of progesterone sometimes benefit from local delivery with a LNG IUD; otherwise the endometrium should be scanned regularly and a biopsy taken if there is any doubt (or hysteroscopy). Occasionally a hysterectomy is required to facilitate unopposed estrogen usage.
Martha Hickey	137	4061	Similar lack of consideration of evidence quality around risk of stroke and HT after surgical menopause. This is a retrospective cohort study so the evidence is weak. Throughout this section (and others) studies are just listed without any critical appraisal of the ability of each study to address the clinical questions.	There is a lack of data for POI and stroke. The limitation of the data has been indicated in the text.
Martha Hickey	137	4092	What exactly is "real world survey data" and what level of evidence is this?	We have made changes to text to indicate the design of the study
Martha Hickey	138	4102	There are several instances where speculative assertions are made without substantive evidence – this is another one. The authors should decide whether unsubstantiated speculation has a place in clinical guidelines.	The speculation is qualified in this sentence to indicate the lack of data.
Martha Hickey	138	4183	What exactly is the evidence base for recommending HT until age 50 years following POI?	We say until usual age of menopause which is 45-55 years, not 50 years.
Martha Hickey	142	4214	We note from the Fine et al SR in 2022 that the total world evidence for HRT/OCP on bone following POI is based on n=146 women (+625 with TS). This is not a strong evidence base and the findings were mixed. Whilst this reinforces the importance of the ongoing POISE study it certainly does not endorse the use of HT/COCP until age 50 years.	We say until usual age of menopause which is 45-55 years, not 50 years. The Goncalves and Costa systematic reviews cited in the bone section and consideration of underlying pathophysiology (increased bone resorption with estrogen deficiency) provide additional evidence regarding the importance of estrogen therapy.
Martha Hickey	142	4219	Similarly, the Langrish et al 2009 study included only 30 women.	Noted that the numbers were small hence the need for the POISE trial.

Martha Hickey	143	4252	We are particularly concerned by the reference to "evidence" showing that MP has a more favourable CVD and breast safety profile. The reference here (Mueck 2012) is a single author review, funded by Besins (the manufacturers of MP)! This is completely inappropriate. Note that neither USPTF in 2022 or NICE in 2024 have found evidence to confirm that the risk of breast cancer with MP differs from that of synthetic progestins. This comes across as a statement influenced by Pharma. The COI of the authors were not presented and this is problematic. Similarly, the quoted Davey et al 2013 paper does not contain any relevant data on MP and breast cancer. The Vinogradova study did not reach any conclusion about MP and BC risk, so the statement on Line 4261 completely misrepresents the evidence.	The PEPI trial showed a more favourable effect on lipids in MP v MPA users and E3N study showed a lower risk of breast cancer in women using progesterone containing HRT. The concern about industry supporting an author (or a study) is noted but this does not necessarily invalidate the conclusions. The data from PEPI and E3N should be considered here.
Martha Hickey	143	4262	Discussion of MP and endometrial safety do not mention the increased risk of endometrial cancer reported in the E3N study. This is concerning because the purported safety and benefits of MP are strongly promoted in this guidance. However, there are concerns about endometrial protection with MP (E3N) and earlier in the guidance increasing progestogen/progesterone dose with higher estrogen dose is only suggested unless there is "progesterone intolerance". This is a concerning message that high dose (e.g. 100 mcg) estrogen does not necessarily require high dose progestogen/progesterone. If the authors are proposing high dose progesterone, they need to explicitly say what the progestogen/MP dose should be since most will need a combined product. Note that the reference to the endometrial safety data on progesterone is also funded by Besins (Stute et al 2016).	The recommendation regarding the need for higher doses of progesterone being required with higher doses of estrogen has been changed. In studies where women have had to use MP because it was combined with estrogen eg PEPI / REPLENISH there have been no concerns about endometrial safety. Progesterone was used separately to estrogen in E3N so compliance could not be ensured.
Martha Hickey	145	4357	We were a bit alarmed about the comment suggesting that MP could safely be used vaginally for endometrial protection "may have the benefit of achieving endometrial protection". What does that mean? No reference provided. The manufacturer may be promoting this but looking on Pubmed, I cannot find any endometrial safety studies with MP. Are we missing something? If safety is not established then this should not be in the guidelines. The evidence from UAM is scanty and largely irrelevant in POI where higher estrogen doses are being advised. Alarmingly, the Sriprasert study quoted to support endometrial protection with MP actually did not find this! As a clinician, this kind of misrepresentation of the evidence undermined my confidence in what was being recommended	Off label PV use of progesterone is only suggested as an option in patients where oral use has resulted in progestogenic adverse events. There are studies that indicate that vaginal progesterone use can achieve adequate endometrial protection as long as an adequate dosage and frequency is used. The Sripasert publication was actually reviewed as a warning that inadequate doses of vaginal progesterone do not adequately protect the endometrium - the study was not included to support the vaginal use of MP. The wording in the text has been modified and this warning is already in the text. "Caution should therefore be exercised in assuming that vaginal progesterone will always provide adequate endometrial protection and endometrial surveillance should be instituted when lower dose / reduced duration regimens are prescribed [Hamoda, 2023 #2759]."

