European Society of Human Reproduction and Embryology

External Review report

"Management of women with Premature Ovarian Insufficiency"

Review period: 11/06/2015 – 06/08/2015

INVITED REVIEWERS

Open invitation:

- Email sent to members of the SIG Reproductive endocrinology (primary or secondary interest)
- Slide on the ESHRE website
- Social media
- In the ESHRE 2015 conference app

Personal invitation (relevant stakeholders)

- Coordination of the SIG SQUART and SIG Reproductive endocrinology
- Experts as suggested by the members of the guideline group
- Interested reviewers
- Representatives of relevant professional organizations
    - Societies on infertility and reproductive medicine
    - Reproductive endocrinology & menopause societies
    - National European societies on infertility and reproductive medicine
    - Societies on (reproductive) endocrinology

Reviewers were requested to use the provided "reviewers' comments form" for submitting comments. The form requested information on the reviewer, and his/her COI, and comments for each of the sections of the guideline.

REPORT ON THE REVIEWERS

In total 34 reviewers responded to our invitation and have sent in their comments to the guideline. In the table below, the reviewers are sorted based on the invitation they received and the continent / country they are located in.

Reviewers per method of invitation and response rate

Invitation	Stakeholder	Number of reviewers
Open	Members of the SIG Reproductive endocrinology, or general ESHRE public	11
Personal	Coordination of the SIG SQUART	3
	Coordination of the SIG Reproductive endocrinology	2
	Representatives of relevant professional organizations	7
	Interested reviewers	5
	Experts as suggested by the members of the guideline group	6

Number of reviewers per country

Europe	*29 (85.3%)*
UK	*9*
Italy	*4*
Belgium	*2*
Greece	*2*
Spain	*2*
Austria	*1*
Finland	*1*
France	*1*
Ireland	*1*
Norway	*1*
Poland	*1*
Portugal	*1*
Romania	*1*
Switzerland	*1*
The Netherlands	*1*

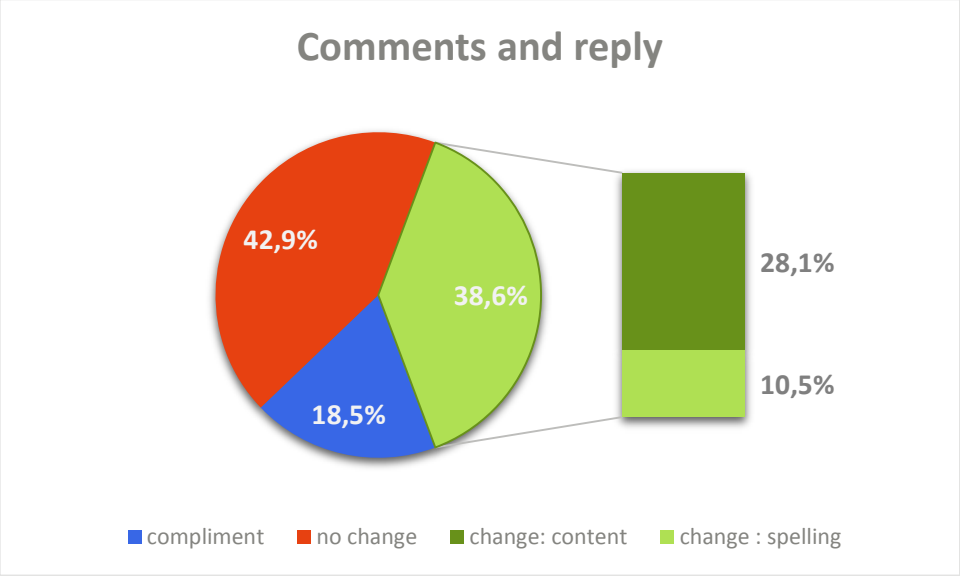
Non-Europe	*5 (14.7%)*
Brazil	*1*
India	*1*
Malaysia	*1*
Thailand	*1*
USA	*1*

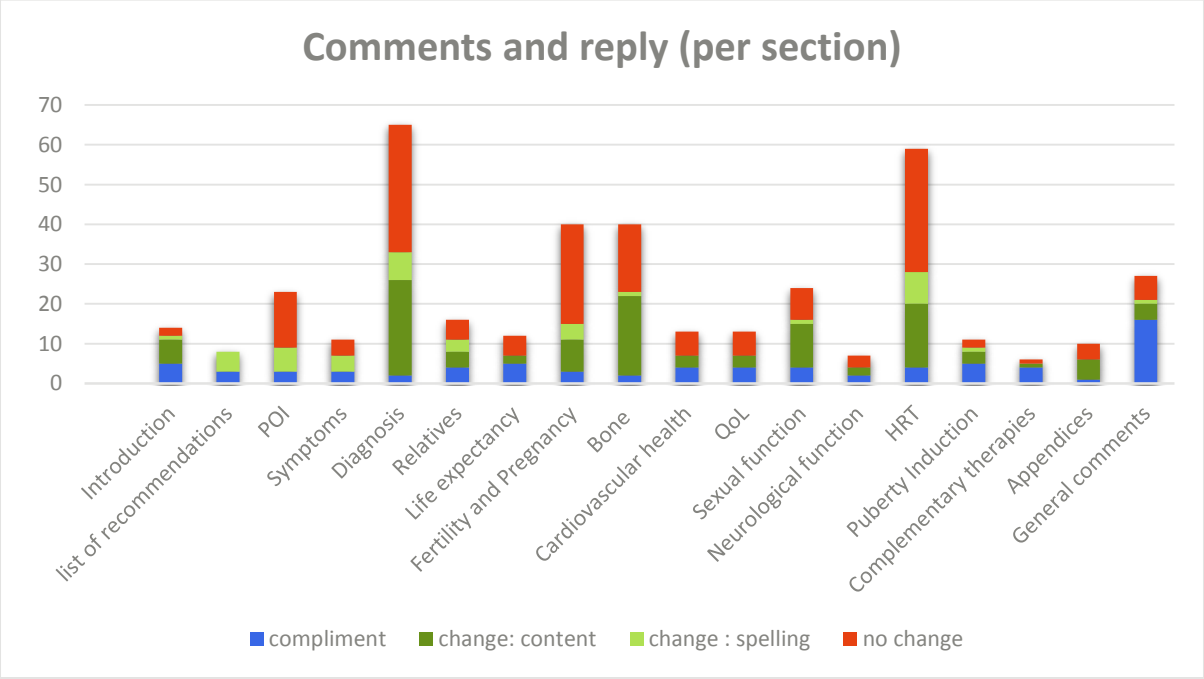
LIST OF EXTERNAL REVIEWERS

Name	Country	Organisation	COI
Patsama Vichinsartvichai	*Thailand*	*Faculty of Medicine Vajira Hospital*	*No*
Giampaolo Mainini	*Italy*	*San Leonardo Hospital Castellammare di Stabia- Naples*	*No*
Arianna d'Angelo	*UK*	*Cardiff University*	*No*
Adam Balen	*UK*	*British Fertility Society & ESHRE*	*No*
Ioana Rugescu	*Romania*	*AER EMBRYOLOGISTS ASSOCIATION*	*(Yes)*
Dr. Michael Feichtinger	*Austria*	*Medical University of Vienna, Department of Obstetrics and Gynecology*	*No*
Roberto Matorras	*Spain*	*1)Basque Country University, 2)IVI Bilbao, 3)Cruces Hospital*	*No*
Jan Bosteels	*Belgium*	*staff member of CEBAM, the centre for EBM, Belgian Branch of the Dutch Cochrane centre and editor of the Menstrual Disorders and Subfertility Group of the Cochrane Collaboration.*	*No*
Dr. Joe Leigh Simpson	*US*		
Dr. Gianluca Di Luigi	*Italy*	*University of L'Aquila-Department MeSVA*	*No*
Katharina Schiessl	*Switzerland*	*gynécologie Suisse* *Swiss Menopause Society*	*No*
Prof. Andrea Lenzi	*Italy*	*Italian Endocrine Society*	*No*
Annemieke Hoek	*The Netherlands*	*Universitair Medisch Centrum Groningen*	*(Yes)*
Mukhri Hamdan	*Malaysia*	*University Malaya*	*No*
Stephen Franks	*UK*	*Society for Endocrinology*	*No*
Dr Nidhi Sharma Chauhan	*India*		*No*
RCOG - Dr Mostafa Metwally	*UK*	*RCOG*	*No*
Michał Kunicki	*Poland*	*Invicta Private Fertility Center; Warsaw, Warsaw Medical University, Gynecologial Endocrinology Department,*	*No*
Cristina Laguna Benetti-Pinto	*Brazil*	*University of Campinas - UNICAMP*	*No*
George Basios	*Greece*	*Assisted Reproduction Unit, 3rd Department of Obstetrics and Gynecology, Attikon University Hospital, Athens*	*No*
Beatriz Alvaro Mercadal	*Belgium*	*Hôpital Erasme, Université Libre de Bruxelles*	*No*
Zdravka Veleva	*Finland*	*Department of Obstetrics and Gynecology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland*	*No*
B Mallikarjuna Kirthi	*UK*	*NHS GRAMPIAN . SCOTLAND*	*No*
Fernanda Águas	*Portugal*	*Portuguese Gynecology Society*	*No*
Stratis Kolibianakis	*Greece*	*Aristotle University of Thessaloniki*	*No*
Sophie Christin-Maitre	*France*	*AP-HP, Hôpital Saint-Antoine, University Paris VI, Paris, France*	*No*
Daniela Romualdi	*Italy*	*Università Cattolica del Sacro Cuore - Rome*	*No*
Kate Maclaran	*UK*	*The Daisy Network*	*No*
Inger Overlie	*Norway*	*Eli Lilly Norway*	*Yes*
Nivedita Reddy	*UK*	*dept of reproductive medicine , guy's hospital. london*	*No*
Professor Philippe Bouchard		*European Society of Endocrinology*	*No*
Nick Panay	*UK*	*British Menopause Society*	*Yes*
Manuel Puig Domingo	*Spain*	*President of the Spanish Society of Endocrinology and Nutrition*	*?*
Mary Wingfield	*Ireland*	*Merrion Fertility Cl*	*?*

STRATEGY

399 comments were received from 34 reviewers. All comments are summarized in the tables below (per section). Each comment was assessed by the chair of the guideline group, the research specialist, and if needed the guideline group members. 74 comments were compliments to the guideline, or statements of agreement with the content. 325 comments were formulated requesting a change in the guideline, of these 154 were considered valid and resulted in a modification in the guideline text, either the correction of a spelling error, a typo or a request for rephrasing (42 comments), or a modification of the content of the guideline (112 comments). The remaining 171 comments were assessed, but did not result in a change in the guideline. A reply to the reviewer was formulated in the tables below.
The numbers for the entire document, and the individual chapters are summarized in the graphs below.





COMMENTS (PER SECTION)

Comments to "Introduction to the guideline"

Reviewer	Comments	Reply
Patsama Vichinsartvichai	- Page 5 line 5-8: there is also other guideline by the International Menopause Society in 2013 (de Villiers TJ, et al. Climacteric 2013;16:316-37) that mentioned about the optimizing hormone therapy of POI patient	We have added the reference to this guideline.
Adam Balen	This is excellent.	Thank you.
Ioana Rugescu	page 5 line 8 (comments) : the following guidelines also mention Premature Ovarian Insufficiency [POI] : 1. Long term follow up of survivors of childhood cancer. A national clinical guideline. 2004 Jan (revised 2013 Mar). NGC:009786 Scottish Intercollegiate Guidelines Network - National Government Agency [Non-U.S.]. 2. Advanced reproductive age and fertility. 2011 Nov. NGC:008838 Society of Obstetricians and Gynaecologists of Canada - Medical Specialty Society. 3. The 2012 hormone therapy position statement of The North American Menopause Society. 2002 Oct 6 (revised 2012 Mar). NGC:008998 The North American Menopause Society - Nonprofit Organization. 4. Genetic counseling and testing. In: Guidelines for preventive activities in general practice, 8th edition. 2012. NGC:009640 Royal Australian College of General Practitioners - Professional Association. 5. Cardiometabolic risk management guidelines in primary care. 2008 (revised 2011). NGC:008626 Qatif Primary Health Care - National Government Agency [Non-U.S.]. 6. ACR Appropriateness Criteria® follow-up of Hodgkin lymphoma. 1999 (revised 2014). NGC:010469 American College of Radiology - Medical Specialty Society.	Thank you for your suggestion. We have added some guidelines of which we felt they were relevant.
Gianluca Di Luigi	Page 5, lines 26-27 and "the oncological aspect?"	The “oncological aspect” was not included in the scope or the key questions for this guideline. The “oncological aspect” is only discussed in as a special circumstance.

Andrea Lenzi	This referee found the the introduction clear and concise	Thank you.
Stephen Franks	Good introduction	Thank you.
Nidhi Sharma Chauhan	Well described. A guideline lije this was necessary for the practising gynaecologist as well as other healthcare professionals as to help them in understanding POI and referring women where necessary	Thank you.
George Basios	Page 1, line 5: Add a sentence about the lack of a clear and universal definition of POI? (eg often mentioned wrongly as "ovarian failure" etc) Page 1, line 26: Add also mental health?	Thank you for your comment. We have added a sentence on the definition of POI in the scope section.
Stratis Kolibianakis	Please give reference for "grades of recommendation" (page 7)	A reference was added for the grades of recommendations
Inger Overlie	PART A. Introduction to the guideline consists of definition and epidemiology of POI and that the target users of this guideline is primarily gynecologists, but also targeted at healthcare professionals of other disciplines.	We feel this comment does not require a modification of the guideline or a reply.
Nick Panay	Page 5, lines 26-27 : Contraceptive issues?	As contraception was described, it has been added to the list, as suggested.
Mary Wingfield	Guideline Scope - page 5: As many readers, including myself, will be working in the fertility area and as women increasingly seek to have their AMH levels measured, it is likely that medical professionals see many more patients with reduced ovarian reserve rather than POI. I therefore suggest that the distinction between premature ovarian insufficiency and low ovarian reserve be mentioned under the paragraph on guidelines scope. I suggest that a line, something similar to lines 86 to 88 on page 23, be added to the "Guideline scope", mentioning that the guideline does not apply to women with low ovarian reserve per se. I find that the titles of sections on the contents page is not followed throughout the gu ideline either in the list of recommendations or the body of the guidelines. This is a little bit confusing (e.g. the list of recommendations and the body of the guidelines talk about part A and part B but this is not reflected in the list of contents).	Thank you for your comment. We have added a sentence on POI versus low ovarian reserve in the scope section. Also, we have reviewed the content page. The indication of Part A,B,C seems to have disappeared. We have corrected this.

Comments to "List of all recommendations"

(some comments were added to the specific chapters)

Reviewer	Comments	Reply
Patsama Vichinsartvichai	- There's no line number present in "List of all recommendations" section.	Line numbers will be deleted in the final version.
Adam Balen	These are excellent, appropriate and I agree with them.	Thank you.
Roberto Matorras	I miss a recommendation saying "Ovarian conservative surgery is highly recommended in women under 40 in order to avoid POI. If not possible such in some malignancy cases, ovarian tissue preservation should be considered"	After discussion within the guideline group, it was decided not to include the topic of fertility preservation, or the prevention of POI in the current document. We decided to focus on the management of POI. Fertility preservation and the prevention of POI may be considered for future ESHRE guidelines
Andrea Lenzi	The list of recommendations seems to be complete. Just wondering whether some dermatological aspects could be of any relevance since an early senescence could be associated	Thank you. We have assessed you comment, but dermatological aspects were outside the scope of this document.
Mukhri Hamdan	List of all recommendations are well written and concise.	Thank you.
Nidhi Sharma Chauhan	Mention can be made point by point to highlight the areas where this guideline will cover POI (i.e. implications of POI on bone health, neurological health, cardiovascular health)	Thank you for your comment. We believe the areas discussed are clear from the key questions in the list of recommendations.
Stratis Kolibianakis	The logical sequence is first to define the condition("how should POI be defined") and then to ask "how should this condition be called" (page 8)	Thank you for your comment, but we feel that naming the condition should be discussed first, hence we did not change the order of the sections.
Inger Overlie	Interpretation on the grades of recommendations are listed, which gives the reader easy access and understanding of the importance of the supporting studies and data.	Thank you.

