ID	If submitting feedback on behalf of an organisation, name of organisation	Guideline recommendation to which feedback is targeted.	Comments	Guideline development group consensus response
19	Department of Health Western Australia	General comment	With regards to the implementation and dissemination of the Guidelines, will there be alignment with or dissemination to commonly used online clinical practice guidelines such as Up To Date and BMJ Best Practice? The implementation program does not specify ensuring of alignment with commonly used clinical practice guidelines	This was intended and has now been added in to the implementation plan.
62	SA Health	General comment	Over all a well presented document. I wonder if the authors considered weight gain as a causative factor of PCOS and the effects of weight loss on the disease and outcomes. For example, 'Does weight loss increase fertility?'. Another question would be, 'In some cases, can PCOS be solely due to obesity?'. The structure of the document would suggest that the weight gain is caused by PCOS and that diet and exercise have little benefit beyond general wellbeing. Given this, it risks normalising obesity and hampering obesity treatment in the community.	The question 'Does weight loss increase fertility? Was considered under the section on effects of lifestyle and weight loss. Evidence is currently inadequate to demonstrate increased fertility with weight loss. For the question , 'In some cases, can PCOS be solely due to obesity?', the guideline does not explore causation which is out of scope, however whilst not covered here directly, there is evidence of so called secondary PCOS and evidence of resolution after weight loss. This is noted in the section on bariatric surgery.
104	NT Health	General comment	The Key Principle focused on the needs of Indigenous and Torres Strait Islanders as high-risk populations n Australia Indigenous and Torres Strait Islander people are a high-risk population and within the Northern Territory our largest stakeholder group making up approximately 27% of the population (Northern Territory: Aboriginal and Torres Strait Islander population summary | Australian Bureau of Statistics (abs.gov.au)). A principle focusing on high-risk populations ensures the guideline's relevance to First Nations' people with high need and who may be otherwise marginalised.	A strong focus on high risk population is integrated in the dissemination plan including Indigenous Australians. An Aboriginal and Torres Strait advisor has been engaged throughout and will be actively involved with other broader indigenous stakeholders in the national implementation and dissemination plan. Our diverse international partnerships include culturally and linguistically diverse representatives across world regions engaged in all phases of guideline development and will lead dissemination including language translation with their communities globally.
104	NT Health	2.6.1 Information needs	Section 2.6 includes a recommendations on Information resources, models of care, cultural and linguistic considerations It is imperative that all people receiving health care are able to understand their treatment in order to provide informed decision making. This recommendation ensures high risk populations and diverse cultural and linguistic groups are provided with appropriate models of care and information to enable informed decision making..	This is addressed in Chapter 2 of the guidelines. An Aboriginal and Torres Strait advisor has been engaged throughout and will be actively involved with other broader indigenous stakeholders in the national implementation and dissemination plan. Our diverse international partnerships include culturally and linguistically diverse representatives across world regions engaged in all phases of guideline development and will lead dissemination including language translation with their communities globally. The implementation and dissemination plan also incorporates this. Also the strong emphasis on Indigenous engagement in the implementation and translation plan includes coproduction of an array of translation resources with this community
Other invited Government stakeholders				
Consumer health forum. No response				
Department of Health Victoria. No response.				
Department of Health Qld. No response				
Department of Health NSW. No response.				
Department of Health Tasmania. No response.				
Department of Health ACT. No response				
Australian Government Department of Health and Aged Care. No response.				