Martha Hickey	146	4377	What is the evidence that at least 2mg of oral estradiol or 100mcg of transdermal estradiol is required to reliably prevent bone loss? The Costa SR concluded that data are lacking and further studies are required to establish long-term side effects as well as the doses and formulations required to provide optimal bone protection. To date there have been no head-to-head studies comparing standard with high dose estradiol in POI. Costa highlighted, however, the importance of early diagnosis and treatment as well as uninterrupted use of therapy. Of note, the study by Giraldo regarding standard hormone therapy referenced by Costa did not compare standard with high dose therapy and involved women who delayed commencement of treatment.	The recommendation is conditional and strength of evidence is one plus so reflects evidence. All studies are short term and there is an urgent High dose transdermal estrogen was associated with BMD gains in both the Crofton and Popat studies as noted in the Costa SR. It is important to remember that many women with POI may not have acheived peak bone mass and therefore an increase in BMD is desired. Further research is required to confirm the optimal dose and determine if estrogen dosing should change across the life course.
Martha Hickey	146	4385	What exactly is the evidence base for aiming to achieve circulating estradiol levels in the premenopausal range in POI? We understand that it is commonly suggested but am asking why? What benefits and risks has this shown in clinical trials? If this is just a convention, then the guidelines should not recommend this as evidence based. The evidence to support replacing estrogen to premenopausal levels is certainly not obvious in the guideline. If one outcome is bone density, what is the evidence for use BTM to gauge the "right" amount of estrogen? This issue of recommending high-dose estrogen is important because it requires high dose progestogen/progesterone and because risks of estrogen (such as VTE) are dose related.	The principle is that a fully effective dose is used for symptom relief and primary prevention purposes - we have some data from short term RCTs and observational data but longer term trials would be welcomed to provide further evidence. The incidence of VTE is not increased by transdermal estrogen.
Martha Hickey	146	4408	This is very important. Longer duration of combined HT use increases breast cancer risk. We don't know this for women age <40 but we do for 40+ (Lancet meta-analysis). The InterLACE study (Zhu et al) used to justify longer term use of HRT after POI is incorrectly represented. The study found that POI and EM women who took HT had a higher risk of stroke (doubled) vs non-users. As stated, those who used HT for 10 years had a lower risk of CVD vs non users. It is selective and disingenuous to only present the CVD outcomes from this study without the stroke outcomes	I agree. It is important to weigh up the pros and cons with all treatments. The total number of stroke cases were small in the Zhu study and please note that risk was elevated in non users of MHT as well as users of MHT: <40 +MHT = 67/1940 (2.06, 1.52-2.52 p<0.0001) versus <40 +no MHT 59/1472 (1.45, 1.11-1.89; p=0.0067); also, the number of CV / CHD cases was greater. Finally, the route dose and type of HT administration may be a key factors with regards to stroke risk with transdermal administration but data on types of MHT were absent in this study. A clarification was added
Martha Hickey	146	4408	The recommendation about continuing HT until the average age at menopause was a group consensus but no evidence is presented to support this. How does the guidance for adherence meet "strong evidence" criteria when it is based on a world total of 69 patients who stopped their HT? (Bachelot et al 2016)	As previously discussed, GRADE recommendations are not based purely on the level of evidence.
Martha Hickey	150	4472	If the guidelines advise achieving a premenopausal level of estrogen, how does this not require regular measurement of estrogen levels?	Assuming estradiol dosing is maintained within licensed limits using the recommended regimens it can be assumed that physiological levels of estrogen are being achieved unless there are adverse effects, inadequate symptom relief or inadquate bone protection as measured by BMD.
Martha Hickey	150	4472	How does measuring estradiol prevent tachyphylaxis with estrogen implants?	It prevents reimplantation where estradiol levels are too high.

Martha Hickey	152	4513	Given the almost total lack of efficacy and safety data for testosterone in POI, we were concerned by the statement "not all women with POI require androgens but all should be counselled about the possibility of using androgens if they have distressing symptoms not alleviated by conventional HT? Because 1. The guidelines advise that they should not be on conventional HT (rather, high dose) 2. OCP has a known adverse effect on sexual function The Soman et al study did not appear to have a strong methodology and (as stated) these data are clinically somewhat meaningless.	The text was modified accordingly.
Martha Hickey	152	4513	The guidelines state that BSO leads to a reduction in circulating testosterone. Whilst this seems self-evident, the only prospective studies we could find showed no decrease in testosterone after BSO and here. For these reasons it appears that androgen status in POI or surgical menopause is uncertain.	We consider to have highlighted in several locations in the text the unclarity on testosterone assays, impact of POI on testosterone levels etc, and have now further revised the text to address this comment
Martha Hickey	152	4543	The neurological evidence for testosterone by Barb Sherwin is based on small numbers and high dose injectable hormone treatments. It cannot be used to justify testosterone treatment today. Similarly, studies in TS are not generalizable. Bit worrying that the RR 2.48 increased risk of breast cancer with testosterone in NHS was dismissed as "not being physiological replacement"! Previous statement has correctly confirmed that physiological replacement cannot be measured. Overall, considering the paucity of data showing benefit in POI and evidence for harm, we were surprised to see a "strong" recommendation for considering testosterone in POI	We did not mean to use this reference to support tesosterone but we included because it showed an effect in surgical menopausal women
Martha Hickey	152	4671	Regarding use of HT in women after chest radiation, these women are at very high risk of breast cancer (=BRCA1/2) – as above. Whether or not HT increases this risk is largely unknown and the Krul et al 2017 paper cannot be used as evidence for safety.	We consider this aspect is covered and following revision did not consider this needed further exploration
Martha Hickey	157	4729	It was disappointing to see a review article referenced stating that "menopausal symptoms tend to be more severe" after surgical menopause. Whilst this is commonly repeated it is not actually evidence based. The only prospective controlled study of surgical menopause (WHAM) found that whilst 80% had VMS after RRSO, 84% described these as "mild".	We have adapted the sentence in line with the comment
Martha Hickey	157	4729	Similarly, the statement that "HT relieves symptoms and decreases risk of death, CVD, osteoporosis and cognitive decline" is simply not established. The reference given is to a Thai consensus statement, not to evidence. There are no RCT data and best evidence for observational data are from InterLACE which do not endorse this wild statement.	We have removed the references, but did not amend the sentence, as it is in line with the evidence and conclusions presented in the other sections of the guideline
Martha Hickey	157	4729	We were alarmed to see our own data from WHAM being misquoted. For example, we did not find that cardiometabolic risk was increased after RRSO (as stated). Similarly, anxiety levels increased at 3-6 months but were at baseline by 12 months. We also did not report decreased quality of life – just decreased menopause related QoL	We have double checked the quoted data and made the necessary correction
Martha Hickey	157	4729	What evidence justifies the statement "HT should be considered as early as possible after RRSO in women under 50 years". As above, NICE found no benefit for HT in women over age 40 years (EM). There is certainly no established preventing benefit after menopause at the average age (45 or above). The statement urges HT from 45 years onwards with no supportive evidence	The NICE 2019 guidelines mention the long-term benefits of HT and cite some RCT evidence (including WHI). At least in terms of preventing bone mass and improving Vasomotor symptoms. The RCOG recommended in 2022 that pre-menopausal women with RRSO start HT as early as possible if there is no contraindication.