Comments to - 1 : Premature Ovarian Insufficiency

Reviewer	Comments	Reply
Arianna d'Angelo	page 23 line 93: should we add low AMH?	Thank you for your comment. The GDG strongly believes AMH should not be added, the explanation is mentioned on p30 (lines 29-38)
Adam Balen	Excellent and well written.	Thank you.
Ioana Rugescu	page 20 line 17 : maybe a evolution of terminology it will be important. page 21 line 27 : in the context of the Figure 1.1Number of PUBMED citations using the term "Premature Ovarian Insufficiency" per year it will be interesting the no of citation per year for other terms.	Thank you for the suggestion. We agree with you, but as the document is already extensive, and adding these data will not necessarily impact on clinical practice, it was decided not to expand this section.
Michael Feichtinger	Page 22, line 57: Women with POI do not only suffer from vasomotor symptoms and symptoms associated with estrogen deficiency, but they can also experience infertility and psychological problems with a significant impact on their quality of life. When patients already suffer from symptoms of estrogen deficiency they are usually already infertile so it would be clearer to take away the "can" in the sentence "they can also experience infertility"	Thank you for your comment. In theory not all women will suffer from vasomotor symptoms, and not all women may suffer from infertility, Certainly, not all women will have psychological problems. We have changed the sentence, which now states that "Women with POI MAY not only suffer from vasomotor symptoms…." reflecting that not all women with POI have symptoms of low E2
Michael Feichtinger From comm to list of recs	Page 8: How should POI be defined? POI is characterised by menstrual disturbance (amenorrhea or oligomenorrhea), raised gonadotropins, and low estradiol. Maybe menstrual irregularities would fit better?	Thank you for suggestion, but we prefer disturbance as it covers the episodes when there are regular cycles. Also an irregular cycle has a different connotation – usually used to mean something between regular and oligomenorrhoeic. Therefore, we decided to keep "menstrual disturbance" in the guideline

Roberto Matorras	p.21; l 41 I fully agree with the considerations made regarding the terms "primary" and " secondary".	Thank you.
Joe Leigh Simpson	Part A - p. 22-23 1 I am on record as not favoring the term POI as the only term encompassing so many heterogeneous conditions under its umbrella. I am a splitter (most geneticists are) and not a lumper. However, I realize those on this committee have a different perspective. Puzzling, however, is the exclusion of Low Ovarian Reserve (LOR); many conditions covered in this opus have LOR, either congenital or because of diseases that arose after birth. The usual sequence is first LOR and then PPOI. Not infrequently, autosomal genes causing "POI" manifest as secondary amenorrhea after a few years of menses; subjects were born with fewer follies, i.e., low reserve. Sometimes they have a sister with primary amenorrhea. So far as "insufficiency" per se is concerned, how can one justify the logic of "iatrogenic" (surgical extirpation) being labelled POI. If POI connotes reversibility this is logical for autoimmune cases but illogical after surgical extirpation. 2 It should also be mentioned that OMIM and the Human Genome Organization (HUGO) has long designated genes causing ovarian failure as POF (now POF 1-9). Thus, the POI nomenclature may be favored among REI but it will not be universally accepted. In addition, the Disorders Sexual Development classification (DSD is used by clinical geneticists and universally by pediatricians). POI as defined here (including 45,X) could be classified under DSD. In this discussion on choosing POI as being more "correct", I would have thought the Committee would have covered DSD as well. In brief, announcing committee consensus without examining alternatives seems less than rigorous.	Thank you for your comment. We realise that the terminology is problematic and emotive and that we have been controversial in this decision. However, it was felt that this guideline should revise and lead, rather than follow past, perhaps out-dated terminology for the benefit of patients. 1. LOR was excluded from the scope of the Guideline, as the aim is to inform on the management of the end stage of this condition. Most of the consequences of POI (apart from infertility) arise once the condition is established. 2. There was a universal and strong consensus from both the committee and the workshop that the word failure was both inaccurate and undesirable. There is clearly an overlap with DSD, but not all POI would be classified as such e.g. iatrogenic. In addition, whilst some "idiopathic" cases may be born with a LOR, we do not (yet) know that for all (the majority?) of cases.
Katharina Schiessl	p8 How should POI be defined? The definition includes low estradiol, even it is very difficult, to define this. Otherwise in the "perimenopausal" situation there might be times of highly elevated estradiol in relation to persistent follicles.	Thank you. Since most of the consequences of POI are due to low estrogen, it is not until the estrogen falls that the definition applies. Therefore, we have not altered the definition as suggested.
Nidhi Sharma Chauhan	In prevalence, a line or two about varied ethnicity can be made. The prevalence rates across Europe is small in comparison with the Asian countries (incidence and prevalence in Asian countries) [page 8]	Thank you for your comment. We had already included a sentence on ethnicity in the prevalence section.

Michał Kunicki	Page22, line 67: the information is provided that the natural menopause under 40 year is approximately 1 %. I think that the frequency of POI should be specified in age categories: to 20, 20-30 and-30-40 years old. Are there any race differences in the prevalence of POI?	Thank you for your comment? The frequency of POI in the different age categories in illustrated in figure 1.2, so we decided not to add this to the text. Also, ethnical differences have been described.
George Basios	Page 24, line 110: Natural Menopause highlighted in bold. 2-3 lines for natural menopause and then factors...	We assume you suggest a formatting change and expansion of comments on natural menopause, but we decided not to change the text.
George Basios From comm to list of recs	Page 8: How should POI be defined? POI is characterised by menstrual disturbance (amenorrhea or oligomenorrhea), raised gonadotropins, and low estradiol - Should we mention If 3 out 3 criteria must be present?	We have clarified this comment by modifying the recommendation (we added "with" between oligomenorrhoea and raised gonadotropins)
Zdravka Veleva	p. 23/line 93 - perhaps the word "depletion" is not correct since it suggests previous follicular activity, yet in the cases of women with Y-chromosome (included in POI) this is not true. Also, maybe the definition should mention that menstrual disturbances can be either primary (specifically primary amenorrhea) or secondary including iatrogenic causes?	Thank you for your comment. We have decided to change the definition to "Premature Ovarian Insufficiency is a clinical syndrome defined by loss of ovarian activity before the age of 40. "
Stephen Franks From comm to list of recs	P8 "How should POI be defined?" Although there clearly is depletion of the follicle pool in POI, this is a continuous process that goes on from before puberty, so "depletion of follicular activity before the age of 40" seems a bit ambiguous.	Thank you for your comment. We agree that depletion of follicular activity is a continuum, but nevertheless it is a central part of the condition: perhaps this highlights the need for greater understanding of the pathology of the condition. We have decided to change the definition to "Premature Ovarian Insufficiency is a clinical syndrome defined by loss of ovarian activity before the age of 40. "
B Mallikarjuna Kirthi	Page 22 line 64 The age of 40 is for all women worldwide? Or for European population? Page 23 line 93. What is the accepted follicular activity before 40 ? How to measure depletion?	Page 22: As this guideline is targeted at a European population, we have mainly considered the European context. In theory, each region could set an age based on the regional average age of natural menopause, but a pragmatic approach would be to use 40 yrs worldwide. Page 23: Based on other comments we have changed the definition to: "Premature Ovarian

		Insufficiency is a clinical syndrome defined by loss of ovarian activity before the age of 40. “
Sophie Christin-Maitre	this section is very interesting and very documented. In the prevalence section, the recent Chinese study, Shangai women’health study mentionned later in the text could be added. The prevalence of POI is 2.8%.	Thank you for your comment. There is indeed a discrepancy between the study of Luborsky that investigated prevalence in different ethnic groups in the US, and the study of Wu (2014) describing a prevalence of 2.8% in Chinese women. We have adapted the sentence and added the reference.
Inger Overlie	PART A. Introduction to the guideline : consists of definition and epidemiology of POI and that the target users of this guideline is primarily gynecologists, but also targeted at healthcare professionals of other disciplines.	We feel this comment does not require a modification of the guideline or a reply.
Nick Panay	How should POI be defined? Recommendation Why follicular "activity" rather than follicles?	Thank you for your comment. Follicular activity implies follicle growth. We can’t say follicle absence since follicles are clearly still present. We understand this is not ideal, but have kept follicular "activity" in the recommendation
Nick Panay	BMS AGREES WITH THIS TERMINOLOGY	Thank you
Mary Wingfield	Iatrogenic Menopause - page 24: While hysterectomy and oophorectomy rates are important, I would feel that it is equally important to mention other surgical causes of premature ovarian insufficiency, particularly surgery for benign conditions such as ovarian cysts and in particular, endometriosis? and uterine artery embolization for fibroids. Ovarian surgery is mentioned in section 3.2 d but uterine artery embolisation is not.	Thank you for your comment. We have added a sentence on endometriosis is section 1.3 which makes it consistent with section 3.2d This guideline is about management of POI, not prevention, so we have kept the information on prevention limited. Furthermore, there is a lack of evidence on the topic and a recent review by Kaump et al (2013) states: Data from randomized trials and prospective case series suggest that degradation of ovarian function may occur after UAE, but is concentrated in women older than age 45 years, with little evidence of an impact in women younger than 40 years of age. Therefore we have not highlighted UAE as a cause of POI in the guideline

PART B: Diagnosis of POI

Comments to - 2 : Symptoms of POI

Reviewer	Comments	Reply
Arianna d'Angelo	Page 28 line 4 is not necessary.	We have not deleted the reference to the chapter on diagnosis.
Adam Balen	Excellent and well written.	Thank you.
Michael Feichtinger	Page 28 line 10: "Vaginal symptoms, dyspareunia and dryness, may be very distressing for the patient" I would write line 12: altered or lowered urinary frequency?	We have incorporated your suggestions in the guideline text.
Andrea Lenzi	I agree with the authors	Thank you.
Stephen Franks	Excellent section	Thank you.
Nidhi Sharma Chauhan	Small questionnaire highlighting two main clinical symptoms of estrogen deficiency so the clinician can do an objective scoring of the patients. This may help in charter analysis later [page 9]	Thank you for your comment. Developing a questionnaire and validating it was outside the scope for this guideline. Regarding scoring menopausal symptoms, the Menopause Rating Scale could be used.
RCOG - Mostafa Metwally	line 296 - Disclosure and screening related recommendations to be placed before antenatal recommendations. We suggest moving 298 and 299 at 296 (ie after first recommendation of this heading).	Thank you for your suggestion. We put the recommendations in this order as we started with spontaneous pregnancies, then moved to egg donation, but actually those with uterine irradiation are very unlikely to be spontaneous (although TS could be) Therefore we have changed the order of the recommendations, as suggested.
George Basios	Page 28, line 16: Add a sentence mentioning that menstrual disturbances sometimes might proceed or be the first symptom or prelude of POI	Thank you for your suggestion, we have modified the sentence accordingly by adding "sometimes preceded by menstrual cycle changes".

Stratis Kolibianakis	Page 9: The answer to the first question: "What are the symptoms of Premature Ovarian Insufficiency?" is indirect. A direct answer to the question asked would be : estrogen deficiency symptoms (perhaps with more details), oligomenorrhea or amenorrhea. page 9: "POI needs to be excluded in women with amenorrhea or estrogen-deficiency symptoms below the age of 40 years." I would add: POI needs to be excluded in women with amenorrhea/oligomenorrhea or estrogen-deficiency symptoms below the age of 40 years.	We agree with your comment, but decided not to change this in the guideline. Regarding the second comment, we have added oligomenorrhea as suggested
Inger Overlie	PART B. Diagnosis of POI including symptoms, covering initial assessment, chromosomal and genetic defects as a cause of POI, especially Turner Syndrome and Fragile X syndrome and discussing the implications of POI also in terms of relatives of women with POI.	We feel this comment does not require a modification of the guideline or a reply.

Comments to - 3 : Diagnosis and initial assessment

Reviewer	Comments	Reply
RCOG - Dr Mostafa Metwally	line 98 -An FMR1 premutation is defined as more that 55 but less than 200 CGG repeats, so we feel that this should be stated rather than using 60-200 repeats. We think the term intellectual disability should be used instead of mental disturbances. We recommend the wording 'women who carry the premutation (55-200 repeats) do not have an increased risk of intellectual disability'	Thank you for your comment. We have modified the sentence as suggested.
Patsama Vichinsartvichai	No comment. All appear systemical order and clearly explained.	Thank you.
Arianna d'Angelo	1. page 30 lines 9 and 10: do we need to write in anticipation what happens in the following chapters? 2. page 31 : should we add the timing for the FSH assessment? If someone has a period the test should be assessed between day 2-4 of her cycle. 3. page 31 line 50: I would add low AMH as addition to the other two symptoms/signs. 4. page 33 line 88:Chromosomal analysis should be offered to all women with POI except when this was caused by gonadotoxic drugs (chemotherapy) 5. page 33 line 117: rephrase, it does not sound correct english 6. page 39 line 326: mumps spelling mistake	1. We have considered shortening the introductions, but we think it is important here to break down diagnostic tests 2. We decided not to add a timing for FHS assessment as it will encourage waiting for a period to do the test and most will be amenorrhoeic. 3. We have discussed AMH extensively in the GDG group and it was decided that low AMH should not be added to the POI symptoms. 4. Based on this comment, we have added "non-iatrogenic POI" to the recommendations 5. The phrase in line 117 was corrected 6. The spelling mistake was corrected
Adam Balen	Excellent and well written.	Thank you.
Dr. Michael Feichtinger	1. Page 30 line 18: Maybe "(FSH) levels are used as the gold standard in establishing a diagnosis of POI but there is insufficient high quality evidence on adequate cut-off levels" 2. Page 40 line 355: there is no recommendation for iatrogenic causes of POI	1. We have improved the guideline text based on your comment 2. We have added a recommendation for iatrogenic POI: "The possibility of POI being a consequence of a medical or surgical intervention should be discussed with women

		as part of the consenting process for that treatment"
Roberto Matorras	1. Pag 30/ line 28: Concerning FSH values > 25 mUI/ mL, I would higlight the need to rule out the possibility of an ovulatory peak 2. Pag 37/ line 231 : I my oppinion in POI cases due to surgery or radiotherapy or genetic causes, immunology studies would be of little help. This, I would suggest this small change in the recommendation. Screening for 21OH-Ab (or alternatively adrenocortical antibodies (ACA)) should be performed in women with POI of unknown cause or if an immune disorde is suspected. Refer..... 3. pag 37/ line 259 : I my oppinion in POI cases due to surgery or radiotherapy or genetic causes, immunology studies would be of little help. This, I would suggest this small change in the recommendation: Screening for thyroid (TPO-Ab) antibodies should be performed in women with POI of unknown cause or if an immune disorde is suspected. 4. Pag 41/ line 388: In the figure, I would change the term " malignant" by " after cancer treatment". (If not changed someone could think that in POI a through study should be done to rule out malingancy). Similarly I would change the term benign by " benign (including ovarian surgery)".	We state that a cut off level of FSH > 25 mIU/l is above the physiological range for FSH even at the pre-ovulatory peak.Furthermore, we also mention Low estradiol. We have modified the recommendation by adding "of unknown cause or if an immune disorder is suspected, as suggested. The recommendation was changed as suggested We have changed the figure, as suggested.
Dr. Joe Leigh Simpson	1. p. 32: This section does not mention copy number variants (CNV), those micro deletions smaller than the 5-7 Mb needed for a visible karyotypic abnormality. This deserves its own heading for CNV changes are being found in POI cases. 2. p. 33 : The main reason one should counsel relatives after detection of Fragile X is that in any female carrier premutation expansion can occur during meiosis and lead to a male offspring with mental retardation (7200 CGG repeats). It is, in my opinion, below standard not to offer testing in all first or second females relatives especially if the pedigree reveals any males with mental retardation; "careful counseling" is too nonspecific. 3. The exact definition of a FMR premutation is 55-199 CGG repeats, not 50-200. There is a "gray" zone of 40-54, a concept not mentioned. 4. p. 34: The "autosomal gene" mutation section could be greatly expanded. As examples: a. FSHR mutations are a common explanation for POI in Finland; I would imagine this is being routinely tested. Half of all cases are due to a single missense mutation, so this would be inexpensive. b. Today there are quite a few more mutant genes than mentioned (e.g., NOBOX, FIGLA as examples for which functional studies have proved causations). The key message is not a gene list but stated in that usually these perturbations are found in only 1-2% of POI within a given ethnicity.	1. Based on this suggestion we have added a paragraph on GWAS and CNV 2. Thank you for your comment. This guideline focusses on women with POI, and states that FRAXA testing should be offered to probands but only after counselling: some do not want to know, sometimes because they don't want to face the implications for relatives. However, as we agree with your comment, we have added more specific information on genetic counselling for FMR1 to the discussion. 3. We have used the number of repeats as mentioned in the Wittenberger paper. We have added the intermediate sized CGG repeats to the evidence, although the implications are not well understood.