ID	Comments	Guideline development group consensus response
2	Practical recommendation for PCOS	Nil needed
5	Compiled document showing evidence for each point.	Nil needed
12	This is a very welcome update to the previous International evidence-based guideline. The authors are to be commended for a rigorous and comprehensive review	Nil needed
12	Abstract. Page 1. Process. Change ˜European Endocrine Society" to ˜European Society of Endocrinology".	Changed throughout the document
12	Abstract. Page 1. Process. Suggest "Committees members nominated by collaborating organisations, provided international peer review, and evidence expert reviewed methods and outputs were submitted to NHMRC for independent review" is changed to "Committee members nominated by collaborating organisations provided international peer review, and evidence expert-reviewed methods and outputs were submitted to NHMRC for independent review"	Wording changes made
12	Recommendations to avoid ultrasound in adolescence (due to poor specificity) and to obviate the need for ultrasound or AMH when the diagnosis is otherwise established are welcome.	Nil needed
12	We welcome the emphasis on lifelong care and the importance of screening for non-reproductive (psychological, dermatological and cardiometabolic) as well as reproductive sequelae.	Nil needed
12	Abstract. Page 1. Recommendations. Suggest "Weight bias and stigma should be minimised and healthcare professionals should seek permission weigh women, with explanation of weight related risks" to "Weight bias and stigma should be minimised and healthcare professionals should seek permission to weigh women, with explanation of weight-related risks".	Wording changes made
12	Abstract. Page 1. We welcome the recognition that inositol may offer little clinical benefit as this is used widely by patients and is a common question at consultation.	Nil needed
12	Abstract. Page 1. Clarification of the positioning of metformin as a therapy predominantly in metabolically at risk patients rather than for other indications is also helpful.	Nil needed
12	Abstract. Page 1. We agree that antiandrogens have a limited role. Expectation management is an important part of the counselling around use of these agents as second-line therapy for hirsutism, with modest benefits at best. Should a practice point to this effect be considered later in the guideline?	The GDG considered this feedback but agreed that the point was made in current recommendations.
12	Abstract. Page 1. The recommendation for laser therapy is new and helpful but access to treatment can be difficult in some healthcare economies, including the UK. The evidence-base is quite limited and we would support a call for more studies on clinical- and cost-effectiveness when added to first-line therapy such as the combined oral contraceptive pill. Patient surveys place a high importance on the need for effective therapies in improving hirsutism.	Added to research priorities
12	Abstract. Page 1. Whilst we do not dispute the recommendation for letrozole over clomiphene first-line for ovulation induction, the LOCI trial (LOCI trial - University of Birmingham) will clarify this question as well as the potential added benefit of metformin. Would it be helpful to include a reference to this effect later in the guideline, in the expectation that this study will report before the guideline is next updated?	We are unable to refer to all pending studies but this is a living guideline hence if significant studies emerge evidence will be updated and recommendations altered if warranted.
12	We strongly endorse the call for more funding and research, and welcome the provision of evidence-based resources for consumers, policy makers and healthcare professionals.	Nil needed
12	General. There is no section commenting on the utility of specific cosmetic measures in the management of hirsutism (such as waxing, shaving, plucking, threading). Should there be a practice point stating that these can be useful, with choice determined according to individual preference, and no evidence of an adverse effect on hair re-growth (which is a common misconception)?	These topics were not prioritised by consumers or health professionals and whilst this appears a reasonable request, evidence around lack of adverse effect on hair regrowth has not been sought. This can be considered in the next guideline.
12	Should there be an EBR or CR commenting on the usefulness (or not) of topical eflornithine in the management of hirsutism?	This topic was not prioritised by consumers or health professionals hence is not included here.
16	Congratulations to you all. I have no comments to make	Nil needed

23	Inclusion and stigma comments page 10 As discussed previously this section (if included) should be in chapter 6 where it explains the methods and reasoning behind this wording. As discussed previously, I question the length and necessity of several paragraphs which add little to the document considering the relatively uncontroversial wording of the recommendations. These paragraphs in my view advocate a progressive, culturally contested view of sex and gender which is not needed in these guidelines and is unique in any reproductive guideline published so far. It could be shortened to commence at "To this end, we have applied the following approaches throughout the guideline update:.....". In addition if retained it should highlight the observation that not all cultures and ethnicities share the same viewpoint on gender description.	The overwhelming feedback support the statement, as such it was retained. However, the observation that this varies across cultures and ethnicities was added in pg 10.
24	A 'to' is missing in this sentence in the abstract: professionals should seek permission weigh women	This grammatical error was corrected
28	Please consider the impacts of PCOS on sexual health, and add point about offering sexual health screening to discussions with patients	This was out of scope for the guidelines as sexual health is relevant to all women and not specifically to those with PCOS.
30	Overall very comprehensive.	Nil needed
37	Rigor of Development on the guideline; Justifications for few recommendation are short and with little or no references in that section (for example 3.5.1 and 3.5.2 (AGREE instrument- Question 12)	As noted throughout the guideline, there are thousands of references captured in the 55 systematic reviews here and hence not all referenced in the summary document. All are referenced in the accompanying technical document including the 37 papers in section 3.5.