Martha Hickey	157	4729	Regarding the safety of HT in BRCA1/2, the quoted systematic review and the international consensus statement (Nebgen et al 2022) clearly show that only short-term (max 7 years, most 1-3 year) breast safety data are available. Since RRSO is recommended at 35-40 years, if you are advising HT until age 50, that is 10-15 years of use. The breast safety of this is unknown and the benefits of continuing to 50 are unproven,	We have addressed this comment in the text
Martha Hickey	161	4798	When considering the efficacy of non-hormonal, the group may want to consider the "minimally important clinical difference" for an improvement in vasomotor symptoms?	A paragraph has been added regarding this concept at start of pharmacological therapies for vasomtor symptoms. Line 4826
Martha Hickey	162	4864	Several key clinical trials are missing from this section, presumably because a systematic review or even scoping review methodology was not used. For example, the 2019 RCT of oxybutynin. These omissions are important as they are likely to affect the recommendations. For other products (e.g. NK3R), data up to 2024 have been included. I was surprised to see the Astella funded SR quoted verbatim that fezolinetant hs a "similar efficacy to low/usual dose HT". Other publications based on SR did not find this (ICER report). Also, the Astellas funded SR left out the oxybutynin data! Oxybutynin is probably the most effective non-hormonal after fezolinetant. You will be aware that Moonlight, the Fezolinetant study in Asia (30mg) showed no effect. It is disappointing to see this lack of critical evaluation of pharma funded research.	The systematic search PICO only included women with POI and no studies were identified as outlined in Line 4817: "We did not identify any RCTs, cohort or case-control studies evaluating non-hormonal treatments in women with POI specifically". We provided information as an overview predominately from the 2023 North American Society position statement on non-hormonal therapies for peri-/postmenopausal women in general but this was not meant as a systematic review of the non-POI population as stated in Line 4808. Findings from the 2019 oxybutynin RCT (Leon-Ferre et al have been added to the paragraph on oxybutynin. The section on fezolinetant has been amended to note that it was a pharma sponsored meta-analysis, clarification of the findings and inclusion of results from the Moonlight 30mg fezolinetant study.
Martha Hickey	166	5010	Recommendation about non-hormonals is qualified by saying "POI specific data is lacking". We believe that is the case for many of the recommendations made so perhaps this should be added elsewhere?	We agree that for many recommendations evidence in POI is lacking, but consider this is reflected in the text and justification.
Martha Hickey	General comment		The use of multiple outcome measures for the same thing (e.g. VMS) makes comparing treatments and studies very difficult. You may wish to mention that COMMA has now standardized what aspects of VMS and GU symptoms should be measured and how VMS and GU. COMMA has been adopted by NICE, the American Association for Healthcare Research and Quality (US equivalent of NICE) and the American Society of Urology and is supported by the major menopause societies and journals in the field.	We have referred to the COMMA initiative in the respective section and hope this initiative will further improve the quality of studies on GU symptoms
Martha Hickey	171	5210	To state that "complementary treatments do not prevent the long-term sequalae of POI" would require evidence about long-term health outcomes in POI with complementary therapy vs HT. This does not exist. Not even observational.	We have revised the recommendation to read "Complementary therapies should not be used to replace hormone therapy as there is insufficient evidence on their effectiveness for prevention of long-term sequalae of POI. "