	c. Still, in aggregate at least 10-15% of POF/POI cases are caused by a mutation. In the future targeted panels can be expected, as they exist already for DSD disorders and for skeletal or cardiac dysplasias. d. Recall in that POF mutations may involve mitochondrial genes as well as nuclear genes. 5. P 34: There is little mention of the considerable number of pleiotropic single gene explanations for POI. The one mentioned is BPES which, should be noted, is caused by mutations in FOXL2. Others disorders include not just galactosemia, but as examples ataxia telangiectasia (ATM), Bloom syndrome (BLM), Werner Syndrome(WRN), Rothmund-Thompson Syndrome (RTS), and others. 6. p. 35: Care to mention that ovarian failure can be the result of mutation in genes in adrenal pathways, i.e., CYP17 and CYP19. 7. p. 41: This graph is misleading because it is highly doubtful that in 2011 there was any systematical search for gene mutations by molecular testing. WES was not readily used. Absent systematic genetic tests (as routine now in most cancers), the "idiopathic" bar would decrease and genetic increase. At least acknowledge the outdated data. 8. p. 46: Previously (Part B-1 p.33) I commented on the need for stronger recommendation in testing female relatives of a proband with a fragile X mutation 9. p. 47: The statement that no predictive test can identify women who will develop POI is very reasonable but not 100% true. If a younger sister of a patient with proven POI has the same mutation (e.g., FSHR or FOXL2) she will almost certainly develop POI. She should be managed with that expectation.	4. Although autosomal abnormalities have been identified in POI patients, there is not always a causative relationship. 5. We have considered your comment, and have rewritten this section mentioning the pathways in which mutations were found, with some examples of genes. We decided that a list of genes would never be complete or up to date, and as it is not clinically relevant, we should avoid it. We have added that BPES is caused by mutations in FOXL2 6. We have rewritten the section, as suggested before. 7. The "genetic" in the graph refers to genetic and chromosomal causes, as mentioned in the text. We have modified this in the graph. 8. We have addressed this comment by adding "genetic counseling and testing" to the recommendation. 9. We agree with your comment and we have added to the recommendation: unless a mutation known to be related to POI was detected
Katharina Schiessl	1. p9: What investigations should be performed for diagnosis of premature ovarian insufficiency? see above: The definition includes low estradiol, even it is very difficult, to define this. Otherwise in the "perimenopausal" situation there might be times of highly elevated estradiol in relation to persistent follicles. Should there be a comment on this? 2. p9 "what are the known causes... line 6 Is there enough evidence to recommand this? There might be only a few patients detected and a lot tested. Shouldn't we better recommand being aware of symtoms of adrenal insufficiency?	1. Thank you for your comment, however we feel that we have provided sufficient information in the chapter. 2. We agree that there will only be few patients that will have a positive test result, but as there are significant implications if adrenal insufficiency is not identified, we believe testing should be recommended. As this consideration was already included in the discussion, we made no further alterations.

Prof. Andrea Lenzi	I think the paper by Bachelot and coll (Eur J Endocrinol 2009; 161:179) is missing. They described in details phenotyping and genetic studies of 357 consecutive POI patients	The paper of Bachelot is included in the chapter in diagnosis and genetic testing
Stephen Franks	Excellent section	Thank you.
Dr Nidhi Sharma Chauhan	Diagnosis of POI 1) Oligomenorrhea for 6 months rather than 4 months (due to difference in cycle length 2) absolute values of low estrogen to be mentioned [page 9]	1. After long discussion within the guideline group, it was decided to state 4 months, as we wanted to state a specific time, without complicating the recommendation by stating 4 months for amenorrhea and 6 months for oligomenorrhea. Stating 6 months for both would cause a delay in diagnosis, so the group agreed on 4 months, in line with earlier recommendations on the topic. 2. Low estradiol is a characteristic of POI, rather than a necessary measurement for diagnosis. There are no papers validating estradiol as a valuable test for diagnosis of POI, and hence, no absolute values can be presented
Michał Kunicki	1. Page 31 line 50: The authors state that POF could be diagnosed if FSH is elevated (>25) and the measurement should be repeated on two occasions >4 weeks apart. No information is provided what concentration of estradiol should be given to established the diagnosis (if yes) .However authors stated in the text that estradiol should also be taken into consideration (line16). 2. Additionally in some papers secondary amenorrhoea is defined as absence of menstruation 3 to 6 months thus I wonder if 3 to 6 months is more appropriate than 4-6 moths.(as a second part of definition). 3. Finally the question is if FSH should be measured in 3 rd day of menstrual cycle (for those who menstruate) or in any convenient time.	Thank you for your comments . 1. Low estradiol is a characteristic of POI, rather than a necessary measurement for diagnosis. There are no papers validating estradiol as a valuable test for diagnosis of POI. 2. After long discussion within the guideline group, it was decided to state 4 months, as we wanted to state a specific time, without complicating the recommendation by stating 4 months for amenorrhea and 6 months for oligomenorrhea. Stating 6 months for both would cause a delay in diagnosis, so the group agreed on 4 months, in line with earlier recommendations on the topic. 3. We decided not to add a timing for FHS assessment as it will encourage waiting for a

		period to do the test and most will be amenorrhoeic anyway.
George Basios	Page 31, line 50: I believe that based on the text, the recommendation "An elevated FSH level > 25 IU/l on two occasions > 4 weeks apart" should be erased from the guideline box Page 37, line 231: Add gynaecologist of reproduction apart from endocrinologist?	1. We agree with the limited evidence for the FSH level and measurement, but feel we should give clinicians some diagnostic criteria. Therefore we have formulated the recommendation as a GPP rather than an evidence based recommendation. 2. We disagree with adding gynaecologist of reproduction apart from endocrinologist to the recommendation.
George Basios From comm to list of recs	Page 9: What investigations should be performed for diagnosis of premature ovarian insufficiency? Add one more: There is no evidence to recommend routinely screening for AMH in women with menstrual disturbances before age of 40	We have discussed AMH extensively in the GDG group and agree with you that AMH should not be routinely assessed. However, we feel this is clear from the text, and we feel there is no need to add a recommendation.
Beatriz Alvaro Mercadal	1. Page 31, line 50: I would add "low estradiol" as a diagnostic criteria. 2. Page 32, line 80: Turner Syndrome patients should be referred to a genetist, an endocrinologist and cardiologist for testing for other frequent systemic abnormalities in Turner Syndrome. Furthermore, it would be interesting to discuss about the risk of aneuploidy in the offspring of Turner syndrome patients. 3. Page 34, line 133: there is no functional test showing a decreased function of the noggin gene in POI patients in the litterature. Furthermore, there are other genes that have shown a stronger relation to POI that are not cited in this list. These genes should be named in this report: FIGLA (Zhao et al., 2008, Tosh et al., 2015), NOBOX (Qin 2007, Bouilly 2011 and 2015), COHESIN (Caburet et al., 2014), MCM8 (Tenenbaum 2015, Al Asiri 2015), AMH (Alvaro Mercadal et al., 2014), StAR (Banghoo 2005 and 2007) and ATM (Miller 1967). 4. Page 34, line 141: I would add a paragraph about the interest of GWAS, and that the information provided by the first studies of POI and GWAS are not yet clinically useful (ref Wood & Rajkovic 2013). 5. Page 41, line 378: I would add an explanation about familial segregation, and the probability that many idiopathic cases hide a genetic cause that is still unknown (high heritability for age at natural menopause from twin and family studies support this idea).	1. Low estradiol is a characteristic of POI, rather than a necessary measurement for diagnosis, and hence it was not added as a diagnostic criteria 2. Thank you for your suggestion We have added that Turner syndrome patients should be referred to a geneticist also to discuss (in case of a mosaic TS) the risk of aneuploidy in the offspring 3. Based on your and other comments, we have rewritten this section. As the list of genes would never be complete or up to date, and it is not clinically relevant, we decided to mention the pathways in which mutations are found, and some examples of genes. 4. Based on this suggestion we have added a paragraph on GWAS and CNV

	6. Page 42: Table: I would add Turner syndrome as a possible positive result of karyotype, which implicates, referal to an endocrinologist, cardiologist and geneticist. I would also add that if there are clear symptoms of Turner syndrome (high clinical suspition), a second analysis of the karyotype has to be performed in epithelial cells besides of peripheral blood.	5. We already discussed the familial segregation of POI, hence we did not repeat it in the current section 6. We have improved the table as suggested
Zdravka Veleva	p 41, line 373 Since POI includes both primary and secondary oligo/amenorrhea, it would be useful to mention to which group the "idiopathic POI" cases belong. Mean age?	We agree the usefulness of separating the prevalence of the different causes between primary and secondary POI, but unfortunately, these data are not present in the literature.
B Mallikarjuna Kirthi	1. Page 30 line 37. Current guidelines not targeted to fertility clinic patient population, why not? 2. Page 31 line 45 AMH not sufficiently discriminative for diagnosis of POI - how about this conclusion appearing in recommendations box? 3. Page 33 line 89 - Gonadectomy by what age?	1. As explained, the guideline group wanted to distinguish POI from women with low ovarian reserve. A separate guideline on management of women with low ovarian reserve could be considered at a later point in time. 2. We have discussed AMH extensively in the GDG group and agree with you that AMH should not be routinely assessed. However, we feel this is clear from the text, and we feel there is no need to add a recommendation. 3. We did not find any data or recommendations in the literature suggesting gonadectomy should be performed before a certain age. From limited studies, gonadectomy could be postponed until after puberty and pubertal development. A recent case series however, reported gonadectomy in 7 TS patients varying between 5 and 13 years of age (Esposito 2015)
Fernanda Águas	1. P32 – 87 It would be useful to add a recommendation about age of gonadectomy. 2. P37-231 This recommendation is for all women with POI or just for those with unknown etiology or suspicion of auto-imune disease?	1. We did not find any data or recommendations in the literature suggesting gonadectomy should be performed before a certain age. From limited studies, gonadectomy could be postponed until after puberty and pubertal development. A recent case series however, reported gonadectomy in 7 TS patients

		varying between 5 and 13 years of age (Esposito 2015) 2. Thank you for your comment. The guideline group agrees that 21OH-Ab should be assessed in women with POI of unknown cause or suspicion of autoimmune disorder. This was changed in the recommendation
Stratis Kolibianakis	Page 23 :"Premature ovarian insufficiency is a clinical syndrome defined by depletion of follicular activity before the age of 40. POI is characterised by menstrual disturbance (amenorrhea or oligomenorrhea), raised gonadotropins, and low estradiol." Should AFC not taken into consideration in a syndrome defined as "depletion of follicular activity"?	Thank you for your comment, but we do not recommend performing AFC for the same reason that we do not do ovarian biopsies. POI is diagnosed with or without follicles. AFC would only provide supportive evidence? in case of no antral follicles at all. However, in clinical practice the existence of antral follicles, or even larger follicles on ultrasound, is often be interpreted as no POI.
Sophie Christin-Maitre	1. Page 30 line 38 : it could be interesting to mention that ultrasound identifying a large number of follicles is in favor of autoimmunity. This has been suggested by the paper published in JCEM from Welt C et al. in 2009 and confirmed by La Marca et al. JCEM 2009 : 94 : 3816. Furthermore it could be mentionned that ultrasound is interesting before oocyte donation procedure in order to evaluate the uterine size 2. page 32 line 80 : the methods used for chromosomal analysis are not mentionned. Karyotype or CGH array could be discussed. As those recommandations are going to be widely used, karyotype should be emphazised but new technologies could be mentionned. 3. It could be interesting to mention that at least 20 mitosis should be tested and that Turner syndrome is diagnosed when at least 10% of 45X are identified as some patients with less monosomy should not be identified as Turner syndrome patients and their follow up are different. 4. page 34 line 134 : Among the autosomal genes mutations identified in POI, NOBOX gene mutations should be mentionned as it seems quite frequent. Two studies have suggested that it is mutated in 6 % of POI patients. The references are J Bouilly et al. Hum Mut 2011, 1108–1113 ; J Bouilly et al. JCEM 2014. 5. On the contrary, FSHbeta mutations are mentioned but they are not responsible for “real” POI as FSH levels are usually very low in such cases. Furthermore, exogenous	1. We have reviewed the mentioned papers, but found no evidence to change the guideline; La marca 2009 does not measure follicular activity by US. Welt JCEM 2005 concludes : Although FSH levels remain, on the average, increased in hypergonadotropic compared with normal cycling women, it may be necessary to document follicle activity by ultrasound or hormone levels before interpreting FSH levels as normal when the clinical suspicion of POF is high or when confirming a previously elevated value. These careful assessments are critical to accurately confirm such a devastating diagnosis and provide the patient with accurate clinical information. 2. We have added a sentence on Karyotype And CGH array 3. The GDG has considered this comment, but decided not to add this in the guideline

	FSH treatment is able to induce folliculogenesis and this is not mentionned in the treatment section. 6. Another autosomal gene identified recently is STAG3 ref : Caburet et al. NEJM 2014; 370: 10 7. The section on autoimmunity is very developed as compared to other genetic causes. In the near future Next generation sequencing is going to be available in order to test genetic causes. 8. page 40 line 368 : Among potential toxics inducing POI are dyes. Premature ovarian failure has been described in hairdressers, using hair dyes without gloves Gallichio et al. Hum Reprod 2009, 24: 2636-2641. 9. Many animal models of POI secondary to toxics have been described (review in: Beranger et al. Reproductive toxicology 2012, 33: 269-279)	4. As a list of genes would never be up to date, and these genes are not clinically relevant, we decided to mention a few examples of gene mutations per pathway 5. This is a valid comment, and we removed FSHbeta mutations from the list 6. As above, we have changed the list of genes, and we added more information to this section 7. This is a survey based study with a low response rate and many biases. Other studies didn't reveal a correlation. Therefore we did not mention this in the guideline. 8. We do not include evidence from animal studies in the guideline.
Sophie Christin-Maitre From comm to list of recs	page 9 : no autosomal testing should be recommended. This statement will probably be modified in the near future using NGS sequencing. The point of knowing the cause of the disease has been raised by some studies in order to better accept POI.	Thank you. Based on your suggestion, we have added a sentence to the discussion stating; 'New techniques and further research on the genetic background of POI may change this recommendation in the near future.
Daniela Romualdi	1. General comment: Beside Turner syndrome, should we at least mention Triple X syndrome? 2. Page 32, line 80: The sentence "Turner Syndrome women may have Y chromosomal material in their gonads" is not clear enough. 3. Page 39, line 307: "synacthen test"- Is it appropriate to use a brand name? The commercial name of Tetracosactide varies in different countries.	1. We did not add Triple X syndrome, as the evidence that this is related to POI is not conclusive. 2. We added the results of a study of Gravholt 2000 (114 patient) We found 14 [12.2%; 95% confidence interval (CI), 6.9–19.7%] patients who had Y chromosome material by one or more primers applied. 3. Based on your comment, we have changed "synacthen test" to "ACTH (adreno-corticotropic hormone) stimulation test "
Inger Overlie	Adrenal autoimmunity, ovarian antibodies. Autoimmunity as cause of POI? p 35/187: Has there been conducted any studies on DHEA|DHEA/S, either in connection with diagnosing POI or as treatment alternative of POI either together with HRT or alone|? The fact that DHEA plays an important role in autoimmune diseases makes it an interesting	Thank you for your comment. The GDG feels that the data on DHEA is all very speculative, and hence we decided to not include this in the guideline.

	hormone?/pre/hormone to investigate, and one might speculate whether DHEA and?/or would be low or suboptimal in POI patients.	
Nivedita Reddy	List of recommendations: though all the tests defined are appropriate for investigation of POI, within the setting of a health service that is funded as in the UK will it be financially viable. Is there place for perhaps for more defined parameters before undertaking all the tests ?	Thank you for your comment. As this is a European guideline, we aim to base our recommendation only on scientific evidence and opinion of the guideline group members. As health economics are very divers across Europe they are not taken into consideration. We have kept the recommendations as low as possible, in an attempt to stimulate implementation of these guidelines in European countries, if needed adapted to the national context (including cost considerations). Furthermore, the recommendation may stimulate governments to adapt their policies in the benefit of patients.
Philippe Bouchard	A table with the list of known genes would be helpful	Thank you for your comment. We have made some changes to the paragraph on the genes, but we decided not to add a table. As this is a rapid growing field, the table would be outdated before the guideline is published. Furthermore, there seems to be discussion among expert as to which genes should, or should not be included.