38	Page 10 -Inclusiveness and stigma; The last paragraph in this page that starts with "To this end, we have applied..." is redundant since the same statement is repeated in the previous paragraph. Page 15 -Table 1: Categories of the POCS guideline recommendations; There is an extra blue line under PP and there is no line between CR and PP.	"To this end, we have applied..." has been removed to limit repetition. The issue of resources for those with PCOS is vitally important and these will be released alongside the guidelines and have been codeveloped with consumers. Final formatting of the document will occur once all responses to feedback have been agreed by the GDGs.
39	Firstly, we would like to thank the PCOS Guideline team for their concerted efforts to produce such a well-researched guideline. We appreciate the amount of work that has fed in to this draft.	Nil needed as specific points are covered with responses below.
40	Wonderful work, well detailed, easy to read, follow and understand. Thank you very much.	Nil needed
42	RANZCR would be happy to endorse the draft 2023 guidelines As radiologists report the majority of pelvic ultrasounds in Australia and New Zealand, RANZCR respectfully requests that we are cited as being included in the consultation process and would be grateful if the RANZCR logo be included amongst the stakeholders.	We have engaged with RANZCR who are important stakeholders and they have been acknowledged and included.
44	On page 2 under the heading Recommendations summary it begins with table 3, are there any other tables before this? It may also be good to include an introductory paragraph explaining what CR, PP, and EBR mean and a legend for the symbols used under GRADE would be helpful.	This was taken directly from the main guideline document and table order will be rectified in the final published document with explanations of the recommendation types provided.
46	The Summary needs a formatting review	Final formatting will occur once all feedback has been received.

47	This version is much more patient friendly to read and engages with the idea of joint ownership of management of the condition. 2.6.4.2 the patients' own voice in management seems to be missing from this despite the strength of it in other areas. 3.1.7 - refers to life long conditions but then focuses on fertility 3.6 - All supporters spoken to felt that their experiences meant that this section needs to be stronger in terms of GPs 'NEED' to do things as opposed to should do. The patient experience is that should is not strong enough. - still seems a fair bit of 'lean' pcos missing and so wording around pcos management for all is needed - still shows where there is such a need for more research on certain areas such as long term health. - very positive response to inclusion and presentation of quality of life and this feels stronger then 2018 guidelines - the glossary needs extending such as what is male pattern hair loss, what is assay - the document makes assumptions as to patient's language and level of understanding. - numbering consistency between 52 and fifty two - document switches between numbers and words on figures constantly	2.4.6.2 was focused primariliy on patients "Healthcare professionals should recognise the importance of being knowledgeable about PCOS, and apply evidence-based practices when sharing news on diagnosis, treatment and health implications, ascertaining and focusing on patient priorities". This particular recommendation does relate directly to the health professional using evidence based approches to working with patients. 3.1.7 this has been extended to other features. 3.6 In evidence based guideline, "should" is the strongest level of recommendation that can be made. PCOS is used intending to refer to all, and where the evidence is only for higher weight categories this is stated. We have made this clearer in the guideline introduction. Formatting of numbers/ words will be completed in the final guideline and the glossary will be extended to consider patient/ consumer needs. The assumption is that recommendation include lean and higher weight women unless BMI specific recommendations are made.
52	Consider including the following in the Implementation, Translation and Dissemination Plan: Collaborate with ASUM to develop and deliver education and Continued Professional Development (CPD) specific content for imaging professionals (e.g., a webinar). - Write and submit an ultrasound-focused publication to the Australasian Journal of Ultrasound in Medicine (AJUM) (Note: Monash University have an open access waiver with Wiley). Peer review will strengthen the guideline and dissemination. - Submit an abstract to ASUM 2023 to present this work to the ultrasound community. Potential to run a workshop on the implementation or other formats would be welcome. (Abstract submission guidelines and link to submission portal are available here - https://asum.com.au/docs/Events/Call%20for%20Abstracts%20-%20Submission%20Guidelines%20-%20updated%2020230323.pdf?_zs=MUrtl&_zl=PbcT2) - Write a blog (e.g., What's new in the 2023 PCOS updates) for the new Waveforms Blog on ASUM Connect.	These disseminations strategies are welcome and we will reach out during dissemination.
54	Overall, the Guidelines are very well documented and clearly written. They will be very useful to healthcare providers and stakeholders. Congratulations to all!	Nil needed
56	Stronger guidance needed on recommendations from should to need or must	The strongest recommendations allowable in guidelines are "should". Must is avoided as there are always clinical nuances or exceptions in individual circumstances.