Martha Hickey	225	8012	We could not read the "recommendations" section because a figure has been placed on top of the text. We were particularly interested in how the strength of recommendations was classified. The text states that the GRADE approach was used. However, this seems wrong. GRADE has four levels of evidence: very low, low, moderate and high. These ESHRE guidelines grade recommendations as "strong" or "conditional", with most graded as "strong" despite the major evidence gaps for management of POI. According to GRADE, observational studies are generally low quality. A "strong evidence" recommendation suggests certainty. GRADE assesses certainty on 5 domains: ROB, inconsistency, indirections, imprecision and publication bias. Most of the evidence presented here does not appear to meet the criteria of certainty. We do not understand how most of these "strong evidence" recommendations can be made.	We did score the evidence as very low, low, moderate and high (visualised by the well known labels 000+, 00++, 0+++ and ++++. The strength of the recommendations was labelled as strong or conditional, consistent with the phrasing used for the recommendations. This is consistent with the GRADE approach (see https://www.gradeworkinggroup.org/ , and the statement "A recommendation should have one of two strengths (strong or conditional, also called weak) and one of two directions (for or against)."
Wendy Wolfman		1.Diagnosis	Please provide more guidance in this document about differentiating reduced ovarian reserve from POI. In clinical practice, more patients with decreased reserve are being referred with a diagnosis of POI requesting treatments, when they are not symptomatic but may have poor stimulation and low AMH. Their length of time to POI is not currently known. I also think it is wrong to label these patients as having POI. Similarly, there are patients who have oligomenorrhea and increased FSH and are still euestrogenic- please provide recommendations about when to initiate treatments in these patients. Should estrogen level be included as part of the criteria in the diagnosis (as mentioned once in the document under discussion.)	Thank you for your comment. The guideline distinguishes between POI (which is clearly defined) and low ovarian reserve. After discussion, it was decided that oestrogen was not a mandatory diagnostic test.
Wendy Wolfman			Congratulations:-General review of document-Large very complete document. Will be used as a reference. I think the table of contents needs more detail. (for instance I couldn't find the information easily on thrombotic events on HT after the initial read.	We will see to adapt the table of contents
Wendy Wolfman		Recommendations re types of HT	While I totally agree with transdermal HT as first line, most of the comparisons or benefits are with COC. Please comment on the dose used in HT versus COC (the lower doses used that are less thrombotic than COC) As mentioned there is only one study on the risk of thrombosis on oral HTin this younger age group. Also in this younger age group the risks of thrombosis of oral HT are still less than COC and should be placed in context.(although would not provide contraception in the rare chance of unwanted conception.) These comments are appreciated especially for patients who cannot afford transdermal therapies.	The text was modified accordingly.
Wendy Wolfman		3878	Find comment confusing. Would remove reference to osteoporosis and cardiovascular disease or reword this comment.	We rewrote the recommendation in line with the comments of the reviewer.
Wendy Wolfman		3431	Would add prasterone as a possible option for treatment of decreased desire and sexual dysfunction as they have some FSFI data. However more data needs to be accumulated.	We have added a pertinent reference on the topic
EMAS		Care	We recommend referral to a menopause specialist, especially in cases where the desire for pregnancy is no longer relevant.	While we have addressed a section on care for women with POI, we have not provided too much details on the organisation of care, as care pathways and responsibilities vary across regions and a one size fits all approach could not be recommended.

EMAS	11	rec 7	"The guideline group recommends HCPs consider and exclude the diagnosis of POI in women aged less than 40 years who have amenorrhea/oligomenorrhea or estrogen-deficiency symptoms." We suggest that also subfertility is a reason to measure FSH in a woman < 40 years.	We have discussed this comment but decided not to amend the recommendation, but this comment is addressed in the text
EMAS	11	rec 9	We think the diagnosis should be confirmed with a second FSH measurement considering the fluctuation of FSH at early stage of POI and the normal fluctuation of FSH up to 20 IU/L at ovulation. If the blood sample happens to be collected at ovulation there is a risk of a false positive value.	We have revised the recommendations on diagnosis to address this and other comments.
EMAS	12	rec 10	If FSH is low or normal, low value of AMH is not predictive of POI, only if FSH is high. FSH has therefore benefit over AMH. AMH is related to testosterone, and all conditions with low testosterone like functional hypothalamic amenorrhea is associated with low AMH. When energy deficiency is improved in these women, AMH and testosterone increase	We agree that FSH is the primary test and this is clearly presented.
EMAS	12	rec 23	In many countries, not only endocrinologists, but also general practitioners, and in some cases also gynecologists manage uncomplicated hypothyroidism with Levaxin treatment.	The guideline group agrees with this comment and the text and recommendation have been changed accordingly.
EMAS	15	rec 64	"BMD measurement should be repeated within 5 years" sounds like a long time interval. It could be rephrased to "repeated between 1 to 5 years depending on the individual assessment."	We have amended the recommendation in line with recent guidance on the topic
EMAS	17	rec 104	"It is suggested that women with POI be informed that hormone therapy does not appear to increase the risk of breast cancer before the usual age of menopause compared to women without POI in the same age group." To be very clear it could be rephrased to: "compared to women without POI and no hormone therapy in the same age group."	The text was modified accordingly.
ACOG	9	73	I recommend using "spontaneous" instead of "natural" pregnancy. Using "natural" to represent a pregnancy obtained without the use of assisted reproductive technologies implies that using these is "unnatural" and I don't believe that is the message that this document wishes to convey.	There has been substantial discussion on the terms natural, spontaneous and unassisted to indicate a pregnancy not originating from ART. In the absence of an international agreed terminology, and considering a pregnancy never occurs spontaneously, the guideline group opted to use the term "natural pregnancy", but explain in the introduction that other terminology can be used. Due to the substantial previous discussion, it was decided not to revise this.
ACOG	10	73	Is it necessary to describe the "usual age at menopause?" The average age of menopause is around 51 years of age and premature is considered younger than age 40. I am not certain that adding the descriptor "usual" is helpful. It seems confusing to me as it is somewhat arbitrary. I suggest adhering to more stringent definitions.	While we agree, the usual age of menopause varies across regions. In an international guideline, it was felt more appropriate to use this term to ensure the recommendations can be applied worldwide.
ACOG	14	rec 50	Perhaps specify that Turner Syndrome in particular is associated with mortality in women with POI due to risk of aortic dissection	We have added this in the text