Nick Panay	1. FSH level of 25: Why 25 - traditionally 30 or 40? Explained in text re auto immune POI but will the lower levels be universally adopted? Will need universal agreement; need to avoid false positive diagnoses 2. Although no causal relation has been proved for cigarette smoking and POI.. => all women should be advised to stop smoking! 3. Page 31: Not distinguishing but AFC would provide supportive evidence? 4. Page 34: causative instead of causing 5. Page 38: What about type 2 DM / Insulin resistance due to the hypoestrogenic state?	1. We recommended a cut off of 25, because we wanted to include auto immune POI. We hope these recommendations will be universally adopted. Furthermore, the GDG is not worried about false positives as amenorrhoea is also required 2. We agree with this comment, but we only provide information for women with POI. 3. AFC would only provide supportive evidence in case of no antral follicles at all. However, in clinical practice the existence of antral follicles, or even larger follicles on ultrasound, is often be interpreted as no POI. Therefore we did not add that AFC would provide supportive evidence. 4. We have corrected this 5. This is a valid comment, but this section only handles on causes of POI
Manuel Puig Domingo	1. Section comments to the Guideline: In part B (Diagnosis) when referring to "What are the causes…" the second box in pag 9 indicates "Gonadectomy should be recommended to all women with detectable Y chromosomal material". This is perfect but I believe it fits better in Part C (Sequelae) probably as a consequence for life expectancy. This recommendation is a therapeutic one rather than part of diagnosis or cause. It could also be moved to Special issues in pag 16. I also believe that there is a lot of scientific information supporting this message, going further to a GPP support. In fact in pag 32 there is a last and lonely sentences referring specifically to this point without any references. I don't know where this should be treated in the text, but without doubt it is a very important issue deserving a solid comment. 2. Pag 21: fig 1.1 is probably unnecessary for a clinical guideline (this is more academic than useful for the clinical practice). 3. -Pag 33, line 100: it is written "… a prevalence of 0,8 to 7,5%"; it should be expressed as "0.8 to 7.5%". 4. -Pag 37, line 245-247: treatment of overt hypothyroidism is supported by the references of James Haddow in 1999; regarding subclinical hypothyroidism, more recent work is available (John Lazarus, NEJM 2012, CATS study), indicating that the treatment of subclinic hypo is still under debate while there is no doubt of treating overt hypo. In line 251	1. Thank you for your suggestion, and we agree that this recommendation is treatment rather than a diagnostic. However, the recommendation is immediately resulting from diagnosis, similar to referral to an endocrinologist in the other sections. When scoping the guideline, we did not include the need for gonadectomy as a part of the question on life expectancy, as this is valid only for a small group of POI patients. Therefore we have not elaborate on this further, but we will consider it when the guideline will be updated. 2. Thank you, but we think the figure is helpful 3. We have corrected the prevalence

	(Conclusion), it is said that subclinical hypothyroidism should be treated. This is a very controversial issue requiring further research, and I recommend quoting this aspect in the Conclusion section. 5. -Pag 39, lines 287-290: all the definitions of APS are probably unnecessary in a POI guideline.	4. We have checked the paper of Lazarus, and the editorial by Brent, and decided not to modify this. 5. Based on your suggestion, we removed the definitions of APS in line 287-290
Dr. Wingfield	AMH In helping with Diagnosis- page 31: I draw attention to a recent review (Broer S.L et al, 2014)1 which notes that AMH levels are undetectable in the great majority of women diagnosed with primary ovarian insufficiency (Knauff EA et al, 2009) 2. I suggest that it be stated that an undetectable level of AMH is confirmatory evidence of premature ovarian efficiency.	Thank you for your comment. However, the guideline group decided not to change its vision on AMH. They feel it should be kept in mind that women with undetectable low AMH levels often still have regular cycles and thus not POI

Comments to - 4 : Implications for relatives of women with POI

Reviewer	Comments	Reply
Patsama Vichinsartvichai	This section is well elucidated. No comment for correction.	Thank you.
Arianna d'Angelo	page 45 line 22: typo mistake "in a women" should be "in a woman" page 46 line 69: use GDG	We corrected these errors.
Adam Balen	Excellent and well written.	Thank you.
Ioana Rugescu	page 47 line 79 : maybe additional "ongoing surveillance in addition to baseline assessment is advised" and related with "the potential benefit of fertility preservation is unclear" maybe adding also "but current fertility preservation methods can be feasible"	Thank you for the suggestion, but since there is no evidence, we did not add the sentence to the recommendation
Michael Feichtinger	Page 47, recommendations line 79: "should be informed that: by changing their life-style e.g. smoking they can actively lower the risk of POI"	Thank you for your suggestion, but as there is no evidence in support of this statement, we decided not to change the existing recommendation
Gianluca Di Luigi	Page 45 Line 45 Increasing or DECREASING?	Thank you for mentioning this error. The text was changed based on the conclusion from the Bentzen study: From the study conclusion; we found a more pronounced decline per year in serum-AMH concentration and in AFC for participants with early (≤45 years) maternal age at menopause, compared with participants with late maternal age at menopause (≥55 years).
Katharina Schiessl	p10 line 5+6 (implications) I totally agree with this recommendation, but we should communicate the percentage of risk here. I think, this is the most important information for them even, especially for the unexplained cases.	We agree with your comment, but as we stated in the conclusion that "Women with at least one affected family member may be at risk of POI, but currently it is not possible to predict or prevent the onset." We found no studies stating any percentages of risk.
Andrea Lenzi	This paragraph is very clear to the reader	Thank you.

Nidhi Sharma Chauhan	Relatives: first degree or second degree relatives to be offered screening? Any data on risk of familial association of POI? [page 10]	Thank you for your comment, we implicitly included genetic testing in genetic counselling, but to make this more clear, we have changed the recommendation stating that genetic counselling and testing should be offered to relatives.
Beatriz Alvaro Mercadal	Page 46, line 65: I would suggest the possibility of performing PGS to avoid the transmission of the full mutation to the offspring in case of Fra-X premutation. Page 46, line 74: oocyte freezing is not considered an experimental technique anymore and some studies show a comparable pregnancy and obstetrical outcome. What remains unclear is oocyte preservation in this specific group of women at risk of POI as there are very few piblications in the subject and no pregnancies reported after oocyte preservation in this specific group. I would stress this, otherwhise it seems like if , in general, oocyte cryopreservation "remains unclear".	1. We added a sentence; … and should be counselled on the possibilities of PGD to avoid the transmission of the full mutation 2. In the lines quoted, we do not mention that oocyte freezing is an experimental technique, we only state that its benefits are unclear for relatives of women with POI.
Sophie Christin-Maitre	this section is very interesting and very useful	Thank you.
Nick Panay	Page 45: women =>woman Page 45: NP: should this be less per year with increasing age at maternal menopause Page 47: NP: We agree - but do we need to give more detailed guidance .... many women are now requesting testing of their ovarian reserve and are requesting egg / embryo freezing if they perceive a risk of POI or simply missing out due to postponement of pregnancy attempts.	This error was corrected. We have corrected this error based on the conclusion from the Bentzen study. The guidelines mentions “Oocyte freezing may be an option for fertility preservation” We feel that we don’t have to give more detailed guidance.

Comments to - 5 : Life expectancy In women with POI

Reviewer	Comments	Reply
Patsama Vichinsartvichai	Well explained. No comment.	Thank you.
Adam Balen	Excellent and well written.	Thank you.
Michael Feichtinger	No comments	Thank you.
Andrea Lenzi	Well organized chapter	Thank you.
Nidhi Sharma Chauhan	Women/patient education on reduction of cardiovascular risks [page 11]	We feel this comment does not require a modification of the guideline or a reply.
George Basios	Page 50, line 55: Should we add a possible positive influence of SERMs?	Thank you for your comments, we decided not to add any information on SERMs at this stage, but we will consider it when the guideline is updated.
Beatriz Alvaro Mercadal	Page 50, line 62: in the recommendations, I would consider to separate it in two different recommendations and add a grade C to "POI is associated with reduced life expectancy".	Thank you for your comment. We have indeed added a level of evidence “C” to the recommendation
Sophie Christin-Maitre	no comment, very well documented	Thank you.
Nick Panay	1. Untreated POI is associated with reduced life expectancy 2. Add “and a healthy diet” 3. Page 50: Additional Recommendation: Women with POI should be advised that their increased risk of cardiovascular disease / mortality appears to be ameliorated by the use of HRT at least until the average age of natural menopause 4. Page 52-line 54 : Need to point out that this was in women in 50-59 age cohort	1. We have modified the recommendation as suggested 2. We did not add “a healthy diet” to the recommendation 3. We did not add the suggested recommendation. We hope this statement is correct, but as there is little or no evidence to support this statement, we have not added it. 4. We have reviewed the paper, and the analysis was done for age groups, and for years since

	menopause independently. Here we quote the results for starting HRT <10 years since menopause.

Comments to - 6 : Fertility and pregnancy in women with POI

Reviewer	Comments	Reply
Patsama Vichinsartvichai	This section is well structured.	Thank you.
Arianna d'Angelo	page 52 line 17: typo "to 1999" should read in 1999 page 55 line 143: define TS	We corrected these errors
Adam Balen	Excellent and well written.	Thank you.
Michael Feichtinger	Page 49, line 53: The sentence "Eight out of 25 women treated with EE ovulated, compared to none of the 25 women in the placebo group, a significant difference (p<0.005); 4 conceived." is not very well understandable Page 54/55 line 117-136: Maybe the authors should rule out that these studies on oocyte donation where not solely performed because of POI and thus these complications are not typical for oocyte donation in patients with POI, rather to patients with oocyte donation in general including women of advanced maternal age	Thank you for your comments. We have improved the sentence quoted. As there are no studies evaluating egg donation in POI patients specifically, we have based our recommendations on other studies on egg donation, which are appropriate for POI. The statement that the increased risks could be due to increased maternal age, a reason for egg donation, is not valid, as in the study of Stoop controls were matched for maternal age. In the study of Nelson data were corrected for maternal confounders.
Roberto Matorras	1. pag 47/ line 79 : In the recommendation: I would change "the potential benefit of fertility preservation is unclear" by " Fertility preservation appears as a promising option, although studies are laking" 2. Pag 50/ line 62 : In the recommendation I would include: .... and hormone replacement therapy 3. Pag 58. Line 244. Table 6.1 In the table I would change Delivery resulting in live birth 118 82% live birth rate By Pregnancy non resulting in live birth 18%	1 We have modified the recommendation (implications for relatives) as suggested 2 We did not add "and hormone replacement therapy" to the recommendation. We hope that HRT reduces mortality, but there is little or no evidence to support this 3 We did not make any alterations to the table, as this table was copied from the study of Karnis 2012.

RCOG - Mostafa Metwally	Could you please clarify in women who have had anthracyclins/mediastinal radiation, should a cardiologist be involved in all cases or only those with abnormal ECHO?	The recommendation is that these women should have an ECG and an echo. Different healthcare settings would have those tests interpreted by a cardiologist or not. So I guess the cardiologist would only have ongoing involvement if the tests were abnormal.
Joe Leigh Simpson	1 p. 52: The Bidet reference and its 4.9% pregnancy rate deserves elaboration, for ascertainment bias and differences in diagnosis could exist. Other cohorts have shown less favorable results and nil pregnancies. 2 P 54: The paragraph on ovarian slice cryopreservation does not mention oocyte freezing, currently in vogue. What is the committee's opinion on proactively freezing at puberty, before oocytes degenerate, as for example 45,X? This has been explained in 47,XXY? 3 p. 58 lines235 : 45XO = 45.X 4 p. 57-58 and elsewhere - In the U.S. ultrasounds are routinely ordered for aortic dilation before recommending for or against pregnancy in a 45,X patient. - Defining Turner Syndrome as 45,X is limiting and not conventional. A 45,X/46,XX patient with short stature should qualify, as should X-structural rearrangements (Xq isochromosome).	1 Older studies were reviewed in the paper of van kasteren, and we only found the ref of Bidet for the more recent studies. The limitations regarding studies on pregnancy rates have been discussed. No recommendation was based on the study of Bidet. 2 During the scoping of the guideline, it was decided that fertility preservation would not be covered in the guideline, as the guideline is on the management of women with established POI (hence it is too late for preservation) Therefore this topic was mentioned only briefly. Future ESHRE guidelines on fertility preservation will elaborate on the topic. 3 This error was corrected 4 Thank you for this comment. We have used the definition, as stated in the referenced paper, and hence did not change it. However, we added more information on the karyotypes in the glossary of the guideline.
Gianluca Di Luigi	6.3. Page 60 Line 298: Oocyte donation... high risk (HYPERTENSION, PREECLAMPSIA...). Why don't you recommend the use of Aspirin?	We have states this in the conclusion, but the guideline group decided not to formulate this as a recommendation
Katharina Schiessl	1 p11 line 3 (contraception): this should be rethought: the conclusion for a lot of practinioners will be to give them the combined anticonceptive pill which is with risk for thromoembolic diseases and without benefit for bone health. I think, there should be a reccomandation for local or intrauterine anticonceptive methodes.	1 We have considered your suggestion, but decided not to modify the recommendation. Lots of young women with POI use COC for HRT which is regarded as fine if not ideal

	2 line 5 : In my opinion here it needs an advice, that there is a high pregnancy risk for women with turners syndrome, even if it is mentioned later 3 p 10 and 11 line 11 : I dont think, the whole pregnancy has to be managed in an obstetric unit - the birth and all complications will. If there is an experiences gynecologist, there will be sometimes a better situation to manage the pregnancy than in clinical situations with unexperiences young collegues	2 Thank you for your suggestion, but we feel this is clearly discussed in the guideline, and should not be repeated. 3 We feel this interpretation of the recommendation is going to be down to local practice which will vary by country.
Andrea Lenzi	In this section, it could be interesting to add data by Bidet and coworkers (Curr Opin Ob Gyn 2008). In this article they described clinical and ultrasonographic charcteristics predictive of spontaneous resumption of ovarian function in POI patients	The review of Bidet is not a systematic review of interventions for increasing chance of pregnancy. They describe clinical and ultrasonographic characteristics predictive of spontaneous resumption of ovarian function, but again not in a systematic way.
Mukhri Hamdan	Congratulation for a very thorough guideline. Page 54 Line 94. With regard to fertility intervention, are there any evidence on surgical treatment prior to ART for patients with POI, with co-existing endometriosis, will improve the outcomes? If not, could I suggest to add a statement "women with POI secondary to endometriosis (iatrogenically or intrinsically) undergoing oocyte donation treatment, there is no evidence for surgical treatment prior to ART will influence the outcomes. This will hopefully clarify clinicians not to subject patients to surgical treatment prior to ART. It is also good to reiterate ESHRE 2014 Endometriosis Guideline, that "There is no evidence that ART in women with endometriosis will change the course of the disease" Page 56, line 170, May I also suggest that "Women with POI with coexisting endometriosis who fall pregnant, there are additional risks of pregnancy in addition to the existing risks. Thank you.	The current guideline deals with the management of women with POI. In general, most women with POI after treatment for endometriosis should have completed their family before undergoing treatment that can lead to POI (if treated according to the ESHRE endometriosis guideline). Therefore, we have included a small section on HRT in women with POI and endometriosis. We have not reviewed the literature on the best management of fertility issues in women with POI secondary to endometriosis (if existing).
Nidhi Sharma Chauhan	Women with autoimmune disorders, genetic fragile X mutation to be counselled for egg freezing options [page 11]	Thank you for your comment, but the proposed topic was not included in the scope of the current guideline as it is not management of POI
RCOG - Mostafa Metwally	Line 174 - Could you please also refer to HRT in women with POI and special issues where in endometriosis, combined use of estrogen progesterone is required even after hysteroscopy.	Thank you for your comment. We have a paragraph on this in the chapter on HRT.