61	We would like to commend the guideline writing committee for acknowledging that women with polycystic ovary syndrome have a higher prevalence of cardiovascular risk factors and subsequently greater risk of cardiovascular disease and potential mortality. It is important that we raise awareness among health professionals and the public to address and reduce the overall and future cardiovascular disease risk. As stated in the technical report evidence summary there is conflicting and very low/low GRADE certainty of the evidence on cardiovascular disease in women with polycystic ovarian syndrome. We agree that there is a need for more research in this area to strengthen the evidence of the cardiovascular risk (and need for management) in women with polycystic ovary syndrome. In the technical report on page 740, fourth paragraph, last sentence there is a spelling error. Therefore, the results of the meta-analysis on this topic should be interpreted with cautious, since they have a high degree of heterogeneity in terms of design and quality of included studies. Cautious should be caution. Thank you for the opportunity to provide feedback on the draft International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2023. We look forward to seeing the final published guideline. Please let us know when the guideline is published, we could assist with promoting the publication through our networks.	The detected spelling error was corrected in the technical report.

63	Congratulations on a comprehensive guideline and the wide group of stakeholders. Just a few comments to make, 1. the wording of the EB recommendations often use 'should' when the quality of the studies has been graded low or very low. This is not the wording that GRADE recommends using for wording recommendations e.g. 1.2.1, 1.2.3 etc Also using should in a PP where presumably there is no evidence seems a stretch. e.g. "Healthcare professionals, adults and adolescents with PCOS and their first-degree relatives, should be aware of the increased risk of diabetes and the need for regular glycaemic assessment." Presumably no evidence for this as not a EBR. Yet this uses strong words such as "should". Setting up for a lifetime of glycaemic assessment (not defined) seems extreme. 2. The ovarian volume calculation should mention that ovulatory follicles should not be included in the measurements. 3. General mention was made of the wide scope of the guideline. Much of the guideline is of limited interest to gynaecologists especially in clinical settings that are resource constrained and where patients with PCOS only come to gynaecologists if they have a gyne problem - such as abnormal bleeding and infertility. GPs Could manage most of the common PCOS skin symptoms and screening for long term diseases. 4. Some concerns about increasing anxiety amongst young women. PCOS is associated with risk factors but there is no attempt in the guideline to reassure young women - for example what is the likelihood of infertility if there are regular periods. There are many more serious conditions that lead to infertility e.g. STis and endometriosis. Can you try and put PCOS into perspective. It is NOT cancer. it does not necessarily mean they can't have children. How can you stop making them feel anxious. and still encourage safe sexual practices. Many young women with PCOS will assume infertility and not use contraception. 5. the structure of the majority of the recommendation starts with these three words. "Health care professionals should ..." it is rather repetitive . Alternative wording could place the Patient at the beginning of the sentence. e.g. "Women with PCOS who have abnormal bleeding should have an ultrasound to assess the endometrium as EH and EC are more likely to occur" or something similar. In this recommendation 1.11.1 "Healthcare professionals should be aware that premenopausal women with PCOS have markedly higher risk of developing endometrial hyperplasia and endometrial cancer". Can you clarify if this evidence applies regardless of BMI. Is the word 'markedly' justified when it is very low evidence. we note this sentence in the full document. "Routine screening for endometrial cancer in PCOS is not recommended as absolute risk remains low, despite much higher relative risks in PCOS, hence clinician	1) Quality of studies or certainty of evidence do not always directly align with strength of recommendation when using GRADE process. All strengths and certainty of evidence have been reviewed for alignment and where there is an apparent discrepancy, a justification has been added based on the GRADE framework. There is no recommendation or practice point for ongoing glycaemic testing in relatives of women with PCOS. 2) wordings in PP 1.4.11 has been amended to note the comment 3) nil response required 4) We have added comments on low absolute risk on several recommendations and have included a practice point in reassurance around fertility outcomes in those with PCOS. 5) We have amended the recommendations to incorporate this comment regarding 1.11.1 on endometrial cancer - we do not have evidence to show if the risk is independent pf BMI. We also now add to the practice point 1.11.2 that absolute risk is low and routine screening is not recommended
65	GDG1 provided some guidance toward funding bodies regarding the importance of specific research areas in need of support. There is a lack of those types of specific recommendations to funders in GDG2 and I wonder if this is a missed opportunity. Perhaps a CR aimed at funding bodies to recognise the prevalence/higher risk of anxiety and depressive symptoms with diverse aetiology in women with PCOS and the need for greater research support in this area.	Research recommendations will be added onto the guideline as an appendix and also published separately. All research recommendations emanating from all GDGs will be highlighted to stimulate prioritised research in these areas. We have also added a general practice point in GDG 2 for funding bodies should prioritise psychological health in PCOS.