ACOG		4151	This recommendation reads: "Women with POI and migraine with aura should be advised to use transdermal estrogen as this may be the lowest-risk route of administration." However, the section that it precedes does not mention the specific issue of migraine with aura. A sentence should be added in one of the body paragraphs in this section to address this. It is alluded to above in line 4069 on the section discussing stroke.	The text was modified accordingly.
RCOG		General	The guideline is very comprehensive, expanded many sections, adding recent data, Many summary flow charts/ table/ diagram to follow easily and for easy understanding for the HCPs.	Thank you for this comment
RCOG	9	66	Although acknowledged there may be transgenders or other individuals "women with POI" is used. Wondering whether it is appropriate to use "Individuals with POI" or similar	We have clearly addressed this point and the explanation on why we use "women with POI" in the introduction: In this guideline, in line with published research, the terminology and discussion focus on women. The guideline group recognises that there are individuals living with POI who are transgender or who do not identify with the terms used in the literature. For the purpose of this guideline, we use the term "women with POI". The terminology, however, is not intended to isolate, exclude, or diminish any individual's experience nor to discriminate against any group.
RCOG	14	Rec 46	"Women presenting for oocyte donation who are suspected of having POI should be fully investigated prior to oocyte donation, including thyroid and adrenal function as well as genetic testing." Is doing adrenal function necessary, if the adrenal antibodies are negative and if no symptoms s/o adrenal disease?	The recommendations was modified to refer to the POI investigations mentioned in the diagnosis section.
RCOG	14	Rec 50	"Pregnancy in some women can be of such high risk that clinicians may consider oocyte donation pregnancy to be life threatening and therefore inappropriate." This recommendation is very nonspecific and it is not clear what this recommendation means. Please clarify "some women"	There is further information on risk factors and for instance aortic root cut-off in the text and the guideline group agreed it was not required to repeat the information in the recommendation
RCOG	14	Rec 58	"A daily dose of HT containing at least 2 mg oral estradiol or 100 µg transdermal estradiol or equivalent is suggested to optimise bone density" It is generally considered 50mcg transdermal oestradiol is equivalent to 2 mg oral oestradiol. Further comments on this below.	We have revised the table.
RCOG	22	144	"…oligomenorrhoea, for more than 4-6 months…." Best to define as "4 months" as mentioned in further sections (albeit arbitrary)	We have changed this to 4 months or more and checked that we are consistent across text and recommendations
RCOG	31	465	Recommendation of "… modifiable factors may include: - gynaecological surgical practice - modified treatment regimens for malignant and chronic diseases" There was no mention of gynaecological surgical practice or chronic diseases in the body of text above. It would be appropriate to add some evidence/ data on these in the text above.	We have added a sentence to clarify that the causes of iatrogenic risk are discussed in another section

RCOG	51	1144	The recommendation of " The guideline group recommends that HCPs do not perform TPO antibody screening as part of testing for autoimmune causes of POI due to the high prevalence of positive TPO antibodies in the general community" is a change from last ESHRE. The prevalence of TPO antibodies are more than twice with OR of 2.26 in POI compared to general population. Further, the risk of having thyroid dysfunction in people with TPO antibodies is quite high. Therefore, it is appropriate to consider doing TPO antibodies in women with POI.	In the general population there is consensus that TSH is a better predictor of thyroid dysfunction, while TPOABs provide confirmation of thyroid autoimmunity. TPOABs should also be considered in patients with subclinical hypothyroidism as it can provide information on rate of progression to treatment-requiring hypothyroidism. Of patients with subclinical hypothyroidism (with elevated TSH), 4–5% per year with pos TPOAb progress to overt hypothyroidism compared with 2–3% per year for patients without TPOAb. These patients are however identified by elevated TSH levels. No studies have looked at the predictive value of pos TPOABs specifically in POI. The serum concentration of TPOAb may change over time but repeated measurements are generally not recomended. 1. Dwivedi SN, Kalaria T, Buch H. Thyroid autoantibodies. J Clin Pathol. 2023;76(1):19-28. doi:10.1136/jcp-2022-208290 2. Jonklaas, J., et al., Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement. Thyroid, 2014. 24(12): p. 1670-751 3. Garber, J.R., et al., Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Thyroid, 2012. 22(12): p. 1200-35
RCOG	74	1759	"Overall risk for death related to pregnancy for a patient with Turner Syndrome is ~1%". It would be appropriate to tease out for women with and without risks of aortic dissection.	We have added this to the text
RCOG	84	Table 11	Under "general risk factors for low BMD" Age is mentioned. It would be appropriate to be more specific like other factors – like 'advanced age' or even more specific age <xx/ or > xx years	General osteoporosis risk factors listed here are those relevant to the general population and age is an acknowledged independent risk factor on a continuous scale and included in fracture risk tools.
RCOG	89	2288	2 mg oral oestradiol/ 100 mcg oestradiol suggested to optimize bone density. There are some other documents Eg British menopausal society and table 8 (page 149) of this document stating 2 mg oral oestradiol is equivalent to 50 mcg transdermal patches. So best to be consistent to avoid confusion.	We have revised the table.
RCOG	120; 154-155	3468/4647	Some guidance on monitoring whilst on testosterone replacement (with blood tests for testosterone/ FAI levels) would be helpful for the HCPs – incorporating with in the text or under recommendations.	thank you for the comment. Text modified accordingly.
ASRM		#2	Sentence beginning" Even if this group"-- leave out. this gives too much laxity. almost implying that whatever applies to POI applies to early menopause.	We have adapted the recommendations accordingly