Michał Kunicki	Page 53, line 36. I think that the information with regard to DHEA should be given as a potential medicine which can potenentially influence pregnancy rates.	Thank you for the comment. DHEA was mostly studied in women with LOR, but not in POI, therefore we decided not to add this.
George Basios	Page 53, line 116: Possibly add a line about preparation of the endometrium with progesterone vs estradiol favouring progesterone (see latest Cochrane review)	Thank you for your comment but as this seems like a technical oocyte donation point, we judged that it is not specifically relevant for POI, and we have decided not to include it.
Beatriz Alvaro Mercadal	1 Page 11: A sentence could be added regarding the risk of transmission of X Fragile Syndrome to the offspring if spontaneous pregnancy happens in FMR1 gene pre-mutation women with POI. More controversed is the rate of aneuploidy in the offspring of women with Turner syndrome. It has its place here, as spontaneous pregnancies can happen in 5% of patients even after diagnosis of POI. These women should be proposed to have a discussion with a geneticist. 2 Page 50, line 90: consider adding a recent reference: Demeestere I., et al., 2015 Hum Reprod and Imbert R. et al., 2014. 3 Page 58, line 242: the higher risk of pregnancy loss could be explained by the probably higher rate of aneuploidy in Turner syndrome spontaneous pregnancies.	1. Based on your comment, we have added a sentence to the conclusion stating; 'the cause of POI should be considered in a woman who has a spontaneous pregnancy, in case it has implications for the pregnancy and child (eg FMR1 premutation)' 2. Thank you for the reference, but it is published after the literature search was conducted. 3. We have found no evidence supporting the statement that a higher risk of pregnancy loss could be explained by the probably higher rate of aneuploidy in TS, hence we did not add this.
Zdravka Veleva	It is not clear whether the text presents information about obstetric risks in the general oocyte donation population or in women with POI.	As there are no studies specifically assessing the obstetric risks in women pregnant after oocyte donation as treatment for POI; we have presented studies with mixed populations, with mentioning of the proportion of POI patients, where available (cfr the study of Abdalla)
B Mallikarjuna Kirthi	1. Page 55 line 154 less advanced POI means? <3 months,<6months, or FSH<15? 2. Page 56 line 166 incomplete sentence! " in women with POI" 3. Page 56 line 168 "opportunity missed" but when was the opportunity? 4. Page 56 line 183 to 185 Effect of chemotherapy on endometrial receptivity, any data on pregnancy rate in these patients after embryo transfer?	1. We agree that "less advanced POI" may be unclear. Evidence on pregnancy in women with POI suggest that pregnancy occurs mainly in women shortly after the onset of symptoms (amenorrhea) rather than women years after the onset of symptoms. However, this is an observation and the characteristics

		of “less advanced POI” vary significantly among the case reports on the topic. 2. We modified the recommendation to “Oocyte donation is an established option for fertility in women with POI” 3. We agree that “opportunity missed” is a broad description. (non-iatrogenic) POI is characterised by a gradual loss of ovarian activity. In cases of very early diagnosis, fertility preservation may still be an option, but not in cases where ovarian activity is lost (i.e. established POI) 4. We found no studies exploring pregnancy rates in women with POI after chemotherapy?
Stratis Kolibianakis	line 367: "Pregnancy in some women can be of such high risk that clinicians may consider oocyte donation to be life threatening and therefore inappropriate." Although this might be true in Obstetrics in general, I am not sure about the basis of this recommendation in patients with POI, given the evidence presented.	The guideline group felt strongly that in women with Turner syndrome and for instance significant cardiac problems, clinicians should feel supported in recommending against oocyte donation.
Sophie Christin-Maitre	very interesting section DHEA treatment could be mentioned as many patients with POI ask questions about this treatment, although it is mostly used for diminished ovarian reserve and not POI. It would be interesting to mention the study from Wing Yee Yong et al. JCEM 2013, 98: 380-388, a randomized study using DHEA or placebo during 16 weeks. It seems important to mention the small number of patients included and a relatively small effect, only measured on follicle size higher than 10 mm and not on fertility. A case of pregnancy has been reported in a patient with POI, after in vitro maturation of her oocytes. Although the etiology has not been identified in this patient it is interesting to mention this possible treatment in the rare cases of patients with many follicles identified, and/or elevated AMH. ref : Grynberg et al. JCEM 2013 Some patients are aware of the study using Akt for follicle stimulation, by Kawamura et al. As several births have been obtained, it should probably be mentioned, although those results seem quite preliminary. {Kawamura, 2013 #9732}; 110: 17474-17479	Thank you. DHEA was mostly studied in women with LOR, but not in POI, therefore we decided not to add this. We have analysed the mentioned reports. The study of Grynberg reports on a patient wrongly diagnosed with POI, and hence was not included. We feel that the value of the technique described by Kawasura is not established based on the case report, and hence have only mentioned it in the discussion, as an example of ongoing research with the possibility of providing future options to women with POI.

Inger Overlie	Special emphasis on fertility and infertility, psychological issues concerning different aspects of this matter but also states the fact that women who get pregnant after idiopathic POI do not have greater obstetric or neonatal risks than the general population. After oocyte donation, however, the risk at pregnancy, includes hypertension disorders, higher threaten miscarriage and caesarean section and possible postpartum haemorrhage.	We feel this comment does not require a modification of the guideline or a reply.
Nivedita Reddy	pg 59 line 300: as the number of women who have had previous chemo is increasing, pre pregnancy counselling with details of their cancer treatment should be encouraged so that an overall assessment is made of risks and suitability to proceed to pregnancy. It may be several years following exposure to chemotherapy that cardiac problems occur. (pregnancy associated cardiomyopathy in survivors of childhood cancer ; Hines MR(1), Murooney DA., Hudson MM, Ness KK, Howard SC, Krasin M. Metzger ML. J Cancer surviv. 2015 June 5 Other drugs such as bleomycin and cisplatin can affect the lungs and renal function predisposing to respiratory failure and PET respectively (Pregnancy in cancer patients and survivors E Wang, chap 10; Oncofertility medical practice : clinical issues and implementation' C Garcia, TK Woodruff 2012) An oncology assessment to rule out recurrence prior to pregnancy.(personal experience) pg 62 line 363 : all women presenting for OD suspected of having POI are not routinely investigated for adrenal function and karyotype - if this risk is ? high, should this be mediated to fertility clinicians	Thank you for this comment. We agree that the number of women with POI after previous chemo is increasing, and we feel we clearly highlight anthracycline cardiomyopathy, and uterine irradiation. The section “fitness for pregnancy”, is based on the obstetric risks mentioned earlier, and therefore the risk of recurrence of cancer was not assessed. We added the following sentence to the conclusion: In addition to the assessment of fitness for pregnancy based obstetric risk factors, an oncology assessment to rule out recurrence prior to pregnancy could be recommended in women with POI after treatment for cancer.
Nick Panay	Page 53: No comments on the evidence (or lack of) for DHEA / androgens?	DHEA was mostly studied in women with LOR, but not in POI, therefore we decided not to add this
Manuel Puig Domingo	-Pag 60, line 297: Pregnancy in women with Turner sd shows a very high risk of obstetric complications; I would also state “obstetric and non-obstetric complications”.	Thank you, we have added non-obstetric complications to the recommendation

Comments to - 7 : Bone health in women with POI

Reviewer	Comments	Reply
Patsama Vichinsartvichai	1 Page 65, line 23-25; in POI women, Z-score is preferred for BMD reporting and Z-score of -2.0 or lower is defined as ‘‘below the ex- pected range for age,’’ and a Z-score above -2.0 is ‘‘within the expected range for age.’ (Schousboe JT, et al. Executive Summary of the 2013 International Society for Clinical Densitometry Position Development Conference on Bone Densitometry. J Clin Densitom. 2013; 16(4):455-66. 2 Page 67, line 110-111;Although limited data; postulation from postmenopausal women, the most effective type of exercise intervention is combination of weight-bearing and strength training (Howe TE, et al. Cochrane Database Syst Rev. 2011 Jul 6;(7)). 3 - Page 67, line 116-117; current EMAS recommendation on vitamin D supplementation is 800 - 1000 IU/day in healthy postmenopausal women and 4000 - 10,000 IU/day for women with low serum vitamin D (Perez-Lopez FR, et al. Maturitas. 2012.)	1 Thank you for your comment, but we have explained both Z score and T score, and diagnosis of osteoporosis is based on T score 2 Based on the mentioned review, the type of exercise does not need to be specified, as different types of exercise have a small but beneficial impact on BMD. Therefore this was not modified. 3 The guideline group and evidence suggests that a balanced diet will contain the recommended nutritional intake of Calcium and vitamin D, and suggests supplementation only if required.
Adam Balen	Excellent and well written.	Thank you.
Michael Feichtinger	Page 67, line 95: The introduction seems to be better fitting together with the introduction on page 65 line 2	We have merged the introductions based on your suggestion.
Gianluca Di Luigi	It would be useful to stress the need of regular exercise (how many hours a week?)	Thank you for your comment, but currently there is no evidence to support a statement on the type or amount of exercise to be recommended.
Katharina Schiessl	p12 line 9 there should be a comment that the pill (s.a) is not a sufficient estrogen replacement therapy	Based on you suggestion we have added a sentence and a reference to the chapter on HRT : “Estradiol replacement may have a more beneficial effect on BMD compared to ethinylestradiol, as in the COCP, although the data are limited, see section 12.3a.“ Furthermore, we added a recommendation stating “COC may be appropriate for some women but effects on BMD are less favourable”

Andrea Lenzi	OK as it is	Thank you.
Stephen Franks	This is again an excellent section. There is no mention, however, of the utility (or otherwise) of "routine" measurement of biochemical bone profile or Vitamin D levels. This is presumably because such measurements are of little or no value in monitoring bone health or the need for Vit D supplements. Nevertheless, it is common practice to make such measurements in clinics so I think a note about the use (or uselessness!) of bone profile and Vit D would be helpful in this section. One other small point: p71, line 235 onwards - this sentence is very similar to that in the Kanis et al paper to which the guidelines refer. Perhaps it should be paraphrased a little more	Thank you for your comment. We already included a paragraph on biochemical markers of bone turnover, in which we conclude that they are currently not recommended in clinical practice. We decided to not expand on this further. We have rephrased the sentence
Nidhi Sharma Chauhan	Screening for bone health with dexascan and annual measurement of vit D3 and calcium. Weigth bearing exercises [page 70 – 7.3]	Thank you for your comment, but the guideline group disagrees with this statement, especially as it is not supported by evidence
Cristina Laguna Benetti-Pinto	1 Page 65 Section 7.1 : I would like to suggest the inclusion of a paragraph about the use of T score or Z score. Some authors suggest the use of T score for women with POI, regardless their age, as they have ovarian failure, whereas other physicians adopt Z score is some situations. In the section 7.1, the guideline mentioned classic definition to osteopenia and osteoporosis, but in the reference in lines 42-46, Z score was used. Although in some ages the difference between Z and T scores is not important, I believe that guideline should recommend in what age to use T or Z score in future manuscripts, which would make it easier to compare data. 2 Page 66 Section 7 lines 85-87: " In the Million Women Study there was no....." I suggest the inclusion of the mean age when the referred women were submitted to BSO. If this information is not available, this paragraph does not add significant data to POI guideline.	1. Thank you for your comment. We think this is a fair point but we need to stick to T score and feel we cannot add recommendations to use Z score. Furthermore, the basis of both is explained 2.We have deleted the sentence, as suggested
Cristina Laguna Benetti-Pinto (from comments to list of recs)	Page 13. Measurement of BMD at initial diagnosis of POI should be considered …. Some women have a long period with irregularities in their menstrual period before the last period or the diagnoses of POI. During this time, they have periods with decrease in estrogen levels. In my opinion, it is difficult to define "....where estrogen replacement is initiated early. So, in my opinion, DEXA should be performed in all women at initial diagnosis of POI. POI is a risk factor.	We have modified the recommendation to: "measurement of BMD at initial diagnosis of POI should be considered for all women, but especially when there are additional risk factors". We agree that women have menstrual irregularities before the diagnosis of poi, but we believe that they still have fluctuating levels of estrogen, and therefore most of them have normal BMD at diagnosis.

George Basios	Page 71, line 239: What should be the interval in cases of bone loss in the first 5 years after POI diagnosis?	We have changed the recommendation and now state that "if a diagnosis of osteoporosis is made and estrogen replacement or other therapy initiated, BMD measurement should be repeated within 5 years"
Fernanda Águas	1. P69- L179 The duration of treatment with teriparatide should be between 18 and 24 months. 2. P69 - L 181 EMEA, has recommended a restriction in the use of strontium ranelate following an assessment of data showing serious cardiovascular adverse events. 3. P70 – L 201 I do not agree with this recommendation. In my opinion gyneacologist are competent to treat post menopausal osteoporosis. Only severe cases such as those women with indication for teraparatide treatment, should be sent to a reumatologist. 4. P 71 - L 247 The recommendation is not clear because osteoporosis alone is not an indication to initiate a pharmacological treatment. Treatment should be started based on fracture risk.	1. Up to 2 years was added, as this is how it is mentioned on the EMA website 2. The comment on strontium ranelate is correct. The European Medicines Agency recommends that Protelos/Osseor remain available but with further restrictions. We added that this product should only be used in patients with severe osteoporosis and a high risk of fractures that cannot be treated with other medicines approved for osteoporosis; and never to patients with a history of heart or circulatory problems 3. We do not state that gynaecologists are incompetent regarding treating osteoporosis. As we only mention "advice from a specialist" and not referral, we decided not to modify the recommendation. 4. We are aware that osteoporosis is only an indication for fracture risk, and this may also be a reason to request input from an osteoporosis specialist. We have decided not to change the recommendation based on this comment.
Sophie Christin-Maitre	1. non comment apart from Page 113, line 228: the sentence mentioning a potential role of contraceptive effect on bone density should mention that this risk seems to be related to very early use of oral contraceptives in adolescence. According to different studies, starting OC, within 2 years post menarche.	1. Based on this comment, we added a sentence to highlight that COCP is widely used and frequently assumed to provide adequate bone protection but the evidence for this is unclear.