ASRM		#2	How elevated do the gonadotropins need to be? Does this overlap with decreased ovarian reserve? This question is answered in #9 below, but why not list the actual requirement here?	The current statemebt provides an intrroductory statement on the definiton of POI, with furtehr refinement on diagnostic tests and cut offs in other recommendations
ASRM		#5	Starting at "for prevention of POI…"-- can we say that fertility preservation, prevents POI?	We have revised the recommendations on diagnosis to address this and other comments.
ASRM		#9	Starting at "amenorrhea or oligomenorrhea for at least 4"-- This is confusing how it is written. amenorrhea or oligomenorrhea. so a woman misses a cycle and should be evaluated. There are definitions within definitions here making this confusing. clarify what you mean, which I believe you mean no menses for at least 4 months.	We have revised the recommendations on diagnosis to address this and other comments.
ASRM		# 10 and 11	I do not agree with AMH as part of the diagnostic criteria for POI. It is too sensitive; it is low in patients with DOR and can be undetectable in women with regular cycles, therefore a low or undetectable result will not change the clinical picture or diagnosis.	We do not recommend AMH as part of the diagnosis of POI. We only list it as a test that could be used in case of diagnostic uncertainty and consider it should be evaluated with consideration of the clinical context. We have further clarified the recommendation based on other comments
ASRM		#22	clarify that this can be either a medical or reproductive endocrinologist?	Based on other comments stating abnormal TSH levels could be addressed by a GP, we have removed "endocrinologist" from the recommendation.
ASRM			For header "Care for women with POI at diagnosis"-- There is evidence that an endocrinologist is better than an internist can treat hypothyroidism? by endocrinologist, do you mean medical or reproductive? Maybe just state that this needs further evaluation and treatment by a qualified physician?	There was a similar comment, and indeed we have amended to state that Thyroid function should be addressed, but have removed the specification on the professional.
ASRM			For header "PICO Question: What are the implications for relatives of women with POI?"—insert "as needed"	We have changed the question to : What are the possible implications for relatives of women with POI? To address this comment
ASRM		#39	I recommend rewriting this. These women are not donating their eggs but are recipients of donor eggs. Maybe ART with the use of donor oocytes would be appropriate.	We have amended the recommendation to avoid misinterpretation
ASRM		#40	"established" POI should be defined here. I assume amenorrhea with elevated FSH for > 1 year?	We have removed "established" from the recommendation
ASRM		#41-45	Might flow better if placed before #46-50	We consider obstetric risks should be identified to guide assessment for fitness for pregnancy and therefore have not changed the order of the recommendations
ASRM		#46	previously said not to do adrenal testing if 17 OH labs negative. what do you mean by adrenal testing? genetic testing? they are not using eggs with their own genetic material, why would one do genetic testing?	We have adapted the recommendation to read "Women presenting for oocyte donation who are suspected of having POI should be fully investigated for the etiology of POI prior to oocyte donation. " which makes this consistent with the previous recommendations on diagnosis

ASRM		#49	What is the difference between 46 and 49? how does one assess cardiometabolic function	Recommendation 46 referred to women considering oocyte donation, while 49 referred to pregnancy. The changes to recommendation 46 have probably clarified the issue and removed inconsistencies
ASRM		Table 5	I don't believe genetic (karyotyping) is indicated for all patients with POI -(in general not with prior cancer treatment or surgical) This should be noted	We have changed the table and updated the references. We have added a recommendation reading "Women presenting for oocyte donation who are suspected of having POI should be investigated for the aetiology of POI prior to oocyte donation."
ASRM		#58	in young POI patients my understanding is that transdermal estradiol has greater bone benefit than oral… perhaps this should be noted as the preferred route of delivery here	There is only a single small cross-over RCT [Crofton 2010) which compared 100-150mcg transdermal estradiol to cyclic 30mcg oral ethinyl estradiol in women with mixed causes of POI (34 randomised and 18 completed the study) which showed no difference between groups although there was a significant difference in lumbar spine BMD from baseline in those treated with transdermal estradiol. The 2023 Costa systematic review indicated that continuous use of the 30mcg contraceptive pill maintained BMD similar to 2 mg oral estrogen or 100-150mcg estradiol. However, pubertal induction using transdermal estrogen is preferred and this is stated in the guideline. As stated in the guideline HRT should be personalised.
ASRM		#70	Maybe weight bearing exercise for muscle	The recommendation refers to general lifestyle interventions. More specific interventions for muscle health, including "weightbearing exercise" have been included in another recommendation
ASRM		AMH	In sentence starting "As AMH is a direct product…"--AMH threshold or range for a threshold would be helpful for diagnosing POI, if AMH is going to be offered as a potential diagnostic. As is, its says AMH can be used without guidance as what would qualify in a symptomatic patient	We have revised the recommendations, now clearly stating that AMH should not be used as the primary diagnostic test for POI. As such, we did not define cut off levels for POI diagnosis based on AMH.
ASRM			Sentence starting "The exact molecular mechanism by which…"-- it currently suggests inadequate FMR1 protein is the cause of POI, but studies suggests its the excess mRNA in the permutation range leading to toxicity. The current explanation reads incomplete. 10.1261/rna.280807; https://doi.org/10.1086/302720. In fact, even the cited Rosario study suggests excess mRNA as the culprit, not decreased protein as currently cited https://doi.org/10.1086/302720	Section has been amended to provide greater clarity. "According to Rosario et al 2022, two main hypotheses exist, which describe an mRNA toxic gain-of-function mechanism or a protein-based mechanism, where repeat-associated non-AUG (RAN) translation results in the production of an abnormal protein, called FMRpolyG."
ASRM		Figure 7:	its a nice figure. NGS is a tool and could be used to test any gene. Does this mean a POI panel, whole genome, other?	We consider this is explained in the text, and do not consider it required to repeat it in the summary figure