	2. The concentration of ethinyl estradiol between 20 and 30 microgrammes are not discussed. The data are somehow controversial;	2. All data on dosage are grouped in the HRT chapter
Inger Overlie	Due to early menopause, the risk of lower bone health, with an increased risk of osteopenia and even osteoporosis is thoroughly discussed.	We feel this comment does not require a modification of the guideline or a reply.
Nick Panay	1. POI is associated with reduced BMD, particularly in the early years after onset. … Surprising - give ref. 2. Estrogen replacement is recommended to maintain bone health and prevent osteoporosis; it is plausible that it will reduce the risk of fracture. => conservative 3. Measurement of BMD at initial diagnosis of POI should be considered. I disagree - all women with POI should have a baseline DEXA. POI is a sufficient risk factor in itself to warrant testing and standard HRT does not guarantee complete bone protection e.g. the dose may need to be increased. 4. Repeated measurement of BMD after 5 years => Sooner if sever osteopenia / osteoporosis 5. If BMD is normal : but how will you know if BMD is normal if you are not scanning all women with POI 6. If a diagnosis of osteoporosis is made and estrogen replacement or other therapy initiated, BMD measurement should be repeated after 5 years. sooner! review of estrogen therapy should occur earlier if required. 7. A decrease in BMD should prompt review of estrogen replacement therapy and of other potential factors. Review by a specialist in osteoporosis may be appropriate. => is appropriate - gynaecologist or physician 8. Page 70: NP: No recommendation of choice between HRT and COC? Data are limited but in women with established osteopenia / osteoporosis HRT should be recommended rather than the COC given the more favorable data for HRT on bone turnover. 9. Page 70: NP: should ideally.. 10. Page 70: NP: estrogen replacement does not guarantee adequate bone protection - dose may need to be increased to provide adequate protection. 11. Page 70: as with the previous comment, HRT does not guarantee adequate bone protection - if BMD is not improving the dose may need to be increased 12. Page 71: NP: Also in the initial phase of treatment of women with moderate to severe osteoporosis to ensure adequate response to treatment. 13. Page 71: NP: The BMS strongly disagrees with this recommendation - all women with POI should have a baseline DEXA for the reasons previously discussed.	1. We have reformulated the recommendation to “POI is associated with reduced BMD” 2. We agree that this recommendation is conservative, but we did not find sufficient high quality evidence supporting a stronger recommendation 3. Based on your comment, and other comments, we modified the recommendation to Measurement of BMD at initial diagnosis of POI should be considered for all women, but especially where there are additional risk factors. 4. Based on the suggestion, we have now stated that BMD measurement should be repeated within 5 years. 5. by adapting the recommendation on DEXA at diagnosis, we have also replied to this comment 6. We have changed the recommendation:“If a diagnosis of osteoporosis is made and estrogen replacement or other therapy initiated, BMD measurement should be repeated within 5 years.” 7. We have not modified the recommendation as suggested as whether a specialist in osteoporosis equals a gynaecologist or physician, will vary by country 8. Based on this comment we added a recommendation on the COCP: The combined oral contraceptive pill may be appropriate for some women but effects on

	14. Page 71: NP: Intervals should be adjusted according to degree of concern for patient - should be shorter in women with more severe bone de-mineralisation 15. Page 71: Np: One of the difficulties is in defining what is adequate estrogen replacement for this population in the absence of long term prospective randomised trials! As such repeated DEXA scanning should be performed to ensure adequate response to replacement. 16. Page 71: NP: .....in our view DEXA scanning should initially be repeated within 2 years in this group to ensure adequate response to treatment.	BMD are less favourable In the chapter on HRT, we already mentioned that in general HRT is better than the OCP. 9. We decided not to change may to should ideally in the sentence "Initial assessment of bone health may include DEXA scan" 10. We agree, and we state in the recommendation that "A decrease in BMD should prompt review of ERT". 11. Same as comment 10 12. We have added "or in the initial phase of treatment of women with moderate to severe osteoporosis" to the paragraph 13. There is not enough data to recommend DEXA for all women at diagnosis, but by modifying the recommendation, we believe we replied to this comment. 14. We have changed this to "within 5 years", allowing to tailor the interval to the needs of a specific concerned patient 15. By changing the recommendation to "within 5 years", this is no longer contradicting with your suggestion of repeating BMD measurement within 2 years. However, the GDG is not convinced of recommending BMD measurement within 2 years.
Manuel Puig Domingo	1. -Pag 69, line 195: HRT in relation to bone physiology; there is no recommendation regarding the length of estrogen treatment. 2. -Pag 71, line 247: "Review by a specialist in osteoporosis may be appropriate"; I would state "…is very recommendable." 3. -Chapter 7 is very long.	1. We have added a sentence and reference to the HRT chapter. 2. We have considered your suggestion, but decided not to change the recommendation 3. We have reduced part of the introduction, but acknowledge the chapter is still extensive.

Comments to - 8 : Cardiovascular health In women with POI

Reviewer	Comments	Reply
Patsama Vichinsartvichai	All statements and recommendations are point taking. No comment.	Thank you.
Adam Balen	Excellent and well written.	Thank you.
Michael Feichtinger	Page 75, line 75: Patients with TS also have a higher risk of aortic dilatation and rupture	We have added this to the conclusion.
Joe Leigh Simpson	1. p.75 line(s)60-62 : Order an ultrasound (aortic root measurement) Bondy, et al. is authoritative but written almost a decade ago. The part also needs an update in its imaging recommendations. 2. p.76 line(s)81 : Add imaging to recommendation	1. We agree with the comment, but there is no evidence that is better (or says different), there are no more recent authorative papers, and there is no consensus. Therefore, we stayed with the Bondy paper. 2. We did not add this as the guideline's scope did not include formulating recommendations for cardiologists with expertise
Andrea Lenzi	I agree with the conclusions proposed	Thank you.
Annemieke Hoek	Please add the literature on long term risk on CVD and stroke to the guideline in pag 74 on the risk of. (I add the article). Cardiovascular disease risk in women with premature ovarian insufficiency: a systematic review and meta-analysis. Jeanine E. Roeters van Lennep1, Karst Y. Heida2,3 Michiel L. Bots3, Annemieke Hoek4, on behalf of the collaborators of the Dutch Multidisciplinary Guideline Development Group on Cardiovascular Risk Management after Reproductive Disorders* . European Journal of Preventive Cardiology published online 20 October 2014. DOI: 10.1177/2047487314556004. POI was related to an increased risk of developing or dying from IHD (HR 1.69, 95% CI 1.29–2.21, P = 0.0001) and total CVD (HR 1.61, 95% CI 1.22–2.12, P= 0.0007) No relation was found for stroke (HR1.03, 0.88–1.19, P = 0.74). This reference adds to the literature for the guideline since is specifically focusses on natural occurring POI. Please downgrade the conclusion in: POI is an independent though modest risk factor of IHD and overall CVD but not of stroke.	Thank you for your comment, which resulted in the addition of a paragraph on the review of Roeters van Lennep to the chapter.

	Argument: see discussion section of the article: We found that the impact of POI as cardiovascular risk factor is modest especially compared to classical risk factors for CVD, such as hypertension odds ratio (OR) of 2.95 (95%CI 2.57-3.39), current smoking OR 2.86 (95%CI 2.36-3.48-) and diabetes OR 4.26 (95%CI 3.51-5.18). (28) Therefore, we consider it unlikely that POI will be implemented as modifier of cardiovascular risk classification.	
Nidhi Sharma Chauhan	Clear recommendations to reduce risk of CVS. Table 8.1 very clear and informative to be given as patient reminder leaflet [page 80]	Thank you.
RCOG - Mostafa Metwally	Line 52 - This paragraph (particularly line 55-56) requires a reference.	Thank you. We have added the appropriate references.
Inger Overlie	Extensive focus on CVD where it states that POI increases the risk of CVD and early death compared to general population, developing endothelial dysfunction due to pre/menopausal estrogen deficiency, and again women with Turner syndrome are of greater risk. The importance of monitoring CV risk factors especially among Turner patients, who either have a cardiovascular disease or congenital heart defect, and have an excess of several CV risk factors including hypertension, obesity, impaired glucose intolerance, and hyperlipidaemi is discussed. p.76/108 Add?? another danish study; Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial BMJ 2012;345:e6409 doi: 10.1136/bmj.e6409 (Published 9 October 2012) Louise Lind Schierbeck registrar1, Lars Rejnmark associate professor, consultant2, Charlotte Landbo Tofteng staff specialist 1 1, Lis Stilgren consultant 3, Pia Eiken consultant, senior endocrinologist 4,Leif Mosekilde professor, senior consultant 2, Lars Køber professor, consultant 5, Jens-Erik BeckJensen associate professor, consultant 1	Thank you for your comment. This paper was included in the papers selected and evaluated for the guideline, but it was decided not to mention this paper in the summary of evidence, as it describes postmenopausal women (mean age 50 years). Evidence on not-POI women was only described in the absence of studies in POI (in this case the study of Lokkegaard 2006 was cited)
Nick Panay	1. Despite lack of longitudinal outcome data, hormone replacement therapy with early initiation is strongly recommended in POI to control future risk of cardiovascular disease in women with POI, by extrapolation from window of opportunity data.. 2. Page 80: Why not annual?	1. We have added in “women with POI”, but we are not convinced that we should add “by extrapolation from window of opportunity data” 2. We have updated the table, including annual screening of BP and weight, but we have erased the other tests for women with POI (not TS), which were the reason we did not mention “annual” in the original table.

Manuel Puig Domingo	Pag 78: I would eliminate the paragraph in lines 176-180, as the info given is not very helpful for a clinical guideline.	Thank you for your suggestion, but we decided to keep this paragraph, as it stated the reason why we not recommend monitoring of glucose;

Comments to - 9 : Quality of life In women with POI

Reviewer	Comments	Reply
Patsama Vichinsartvichai	No comment. All staments are clear.	Thank you.
Adam Balen	Excellent and well written.	Thank you.
Ioana Rugescu	page 85 line 111 : Assessment of a woman's perceived QOL is valued as a therapeutic outcome and may be a determinant of her adherence to a recommended plan of care	We are unsure whether the reviewer wants to add this as a recommendation. Anyway the guideline group decided not to add this to the recommendation
Michael Feichtinger	Page 86,87: In the chapter on psychological interventions the sentence structure in general is hard to follow. Maybe the authors could try to make shorter, more concise sentenses.	We have attempted to rewrite the chapter to make it less complex
Katharina Schiessl	p13 Women with POI have a higher risk of depression, lower sexual wellbeing and low quality of live, I think, this should be communicated at this point, so that the practitioners are aware of it.	This information is communicated in the text, but we feel clinicians should offer support, rather than being aware of the impact on QoL
Andrea Lenzi	No comments on this	Thank you.
Nidhi Sharma Chauhan	Questionnaire to be designed to assess psychiological and mental health of the woman. Yp be assessed yearly email, per form or clinical visit with questionnaire	Good point, but this is outside the scope of the guideline. We could consider adding appropriate questionnaires as an implementation help to this guideline.
George Basios	Page 84, line 54: Subtitle "Depression" instead of "POI"?	The section is split up between the different aspects of POI, being, longterm, infertility, vasomotor symptoms, and the impact of POI in itself. The paragraph describes more than depression.
Fernanda Águas	P 86 – L 142 : Paroxetine, 7.5 mg once a day is the only SSRI approved for FDA for the treatment of vasomotor symptoms in postmenopausal women.	Thank you for your comment,, but we did not add this information, as we could not verify this on

		the EMA website and hence we are unsure whether in the European context, paroxetine is indeed the only SSRI approved and used.
Sophie Christin-Maitre	interesting chapter	Thank you.
Inger Overlie	Testosterone treatment for QoL and sexual dysfunction is being discussed, and some studies shows beneficial effects, but long term data are missing	We are not sure what is being requested, so no action was undertaken in reply to this comment.
Nick Panay	1. Page 87: NP: additional ref 1: Singer D, Mann E, Hunter MS, Pitkin J, Panay N. The silent grief: psychosocial aspects of premature ovarian failure. Climacteric. 2011 Aug;14(4):428-37. 2. "if required" ... is this required?psychological interventions should always be accessible whether required or not	1. This paper was included in the evidence table, but not in the summary of evidence, as the paper describes the same patient population as Mann 2012, which we did refer to. 2. We have deleted “if required” from the recommendation

Comments to - 10 : Sexual function In women with POI

Reviewer	Comments	Reply
Adam Balen	Excellent and well written.	Thank you.
Michael Feichtinger	Page 92, line 100: Due to the lenght of this very detailed guideline, long sentences with little content like the one in line 100 should be avoided.	We have deleted the paragraph based on your comment
Jan Bosteels	page 96 rule 230: recommendation of local estrogens are effective in treatment of genito-urinary symptoms is graded C but available evidence is from a Cochrane systematic review with meta-analysis: this should be graded as A	Agreed and adapted
Gianluca Di Luigi	What can we use in case of oncological patients?	HRT in oncological patients is described in chapter 12 on HRT. We decide not to cross reference, as we would have to cross reference in every chapter
Andrea Lenzi	I agree with the recommendations	Thank you.
Annemieke Hoek	Concerning: sexual functioning pg 91 and further: add reference: Decreased androgen concentrations and diminished general and sexual well-being in women with premature ovarian failure. Jolande G. van der Stege, MD,1 Henk Groen, MD, PhD,2 Saskia J. N. van Zadelhoff, MD,3 Cornelis B. Lambalk, MD, PhD,4 Didi D. M. Braat, MD, PhD,5 Yvonne M. van Kasteren, MD, PhD,6 Evert J. P. van Santbrink, MD, PhD,7 Mirjam J. A. Apperloo, MD,3 Willibrord C. M. Weijmar Schultz, MD, PhD,3 and Annemieke Hoek, MD, PhD. Menopause, Jan-Feb 2008;15(1):23-31 In this case control study it was shown that : Women with POF have diminished general and sexual well-being and are less satisfied with their sexual lives than control women. Although women with POF had lower androgen levels, we did not find an important independent role for androgens in various aspects of sexual functioning.(I added the article) This adds to the literature in the guideline since this study specifically focused on sexual behavior and statisfaction of women with natural occurring POI, measured androgen en estrogen levels in the blood and analysed this with respect to the outcome of the validated questionnaires with respect to sexual behavior.	Thank you for correcting this. We had included the mentioned paper in the evidence tables, and have now added it to the guideline.

Nidhi Sharma Chauhan	Relation of sexual function due to decreased libido/mood swings due to premature absence/low levels of estrogen, testosterone can be studied long term	We are not sure what is being requested, so no action was undertaken in reply to this comment.
Cristina Laguna Benetti-Pinto	1. Page 91 line 46: My suggestion: to include the percentage of sexual dysfunction: ".... prevalence of sexual dysfunction (62,1%) compared to.." 2. Page 93 line 142 : We question the treatment that is frequently offered to women that use HT and present dyspareunia, once sometimes they do not present vaginal atrophy. So, I suggest the inclusion of the following paragraph: "However, careful interpretation of this complaint in women undergoing HT is needed. Although dyspareunia in women using HT and adequate vaginal tropism may indicate a failure of genital response during sexual intercourse, in this situation there is no clear evidence dyspareunia constitutes a primary role in the sexual response cycle or if dyspareunia may manifest as an inadequacy of the psychological domains (arousal, desire) of sexual function. 3. Page 94 lines 169-170 : In paragraph highlighted, I suggest the following changes: "Vaginal trophism, assessed through vaginal cytology, vaginal pH and vaginal health index, was worse according to vaginal health index; however, in both groups the scores were trophic".	1. We have added the percentage, as suggested 2. We have covered this in conclusion of management options, and in the section of non-hormonal therapies 3. We have rewritten the sentence as suggested
George Basios	Page 90, line 1: I believe the head title should be "Genito-urinary function in women with POI". Sexual disfunction could be a part of the the gentito-urinary disfunction and not vise versa. The reader finds difficulty to locate the genito-urinary function in POI Page 94, line 192: Add 2-3 lines mentioning estriol (vaginal route) and its possible advantages over topical estrogen?	Thank you for your suggestion. We have changed the title of the chapter to sexual and genito-urinary function in POI We agree with your second comment, but we had already mentioned this point in the guideline
Fernanda Águas	P96 – L 232 Lubrificants are primarily used to relieve vaginal dryness during intercourse and therefore do not provide a long term solution. The alternative for women in whom estrogens are contra-indicated could be moisturizers as they could have beneficial effects on symptoms related to vaginal atrophy although less effective then hormonal preparations.	Women with contraindication for estrogens are discussed in the HRT chapter (chapter 12). We added moisturizers whenever discussing lubricants.
Sophie Christin-Maitre	interesting, no comment	Thank you.
Daniela Romualdi	10.2: THE MANAGEMENT OPTIONS FOR THE EFFECTS OF POI ON SEXUALITY: Probably a sentence on possible surgical correction of vaginal agenesis/hypoplasia in Morris Syndrome should be added.	Thank you for your comment, but the surgical correction of vaginal agenesis/hypoplasia in Morris Syndrome was not included in the scope of this document

Inger Overlie	Testosterone treatment for QoL and sexual dysfunction is being discussed, and some studies shows beneficial effects, but long term data are missing	We feel this comment does not require a modification of the guideline or a reply.
Nick Panay	1. Enquire instead of inquire 2. Testosterone can be of added value : is often 3. Clinicians should be aware that despite seemingly adequate systemic HRT : Good - v important! 4. Page 92: NP: Davis SR, Moreau M, Kroll R, Bouchard C, Panay N, Gass M, Braunstein GD, Hirschberg AL, Rodenberg C, Pack S, Koch H, Moufarege A, Studd J; APHRODITE Study Team. Testosterone for low libido in postmenopausal women not taking estrogen. N Engl J Med. 2008 Nov 6;359(19):2005-17. Panay N, Al-Azzawi F, Bouchard C, Davis SR, Eden J, Lodhi I, Rees M, Rodenberg CA, Rymer J, Schwenkhagen A, Sturdee DW. Testosterone treatment of HSDD in naturally menopausal women: the ADORE study. Climacteric. 2010 Apr;1 5. Page 93: These patches are not commercially available now - this requires the off label use of testosterone gels at 1/5th to 1/10th the male dosage. 6. Page 93: Women with POI should receive adequate counselling about the possibility of using testosterone supplementation so that they can make an informed choice. 7. Page 95: Also IMS recommendations .... Sturdee DW, Panay N; International Menopause Society Writing Group. Recommendations for the management of postmenopausal vaginal atrophy. Climacteric. 2010 Dec;13(6):509-22.	1. We have corrected this in the text 2. (and 6) After consideration of your comment, we have deleted the recommendation and we have written a new recommendation, based on comment 6. 3. Thank you 4. These references were added 5. We have added a sentence on the availability of the patches, which are used in the listed studies 7. We have added this reference
Manuel Puig Domingo	-In no place in the text any mention is made in relation to Dehidroepiandrosterone sulphate substitution treatment when Addison's disease is made. Probably, this issue could be introduced in Chapter 10.2, in pag 92. -Pag 93: In the General Recommendations, at the beginning it is mentioned that testosterone treatment should not be used for more than 24 months, but in no place in Chapter 10.2 this is specified.	Thank you for your comments. The first comment is valid, but outside the score of the current document. Regarding the second comment, we have listed the indications for treatment in the different chapters, but all information on dose, duration, route of administration etc is summarized in the chapter on HRT (section 12.6)

Comments to -11 : Neurological function In women with POI

Reviewer	Comments	Reply
Adam Balen	Excellent and well written.	Thank you.
Dr. Michael Feichtinger	no remarks	Thank you.
Roberto Matorras	Page 100, line 115 I would suggest a small change in the recommendation The possible detrimental effect on cognition should be discussed when planning hysterectomy and/or oophorectomy under the age of 50 years, especially for prophylactic reasons in the absence of hormone replacement therapy	Thank you for your suggestion. After consideration, we decided not to modify the recommendation. We believe that the possibility of HRT is not a reason to perform hysterectomy/oophorectomy without discussing/considering the effects on cognition.
Dr Nidhi Sharma Chauhan	Stress on counselling regarding impairment of cognition while planning for hysterectomy Mention ovarian preserving surgeries for ovarian torsion and ectopic/ovarian [page 100]	Thank you for your comments: the first suggestion is already mentioned in the recommendation. The second comment is mentioned in the discussion of iatrogenic causes for POI.
Nick Panay	1. The possible detrimental effect on cognition: in addition to cardiovascular and bone risks.. 2. at least up to the age of natural menopause => at least until 3. p 101: NP: These data were superceded by age stratified re analysis of the data in 2007	1. As this chapter is only referring to evidence on the neurological function, we decided not to add the reference to cardiovascular and bone risks 2. The text was improved as suggested (at least until the average age of natural menopause) 3. the mentioned sentence was deleted

Comments to - 12 : Hormone replacement therapy

Reviewer	Comments	Reply
Adam Balen	Excellent and well written.	Thank you.
Michael Feichtinger	1. page 107, line 14: maybe the phrase "happy to take it" should be changed to "willing to take it" or something else, 2. Chapter 12.1. should be kept as short as possible since it is highly repetitive to the previous chapters 3. There are recommendations for breast and endometrial cancer but not for e.g. thromboembolic disease on page 112	1. This was corrected in the text 2. We tried to be short and comprehensive 3. We have recommendations for thromboembolic disease in chapter 12.
Roberto Matorras	p 122 ; line 603: I would suggest to include the following paragraph In a randomized prospective trial in women subjected to bilateral adnexectomy (98% also with hysterectomy; mean age 48 years) because of endometriosis , hormonal replacement therapy was associated with a recurrence rate of 3.5% (4 out of 115), or 0.9% per year, versus no case among those non receiving HRT (0/54). Among women receiving HRT, the following risk factors were detected: peritoneal involvement > 3 cm (2.4% recurrence per year vs. 0.3%) and incomplete surgery (22.2% per patient vs. 1.9%). It was concluded that HRT was a reasonable option. However, in cases with peritoneal involvement > 3 cm, the recurrence rate makes HRT a controversial option; if HRT is indicated, it should be monitored closely. (Matorras et al, 2002) Matorras R, Elorriaga MA, Pijoan JI, Ramón O, Rodríguez-Escudero FJ. Recurrence of endometriosis in women with bilateral adnexectomy (with or without total hysterectomy) who received hormone replacement therapy. Fertil Steril. 2002 ;77:303-8.	Thank you for your comment. For the purpose of this chapter, we have not performed a full literature search, as this was already performed for the guideline on endometriosis. We will assess the topic discussed in the paper for the endometriosis guideline.
Gianluca Di Luigi	Page 124. Recommendation: ... route of administration (TRANSDERMAL) ...	We are not sure what is being requested, so no action was undertaken in reply to this comment.
Gianluca Di Luigi From comm to list of recs	Page16: good the section dedicated to BRCA but what can we really do for patients with a previous breast cancer? We need a support e.g. VAGINAL LUBRIFICANT, VITAMIN D, MAGNESIUM...	All options for non-hormonal treatment have been described in the chapter on complementary therapies, and reference to this chapter was made

Andrea Lenzi	In some way conclusions support the guidelines already provided by NAMS (north america menopause society)	Perfect, thank you
Nidhi Sharma Chauhan	Well dezscribed indications of HRt and risks versus benefits of HRT on each and every aspect related to POI Role of mirena / locally releasing (progesterone) hormone devices ?? [page 108-109]	Thank you. The role of MIRENA is included in the section on route of administration, progesterone, but no studies were identified.
RCOG - Mostafa Metwally	'systematic HRT' would be better than 'HRT'.	We assume you mean “systemic HRT”. We have not changed the text as suggested, as this chapter includes both systemic and local HRT. Furthermore, we consider local estrogen a form of HRT, and have therefore used an inclusive approach.
B Mallikarjuna Kirthi	Page 122 line 603. " lead to malignant transformation of endometriosis" - what level of evidence is available?	There is no evidence for a possible malignant transformation of endometriosis. We have toned down the statements regarding this issue
Fernanda Águas	1. P 108 – L 77 Idem.. Lubrificants are primarily used to relieve vaginal dryness during intercourse and therefore do not provide a long term solution. The alternative for women in whom estrogens are contra-indicated could be moisturizers as they could have beneficial effects on symptoms related to vaginal atrophy although less effective then hormonal preparations. 2. P 109 – L 100 Missing the full stop at the end of some sentences of the table. 3. P 110 – L 113 There is no reference to the risk of breast cancer with estrogen only therapy. According to WHI, hysterectomized women who took estrogen-only were less likely to develop breast cancer. 4. 12.3 P 112 L 192/ 195/ Age itself is important when considering thromboembolism risk. Women with POI are younger than other postmenopausal women. 5. Transdermal estrogen have a lower risk of thromboembolism the oral preparations. The VTE risk related to contraceptive pills different according to the associated progestin. 6. 12.3.a P 113 - L 221: Ethinylestradiol should not be considered for hormone replacement therapy unless contraception is needed. 7. 12.3.c P115 – L 309 : The use of local estriol does not carry any risk of endometrial hyperplasia and endometrial surveillance is not recommended. 8. 12.5.d P 125 L 678: Drospirenone is associated with a higher risk of VTE and should not be recommended in women with other cardiovascular risk factors as hypertension.	1. There is a difference between lubricant and moisturizer, but no evidence to prefer either. We have added moisturizer whenever referring to lubricants. 2. Corrected 3. We have removed the introduction,as it apparently may be misinterpreted 4. The guideline deals with young women in general. When aged, rules for all women would imply. 5. Transdermal estrogens are discussed in a later section 6. The general recommendation is to use HRT not OCP, so we believe that a further explanation on OCP is not needed. 7. The GDG is not convinced that there is no need for monitoring with local estrogen, and therefore the sentence was not changed as requested ;

		8. We think it is not relevant to add this to the section, as it would be only used if really needed.
Sophie Christin-Maitre	1. It is very important to mention compliance and the choice of the patient as the authors have mentionned several times in the text. Such a point could be mentionned in a recommandation. 2. page 118 line 440 : as there is now a contraceptive pill containing 17 beta estradiol and a pill containing estradiol valerate, they should be mentionned in the text, indicating that the contra indication of those pills are the same as the pills containing ethinyl estradiol. 3. page 122 line 194 : This section mentions several times the term “menopausal symptoms”. Symptoms related to a lack of estrogen should be preferred. 4. This section is more related to early menopause that POI. 5. The role of tibolone seems too emphazised as no data are published on tibolone use in POI. It should be removed from the recommendation. 6. Page 122 line 603 : lead to malignant transformation of endometriosis should be removed; 7. Page 124, line 652 : In this recommandation, using HRT, the term without aura should be added.	1. We already have a recommendation on the importance of patient preferences in deciding on HRT treatment 2. Based on your comment, we added a sentence: There are now new contraceptive pills containing estradiol, however, as yet, there are no comparative studies on the risks OF VTE with these preparations and so the indications for their use in women with POI should remain contraception. 3. We changed this to vasomotor symptoms 4. We only refer to early menopause if there is no evidence available in POI 5. We have deleted Tibolone from the recommendations 6. We have weakened the sentence on malignant transformation of endometriosis 7. We have added a recommendation on migraine with aura
Sophie Christin-Maitre From comm to list of recs	1. page 15 : synthetic progestins should be preferred. The impact on breast cancer according to E3N study as well as Million women study, although not dealing with POI patients but postmenopausal women should be taken into account in the balance between benefits and risks. 2. page 16 : the section dealing with endometriosis mentions the term menopause which does not seem appropriate, as discussed in the chapter dealing with definition of POI. It is rather unclear why tibolone is mentionned in the recommandation. The authors explain in the text that those recommandations have been previously proposed. However, they seem to be more appropriate for early menopause and not POI.	1. Based on this, and other comments, we have modified the section on progestins 2. We have rewritten the section on women with POI and endometriosis.
Nivedita Reddy	pg 111, line 159. women with previous mediastinal irradiation and stem call transplants should be counselled carefully to differentiate ' no increased risk of breast cancer with HRT prior to age of natural menopause', and the risk of second malignancy including breast cancer in these	Based on your comment we have added a paragraph to section 12.2.a Breast cancer

	patients. These women appear to receive conflicting information from their oncologists who do not always make or appreciate the distinction	
Manuel Puig Domingo	1. Chapter 12 is very appropriate, but replicates most of the info previously given. I suggest shortening it and redirecting to the previous chapters with a link, in which any specific topic is developed more extensively. 2. In Section 12.2 it should be included the paper very recently published in The Lancet Oncology (Endometrial cancer and oral contraceptives: an individual participant meta-analysis of 27 276 women with endometrial cancer from 36 epidemiological studies)	1. We agree that chapter 12 replicates information but this information is limited to the conclusions of the previous sections. 2. We are not recommending contraceptives, so we should nor add a paper on Endometrial cancer and oral contraceptives
Mary Wingfield	12.3 HRT - treatment options - page 112: I suggest that Tibolone be mentioned here	We have deleted tibolone from all recommendations, as we believe it is not an option for young women
George Basios From comm to list of recs	Page 15: What are the options for hormone replacement therapy? Is there a place for SERMs in POI?	SERMS are treatment of osteoporosis and discussed in bone chapter. but they are not indicated for treatment of vasomotor symptoms
Nick Panay	1 HORMONE REPLACEMENT THERAPY IS INDICATED FOR THE TREATMENT OF VASOMOTOR SYMPTOMS IN WOMEN WITH POI and primary prevention purposes (bone, CVS, cognition) 2 REGIMENS WITH SYNTHETIC PROGESTOGENS ARE PREFERRED, PENDING SAFETY DATA ON THE ABILITY OF MICRONIZED PROGESTOGENS TO ADEQUATELY PROTECT THE ENDOMETRIUM FROM THE MITOGENIC EFFECTS OF ESTROGEN. - Disagree, the tolerance, metabolic (and possibly breast) benefits of micronised progesterone at least counterbalance the endometrial issues. - Change to micronised progesterone - Not GPP, PEPI study showed adequate protection 3 Patient preference for route and method of administration of each component of HRT must be considered => is of paramount importance 4 NO ROUTINE MONITORING TESTS ARE REQUIRED BUT MAY BE PROMPTED BY SPECIFIC SYMPTOMS OR CONCERNS : adequate E2, T levels, insulin resistance, lipids? 5 Migraine SHOULD NOT BE SEEN AS A CONTRAINDICATION TO HRT : but estrogen probably better delivered transdermally to minimise prothrombotic risks. 6 Women should be informed that androgen treatment : Very conservative; data for androgen usage are actually considerable. 7 IF ANDROGEN THERAPY IS COMMENCED, TREATMENT EFFECT SHOULD BE EVALUATED AFTER 3-6 MONTHS AND SHOULD POSSIBLY BE LIMITED TO 24 MONTHS : Why 24 months? - treatment cessation would inevitably result in recurrence of symptoms. Androgens should	1 Based on this suggestion we added a recommendation: Women should be advised that HRT may have a role in primary prevention of diseases of the cardiovascular system and for bone protection. 2 We have considered this comment, revised the evidence, and changed the recommendations on progestogen. 3 We have considered your comment, but decided not to change the sentence to “of paramount importance 4 Monitoring is only to look for high levels of E2, T. Insulin and lipids said not necessary if no indications 5 We added a recommendation stating; Transdermal delivery may be the lowest-risk route of administration of estrogen for migraine-sufferers with aura. 6 We agree that this is a conservative approach, but decided to stick with it

	be continued for as long as hrt is used. Although most rcts are of no longer than 1 year, there are observational data for longer term usage.	7 There are no longterm data, and no reason to assume that the symptoms resume. Furthermore, the efficacy is not clear either
8	should use term body identical to differentiate from compounded varieties of HRT. Panay n. Body identical hormone replacement. Post reprod health. 2014 may 22;20(2):69-72.	8 We have changed bio-identical to body-identical!
9	Page 111: Np: also.... Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. Breast Cancer Res Treat. 2008 Jan;107(1):103-11.	9 We have not added the reference for the Fournier paper, as the paper was included in the review we refer to (Davey 2013),
10	Page 112: NP: but not in women using transdermal therapy	10 Page 112: error was corrected
11	Page 112: NP: yet another reason why a POI registry is needed e.g. https://poiregistry.net	11 Thank you, we added the need for a registry to the research recommendations
12	Page 114: NP: There are now many recent studies which support the use of micronised progesterone for endometrial protection e.g. *Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. JAMA. 1996 Feb 7;275(5):370-5.* *Levine H, Watson N. Comparison of the pharmacokinetics of crinone 8% administered vaginally versus Prometrium administered orally in postmenopausal women(3). Fertil Steril. 2000 Mar;73(3):516-21. PubMed PMID: 10689005.* *Di Carlo C, Tommaselli GA, Gargano V, Savoia F, Bifulco G, Nappi C. Transdermal estradiol and oral or vaginal natural progesterone: bleeding patterns. Climacteric. 2010 Oct;13(5):442-6. PubMed PMID: 20575654.* *Kroft J, Klostermann NR, Moody JR, Taerk E, Wolfman W. A novel regimen of combination transdermal estrogen and intermittent vaginally administered progesterone for relief of menopausal symptoms. Gynecol Endocrinol. 2010 Dec;26(12):902-8.* *Files JA, Miller VM, Cha SS, Pruthi S. Effects of different hormone therapies on breast pain in recently postmenopausal women: findings from the Mayo Clinic KEEPS breast pain ancillary study. J Womens Health (Larchmt). 2014 Oct;23(10):801-5.* *Hodis HN, Mack WJ, Shoupe D, Azen SP, Stanczyk FZ, Hwang-Levine J, Budoff MJ, Henderson VW. Methods and baseline cardiovascular data from the Early versus Late Intervention Trial with Estradiol testing the menopausal hormone timing hypothesis. Menopause. 2015 Apr;22(4):391-401.*	12 We have considered this comment, revised the evidence, and changed the recommendations on progestogen
13	Page 114: NP: Given the lack of definitive evidence women should be allowed to choose which regimen they prefer.	13 We had already a recommendation stating ; PATIENT PREFERENCE FOR ROUTE AND METHOD OF ADMINISTRATION OF EACH COMPONENT OF HRT MUST BE CONSIDERED WHEN PRESCRIBING, AS SHOULD CONTRACEPTIVE NEEDS.
14	Page 115: NP: Nasal estrogen is not available in any European countries	14 We understand, but decided to leave it, as there is no harm in mentioning
15	Page 115: NP: Modern low dose vaginal preparations do not carry a risk of endometrial hyperplasia if used in the licensed dosage.	15 We have modified this in the text
16	Page 115:NP: no excess risk of stroke	16 No excess was corrected
		17 We agree that women may like the gel too, but we have not changed the current statement as it was based on a study.
		18 We have added that this was a study in women after HX + BSo. (paragraph already mentioned “surgical menopause”)
		19 We found no evidence supporting recommendation of vaginal versus transdermal progesterone
		20 We have corrected “at least until”
		21 Perfect!