ASRM		Under 1.2.Def of POI	sentence containing "biochemical confirmation of ovarian insufficiency before"-- The definition needs to be clarified. Please state what you mean. no menses for 4 months?	We have added "(elevated gonadotropins and low estradiol)" to the sentence
ASRM			Under POI vs DOR, sentence starting "Low ovarian reserve is a condition…"-- This statement is not correct. There is not evidence that low ovarian reserve results in the loss of normal reproductive potential.	We have adapted this sentence.
ASRM			Next paragraph in this section, sentence containing ", producing poorer quality embryos and reduced…"-- I am unaware of evidence to support this statement that three are poorer quality embryos and reduced implantation rates	This sentence has been revised and adapted
ASRM			Next paragraph starting "It is important to distinguish"-- this does not relate to the two sentences above.	We have reordered the paragraphs, but left the sentence as it reiterates the differences between POI (defined above) and low ovarian reserve (defined in the previous paragraph).
ASRM			II.2—First sentence-- maybe clarify, 4 months of amenorrhea or 6 months of new onset oligomenorrhea? the addition of the oligomenorrhea is new and needs some further clarification	We have removed the term "oligomenorrhea"
ASRM			Sentence beginning "If the clinical presentation and initial biochemical…"-- this needs clarification. estradiol levels are normally less than 50 in women during the early follicular phase. Maybe state <50 in the setting of amenorrhea (meaning they don't have a early follicular phase). need to clarify as you are now including menstruating women in this group.	We have added "in the setting of elevated FSH" to the text.
ASRM			Recommendations starting "Although proper diagnostic accuracy" - As most reproductive endocrinologists are used to checking day 3 FSH and E2, you'll likely need to specify that this should be done randomly during the cycle (in women with oligomenorrhea) and not on day 3.	We have revised the recommendations on diagnosis to address this and other comments.
ASRM		Figure 6	Algorithm for the dx of POI-- This does not match your paper. this adds infertility. please remove. this is saying that all women with infertility need to have their FSH/E2 checked. this is just too broad. maybe add "and"?	We have removed Figure 6 from the guideline.
ASRM		Figure 6	This figure is not helpful and should be removed. if someone came in for oligo/amenorrhea I am checking TSH, prolactin, a pregnancy test, and likely an AMH first.	We have removed Figure 6 from the guideline.
ASRM			Iatrogenic POI, 4th paragraph, sentence containing "the risk of POI was increased with the addition of taxanes…"- please add the comparison group	The text already states "anthracycline versus anthracycline-taxane" to clarify the comparator.
ASRM			Sentence beginning "Gynecological cancers (Estimated"-- clarify comparison groups again, esp. as you state it increases the risk with the addition, but the OR is less than 1	The comment is unclear. The sentence reads "Gynaecological cancers (estimated 1·,8 million diagnosis in women per year) are commonly treated with bilateral oophorectomy, pelvic radiation and/or gonadotoxic chemotherapy, which all potentially induce POI or early menopause [Brennan, 2021 #3092]" and we don't consider this includes a comparator that could be specified

ASRM		Figure 7	Summary of testing to establish…-- just recommend removing refer to endocrinologist.	We changed the wording to "Refer for follow-up testing" as the referral will differ in different contexts
ASRM			Sentence beginning "Two previous meta-analysis…"-- was there an estradiol only group? if so, maybe put all the results in-estradiol only, combo, placebo.? I am confused as to the treatment groups and to whom the results refer.	The two meta-analyses included only studies comparing paroxetine with placebo or no treatment. There was no comparison with estradiol. They showed benefit of paroxetine (compared to placebo/no treatment) for reducing hot flushes in postmenopausal women
ASRM			Section on Gabapentoids-- any studies comparing these agents to HT?	The Shan 2020 meta-analysis included 2 RCTs which compared gapapentin to estrogen and found that estrogen was more effective in reducing VMS frequency (mean difference 1.11; 95%CI (0.69-1.52) and severity (SMD 0.50, 95%CI; 0.14-0.85) compared to gabapentin (low quality evidence). The guideline states that "Gabapentin was less effective than estrogen therapy (2 RCTs)"
ASRM			Under CBT-- maybe educate the reader a little bit more as to what is included in CBT	We have added an explanation reading "CBT is a theory and evidence-based approach to menopausal symptoms using a biopsychosocial model [Hunter 2020]. The CBT intervention for menopausal symptoms provides eight hours of evidence-based information and cognitive behavioural strategies over four to six sessions (one-to-one, self-help or group based) to facilitate self-management of vasomotor symptoms, sleep and mood symptoms [Hunter 2020]. "
ASRM			For sentence beginning "Addition of 5mg melatonin…"—when compared to?	Sentence has been rewritten for clarity: "Compared to treatment with fluoxetine alone, addition of 5mg oral melatonin at night to fluoxetine treatment resulted in increased improvements in sleep quality in an RCT of 64 Polish postmenopausal women [Chojnacki, 2015 #2700]. "
ASRM			CHM vs. HT—how many patients are included in this meta-analysis?	We have added the details (23 RCTs and 1712 patients) to the text
ASRM			Acupuncture vs. HT—number of patients? Quality of evidence?	We have added the details (8 RCTs, 620 patients) to the text together with detail about quality//certainty of the evidence (low to very low).
ASRM			Korean medicine—case series of 3 people. Does this paper really belong in this document. By presenting it, it gives it some credence.	We have removed the case series.
ASRM			Nutrients-- a lot of the studies presented seem to focus on outcomes that are not meaningful. These seem like studies that were designed to "help fertility in women with POI" not sure that all of these papers are really relevant	We have removed the case report.

ASRM			Phytoestrogens: soy, red clover, and flaxseed—recommend removing this paragraph	We have discussed this but decided to keep the introduction
ASRM			Black cohosh—side effects?	We have added the following to text "There have been case reports of hepatotoxicity from black cohosh[Seeff, 2015 #22315] although a 2011 meta-analysis of 5 RCTs (1117 women) did not find differences between adverse event reporting between black cohosh and placebo[Naser, 2011 #22314]. "
ASRM			Recommendation beginning "Women who are considering using other nutrient supplements…"--and not for meaningful outcomes. maybe remove this section?	We have removed the recommendation as suggested
ASRM		Figure 5	The legend could be made a bit clearer as to what each figure represents.	We have revised and where relevant extended the legends for the figures
ASRM	IV-VI.6		Does LVEJ stand for left ventricular "ejaculatory function" or "ejection fraction"?	This is corrected in the text. (left ventricular ejection fraction - LVEF)
ASRM	IV-VI.6	Table V summary	Does "EMBx" refer to an endometrial biopsy? If so, how is it useful? Is it to screen for recurrent cancer? If so, why is it restricted to those with radiation therapy and chemotherapy versus chemotherapy alone?	We have removed this abbreviation
ASRM	VII-X.1		"Females" should be "women"	We have adapted this throughout the guideline
ASRM	VII-X.1		For phrase "once the hormone profile is adjusted"-- Does this refer to hormone replacement regimen? Requires clarification	We have adapted the sentence to read "in addition to adequate HT", without details as these are covered in the HT chapter
ASRM	VII-X.1	3152	"sexuality" should be "sexual". Patients don't change their sexual orientation due to POI… sexual function is used later	This is corrected in the text.
ASRM	XI-XI.6		I feel we are missing data on endometrial monitoring when using estrogen/progesterone (whether data supports or refutes it). Otherwise, well written section.	The Guidleine group doiscussed this comment, but at this stage it was not possible to add another topic and section to the guideline,
ASRM	XII-XIII		"patent medicines" needs definition	We have added an explanation as a footnote
ASRM	XII-XIII		the herbal products should all have a definition with an asterisk at the bottom of the page-only some do. The one listed here does not	We have considered adding additional information on the herbal medicine ingredients, but as none are recommended and considering the length of the document and the limited relevance of this information, we have only included a footnote to say that the reader is referred to the cited references for more details on the composition of the herbal medicines evaluated

ASRM	XII-XIII		Acupuncture: a problem with most acupuncture studies is the lack of a sham/ control arm. The placebo effect lasts 3 months, so it is important that all the studies cited using acupuncture outline how long the trials were. For example, one cited on line 5130 was a 3 month long case series	We have added the following re duration of treatment - "Treatment duration ranged from 3-6 months with most trials providing treatment for 6 months"
RANZCOG			The guideline confirms current practice in her experience and notes the commentary on newer pharmaceutical options that have been released onto the Australian market.Questions regarding what constitutes adequate progesterone replacement in the higher doses of estrogen used in POI women are often top of mind in practice, and this document confirms a lack of data on this topic.	Thank you for this confirmation.
RANZCOG	23	165	Diminished ovarian reserve may result in a reduced ovarian response to ovarian stimulation, the quality of embryos that result really depends on the age of the woman - see ASRM POSEIDON criteria.	This sentence has been amended.
Jennifer Merrill	38	645	Recommend further clarification by saying "fragile X premutation" here rather than fragile X syndrome. The syndrome refers to those with over 200 CGG repeats, and this is not associated with FXPOI, as noted elsewhere). This is important because Fragile X syndrome is also associated with severe intellectual disabilities, while the premutation is not, so correctly naming the distinction is critical. Some clinicians assume women with Fragile X premutation are intellectually disabled and treat patients as such after this diagnosis.	Thanks for pointing this out, we have adapted the text accordingly
Jennifer Merrill	41	799	Two associated conditions, FXPOI and FXTAS, are mentioned in this section. Researchers have also identified Fragile X Associated Neuropsychiatric Disorders (FXAND) (Hagerman et al, 2018). European Fragile X community has decided to call this FXANC, replacing "condition" for "disorder". FXAND/FXANC describes elevated rates of mood and psychiatric conditions associated with the premutation, irrespective of POI status: "Neuropsychiatric disorders are the most common problems associated with the premutation, and they affect approximately 50% of individuals with 55 to 200 CGG repeats in the FMR1 gene. Neuropsychiatric disorders in children with the premutation include anxiety, ADHD, social deficits, or autism spectrum disorders (ASD). In adults with the premutation, anxiety and depression are the most common problems, although obsessive compulsive disorder, ADHD, and substance abuse are also common. These problems are often exacerbated by chronic fatigue, chronic pain, fibromyalgia, autoimmune disorders and sleep problems, which are also associated with the premutation." This is important to mention because women with POI are already at risk for anxiety and depression, and being a Fragile X premutation carrier further increases that risk.	This is important but we consider this is already described in the text

Jennifer Merrill	42	814	There are two leading theories for the mechanism behind FXPOI. Neither is exactly as described here (inadequate FMR1 protein production). According to Rosario et al 2022 (cited in the guidelines): "Two main hypotheses exist, which describe an mRNA toxic gain-of-function mechanism or a protein-based mechanism, where repeat-associated non-AUG (RAN) translation results in the production of an abnormal protein, called FMRpolyG. See also Rosario and Anderson, 2020. Also, the text here is unclear and possibly misleading: "when CGG trinucleotide repeats of the FMR1 gene are duplicated to 55-200 repeats the premutation becomes unstable..." 55-200 CGG repeats is the definition of the premutation, and the premutation is by definition unstable - but this refers to its tendency to expand in subsequent generations, when the affected X chromosome is passed to offspring, not within the woman with the premutation.	We agree that there seems to be uncertainty regarding the exact mechanisms of how FMR1 premutation results in depletion of ovarian reserve. The text has been amended according to suggestions.
Jennifer Merrill	126	3607	The abbreviated version of Fragile X-associated tremor/ataxia syndrome is FXTAS (not FTAS) - this should also be corrected in Annex 2 (Abbreviations)	Thank you for noticing this typing error.