	17 Page 116: NP: Many of our young POI patients like the gel 18 Page 116: NP: not a POI trial 19 Page 116:NP: The absorption of vaginal progesterone is vastly different to transdermal application - we believe that vaginal progesterone can be recommended 20 Page 118: NP: at least until 21 Page 118: NP: Agree 22 Page 118: NP: Disagree - we believe there are adequate data re oral and vaginal micronised progesterone 23 Page 122: NP: not in ER neg cancers 24 Page 122: NP: good 25 Page 122: NP: risk can be minimised through addition of progestogen / progesterone *26* Page 128: NP: see previous comment for additional refs	22 We have considered this comment, revised the evidence, and changed the recommendations on progestogen 23 We did not change the recommendation, based on from the Global consensus statement on menopausal hormone therapy: Current safety data do not support the use of MHT in breast cancer survivors. 24 Thank you 25 Regarding endometriosis, there is a theoretical risk for malignant transformation, and there are no data on whether this risk is minimised through addition of progesterone. 26 We have not added the additional references of Panay and Davis on testosterone treatment as they are mentioned in the next sentences

Comments to - 13 : Puberty induction

Reviewer	Comments	Reply
Patsama Vichinsartvichai	All well elucidated.	Thank you.
Adam Balen	Excellent and well written.	Thank you.
Michael Feichtinger	No remarks	Thank you.
Andrea Lenzi	That's will be very interesting to clinicians	Thank you.
Nidhi Sharma Chauhan	Why puberty to be induced at 12 years when most … taken delayed puberty in girls as not sign of breast developme,nt by 13 years in girls. For all causes or for Turner Syndrome only? ing a [page 137, page 140]	Thank you for this comment. For clarification, we have added a sentence stating "This approach can be considered for other causes of delayed or absent puberty when the condition is known from an early age" in reply to your comment
Fernanda Águas	P 137 - L 37 This sentence about oral etinylestradiol is in contradiction with the recommendation in page 141, line 141, which is clearly against the use of contraceptive pill for puberty induction.	To clarify this concerns, we have changed the paragraph slightly and we have added a sentence. stating: "*Natural estrogens have less pronounced effects on coagulation factors, lipid profiles and blood pressure than synthetic estrogens (Lobo, 1987).*"
Sophie Christin-Maitre	Page 137, puberty induction in this chapter is mainly focussed on Turner syndrome patients, but cases of POI occur in adolescents with normal karyotype. The age of 12 years indicated to start therapy implies that the diagnosis of POI is already made. This is not always the case. Page 137, line 50 the number of the table in the text should be 13.1 and not 3.1	We have pictured the ideal scenario, ie starting treatment early, but we also included information in cases of later diagnosis of pubertal failure. To clarify the message, we have added a sentence stating "This approach can be considered for other causes of delayed or absent puberty when the condition is known from an early age" We have corrected the error in the table
Sophie Christin-Maitre	page 18 : the recommandation states to start pubertal induction at the age of 12 but in some cases, POI is diagnosed much later, especially when it is not a Turner syndrome. This point should be raised in this recommandation.	Thank you for the suggestion, we added more information in the supporting text, but decided not to modify the recommendation.

From comm to list of recs		
Nick Panay	*Puberty should be induced or progressed with 17ß-estradiol, starting with low dose at the age of 12 with a gradual increase over 2 to 3 years.* excellent – not EE! *Begin cyclical progestogens after at least 2 years of estrogen or when breakthrough bleeding occurs.* Endometrial monitoring?	Thank you Regarding the comment on endometrial monitoring. First of all, this is not routinely done by the paediatric endocrinologist during puberty induction, except in a research setting. Breast and pubic hair and bleedings are observed. We acknowledge that gynaecologists would perform endometrial monitoring via ultrasound, but this will not necessarily change management. Therefore, endometrial monitoring is not added to the guideline.

Comments to -14: Complementary treatments in POI

Reviewer	Comments	Reply
Patsama Vichinsartvichai	Page 144, line 73-74; "the majority of controlled trials reported a potential role of black cohosh in relieving hot flushes, vaginal atrophy, and psychological symptoms". According to recent Cochrane review found no significant difference between black cohosh and placebo in the frequency of hot flushes and menopausal symptom scores (Leach MJ, Moore V. Cochrane Database Syst Rev. 2012 Sep 12;9). We also conducted RCT comparing black cohosh and placebo which also found no difference in symptom improvement and quality of life (Tanmahasamut P, et al. Climacteric. 2015 Feb;18(1):79-85.)	Both reviews contradict, and are now both mentioned. The recent study (2015) was not added as it was not published at the end of the inclusion of papers.
Adam Balen	Excellent and well written.	Thank you.
Ioana Rugescu	complementary and alternative medicine and also nonprescription options	Summary
Michael Feichtinger	Complementary treatments play a very important role in patients of POI. Therefore it is really good that ESHRE implemented a section on this kind of treatment. Otherwise no remarks	Thank you.
Andrea Lenzi	It seems exhaustive	Thank you.
Nidhi Sharma Chauhan	Mention about complementary treatments like acupuncture and acupressure and evidence supporting it [page 145]	Acupuncture is mentioned under non-hormonal therapies.

Comments to -Appendices

Reviewer	Comments	Reply
Adam Balen	Excellent and well written.	Thank you.
Ioana Rugescu	ovarian stem cells maybe a subject for future studies.	This suggestion was added to the research recommendations
Jan Bosteels	Appendix 5 methodology: rule 40-41. I would insert that in a first step clinical guidelines were searched but since no guidelines exist, systematic reviews and meta-analyses were searched, the RCTs, cohort studies and case-control studies, following the hierarchy of the levels of evidence. I would consider presenting an overview of the 31 key PICO research questions. Searches were done only in MEDLINE (using PubMed) and the Cochrane Library: as a rule of thumb EMBASE should be searched as well in order not to miss relevant data. I would propose to include the search dates as well: "we searched MEDLINE from inception to e.g. 21 July 2015.	We have changed the text, except for the guidelines, as we started the guideline by searching and checking other guidelines on the topic. Thank you for your suggestion, but as the key questions are clear from the summary of the document, and the document itself is very lengthy, we have decided not to add a list of the key questions. The last suggestion was included in the text
Andrea Lenzi	No specific comments on this	Ok
George Basios	Appendix 1 OGTT instead of GTT, PQCT instead of QCT Appendix 2, page 149, line 28: The term is live birth rate (The number of deliveries that resulted in at least one live born baby or a gestation over 20 weeks, according to Cochrane library definition!)	Thank you for your comment. We have changed OGTT, but kept QCT after discussion. We have not changed the definition of live birth rate, as we have referred to the ICMART/WHO definition.
B Mallikarjuna Kirthi	Page 149 line 26 & 27- Infertility -why not NICE definition?	Thank you for your comment, but we decided to use the ICMART-WHO definitions.
Inger Overlie	p150/ 40 ; definition of osteopenia and osteoporosis? (The T-scores)	As suggested we added a definition of osteopenia and osteoporosis

General comments

Reviewer	Comments	Reply
Patsama Vichinsartvichai	Overall guideline and recommendation are well elucidated with explanation. Thank you to developer group.	Thank you.
Giampaolo Mainini	All is clear, clever and right	Thank you.
Arianna d'Angelo	Please revise Turner Syndrome sometimes is TS and sometimes is written Turner Syndrome. The same occurs with GDG . There are some repetitions in the section on obstetrics outcome and fertility even if topics are seen from different angles.	Thank you for your comment. We have revised the chapter on fertility and pregnancy, and have checked the abbreviations
Adam Balen	Excellent and well written. I would prefer to see the term "natural pregnancy / conception" rather than "spontaneous" as pregnancy is never spontaneous. Otherwise very many congratulations for a huge piece of work that is very comprehensive.	Thank you for your comment, although we like the term natural pregnancy, this implies that pregnancies after IVF are not natural. Therefore we have decided to use "spontaneous" pregnancy
Michael Feichtinger	well designed guideline that covers a wide spectrum of topics. In some subtopics writing could be a bit more fluent to alter understanding to a broad population.	Thank you.
Jan Bosteels	This guideline is scientifically well written and the methodology is rigorous, clearly explained and according to the GIN guidelines. The recommendations are highlighted, graded according to the level of evidence and relevant for clinical practice. Besides strengths the weaknesses of the guideline development are presented as well (preponderance of British guideline developers involved in writing this guideline). This guideline presents an up to date overview of the diagnosis and management of people with POI.	Thank you.
Joe Leigh Simpson	Generally, I have restricted my comments to areas of my greatest expertise (genetics) in the interest of both of our times. For further details and references, a review in HRU is in final stages of acceptance (Qin, Jiao, Simpson, Chen)We would be happy for the committee to peruse that pre-print if the HRU Editor agrees. Information on findings using contemporary genetic tests include CNV or WES, as illustrative examples.	Thank you.

Gianluca Di Luigi	I think we need to clarify the optimal approach for oncological patients. The lack of hormones is worst than the risk of a secundary neoplasia. We need to organize a specific, targeted research about it. Because we need to councel this type of patients and I think that in the nearest future this hard situation will more popular.	Thank you for your suggestion, we have added it to the research recommendations
Andrea Lenzi	I found this article comprhenesive and complete. References are updated and the article is clear, straightforward and very well organized. It is going to be a multicited article and also I think it will be very useful to clinicans in their daily clincal practice	Thank you.
Stephen Franks	I think that this is a truly excellent and comprehensive document that is easy to digest. It has been extremely well researched and the list of references is very long and helpful.	Thank you.
Nidhi Sharma Chauhan	A patient friendly version/leaflet of the guideline should be developed in order to improve patient compliance. Questionnaires should be developed for yearly assessment of bone health; cardiovascular status , neurological status and psychological status	Thank you for your suggestion. We will develop a patient version of this guideline. The questionnaires are a nice idea, but individual clinics should have the ability to develop tailored questionnaires.
RCOG - Mostafa Metwally	These comments are sent by me as the Vice Chair of the Scientiic Advisory Committee of the RCOG; not me as an individual.	Thank you.
Michał Kunicki	Thank you for all authors for an excellent review of the very important clinical problem both for doctors and patients.	Thank you.
Cristina Laguna Benetti-Pinto	I agree that the best term to describe this condition is " Premature Ovarian Insufficiency" and I am sure this guideline is extremely important to reinforce the differences between women with POI and post menopause women, as well as to standardize the medical care offered to these women. Congratulations!	Thank you.
George Basios	1. I believe that references as old as from late 90's or before should be omitted as very old 2. I believe that chapter 12 (HRT) is far too large and analytical for the purpose of this guideline	We agree that one should focus on recent studies, but on some topics discussed In the guideline, there is a lack of recent data, and the only data available are derived from “older” studies. (fi egg donation)

		We agree that chapter 12 is extensive, but we feel it covers all aspects of HRT in a structured manner. Nevertheless, we have tried to reduce the chapter.
Beatriz Alvaro Mercadal	This is a very complete and well organised review that will be very usefull in the clinical practice. Thank you for the effort.	Thank you.
Fernanda Águas	Excellent and very complete guideline on management of POI	Thank you.
Sophie Christin-Maitre	First of all, many congratulations to the group for writing those recommandations. The amount of work is enormous and the data are clearly presented. This work is going to be very helpful to clinicians seeing patients with POI. Indeed, many practical issues are raised and the data presented are uptodate. The authors have performed huge efforts in order to answer all the different questions raised by premature ovarian insufficiency. I have added minor comments in some chapters.	Thank you.
Kate Maclaran	We believe the guidelines should also recommend that women with POI be offered age appropriate written information regarding the condition. They should be advised of the presence of on-line support groups which can provide information and support such as The Daisy Network www.daisynetwork.org.uk	We acknowledge that patients should receive age appropriate information, and we will use this suggestion in eh development of the patient version. Information on where patient can find more support will also be added to the patient version of the guideline.
Inger Overlie	ESHREs Report concerning guidelines about Management of women with premature ovarian insufficiency is a systematic review, covering all aspects of POI, and the review is divided into three parts. It is an extensive review, and I have only one actual comment concerning DHEA and DHEA treatment, see above. This is an important review that will be of great help to clinicians dealing with POI.	Thank you.
Nivedita Reddy	An extremely detailed and comprehensive set of guidelines. The effort and time to put these together has to be deeply appreciated. It may be helpful if some of the recommendations for obstetric risks associated with fertility can be fed into fertility guidelines and improve awareness of fertility specialists as they are in the best place to address these aspects before commencing treatment.	Thank you for your suggestion. We will take this comment to the discussion on the implementation of the guideline.
Philippe Bouchard	Altogether it is excellent , well written, easy to go through.	Thank you.

	The members of task force are to be congratulated for their work.	
Nick Panay	All specific comments have been pasted or highlighted directly on document. General Comments: 1) The guideline group should be commended for the huge amount of work which has conscientiously been carried out to produce this much needed guideline. 2) The guideline is well organised and easy to follow and the literature search appears thorough. 3) There is some duplication in the document which means it could be shortened a little in the future. 3) The specific recommendations are based on the available evidence and easy to understand. 4) One of the limitations of the document is that due to the lack of data many of the recommendations are based on expert opinion rather than research data. 5) Despite the comments in 4) it is important that a guideline has been produced in order to guide health care professionals as to the best practice for managing women with POI given current evidence. 6) The important next step is to ensure implementation of the guideline through widespread dissemination of the guideline in both primary and secondary care. 7) The planned version for the public will also be important to improve awareness and to encourage women with possible to POI to attend their healthcare professionals 8) The absence of long term RCT data has been acknowledged but there has been little mention of the possibility of gathering good quality prospective observational data in the meantime e.g. Panay N, Fenton A. Premature ovarian insufficiency: working towards an international database. Climacteric. 2012 Aug;15(4):295-6. https://poiregistry.net/ and others..... Cooper AR, Baker VL, Sterling EW, Ryan ME, Woodruff TK, Nelson LM. The time is now for a new approach to primary ovarian insufficiency. Fertil Steril. 2011; May;95(6):1890-7.	Thank you for your comments. We have added the need for a POI registry to the research recommendations. The raised limitations of the guideline and available evidence will be used in writing the summary document for publication in Human Reproduction.
Manuel Puig Domingo	This is a superb piece of work with encyclopaedically spirit rather a standart guideline for clinicians. It seems to me more a “textbook of POI” rather than what we use to find worldwide as clinical guidelines. It has taken me quite some hours to review it. However, the format of	Thank you for your comments. We have choosen the format as is, but we may apply the suggested

	presenting in every chapter a paragraph with conclusions and clear messages in a box seems a very good idea. Personally, I would have written the summary/conclusions at the beginning of every chapter and the evidences and comments in a more developed way –as it stands currently-after the box with the key messages. My only general criticism is that sometimes the same concepts and information are repeated in different chapters throughout the text. I image that it has been organized this way to allow the individual lecture of each chapter. The use of more tables for dosages and other specificities would have been in this regard more helpful and, if possible, should be increased, throughout the text. Some references seem old in some cases, although it is clear that recent data is not always available.	approach when developing an online layered version of the document. We indeed organised each chapter to be a stand-alone document, as many clinicians will only consult one chapter when searching for guidance. Finally, we agree on the use of tables, and we have checked the individual chapters for addition of tables.