64	Those leading this project and the contributors to this project are congratulated on developing these comprehensive and rigorous evidence-based guidelines for the treatment of those with PCOS around the world. My comments are largely focussed on Chapter 2, but I have also made a few general comments. I do not take issue with any of the recommendations from GDG2 and the evidence that they are based on, however, I have made some suggestions around clarity and identified a few potential missed opportunities. See additional recommendations for GDG 2.1, 2.2, 2.6	Nil needed here, but responses to specific comments are under the Psychological tab.

66	Page 6- Paragraph 7 and Line 4 (permission weigh..) Sentence needs revision Page 7- Plain language summary - Paragraph 4 and line 4 (The guidelines also recommend..) - Sentence needs revision Page 10/ exec summary- The two paragraphs above ˜Governance" section appear to be repetitive except for the word adolescent.- retain only the later paragraph Page 34 / Section 5.5.1- The statement is confusing as the summary clearly states that gonadotropins are second line therapy - Clarity required for using gonadotropins in treatment naive patients Page 36/ section 5.7.3.1- There is no mention of HMG- While considering urinary preparations, use of HMG should be addressed Page. 46/ Section 1.6 - Line 2, paragraph 2: a comma is required after European Page 53/ Section 1.11- What should be considered as excessively endometrium? Page 109/Section 5.6.2 - The last point - the sentence should be rephrased as above healthy weight? The most important areas which need clarification are: 1.Recommending use of gonadotropins as first line therapy in women with PCOS and infertility. 2.Not including urinary HMG in the discussion. 3.Some guidance on BMI beyond which consideration of anti-obesity medications 4. Inclusion of acanthosis nigricans (page 6) and bitemporal hair recession (page 4) on physical assessment.	Grammatical errors and typos listed were amended in the guideline. Regarding the areas needing clarification: 1 and 2) Extensive consideration of the evidence supported gonadotrophin recommendations and no additional evidence has been provided here to support a change. 3) Evidence does not support any specific any BMI cut-off for antiobesity agent and this has been highlighted as an area for more research. 4) Acanthosis nigricans was not prioritised in this guideline and can be considered in the next update.
68	To the section on "inclusion and stigma" and the approach in the guideline regarding gender inclusive language, ESHRE would like to applaud the guideline developers for their effort and consideration. ESHRE supports all inclusive purposes and understands that the language used is not intended to isolate, exclude, or diminish any individual's experience nor to discriminate against any group.	nil added
69	While the guideline provides extensive information and recommendations on hyperandrogenism, AMH, and ultrasound. There is no upfront recommendation on the diagnosis of PCOS. The diagnostic criteria for PCOS should be stated at the beginning of the document and they should provide information whether disturbances in hyperandrogenism, AMH, and ultrasound are necessary, or whether a combination of two factors is sufficient for a PCOS diagnosis.	For clarity a statement on diagnosis is added upfront in the section "context statement on diagnosis". The algorithm on diagnosis addressed this also.
70	Generally, there have been great improvements in the Guidelines since their original publication and they have been well received. There are some points that our Special Interest Group mentioned (some evidence based - others more general but we have included them too in the interest of providing patient experiences). Wording in some sections is a little confusing and people may interpret the sections differently. It should be more clear and easier to understand and follow for both healthcare professionals and patients. The management options for sexual health related concerns should also be touched upon in more detail. The language currently focuses on PCOS being a condition that can only impact women, however, with certain changes, the language can be made more gender inclusive or they could add a section acknowledging the health care needs of those who might be assigned female at birth but don't identify as women.	Wording in the extensive consumer translation resources will be tailored with and for consumers using plain language targeted to relevant health literacy levels and in multiple languages. Sexual health was not prioritised in the current guideline hence it is out of scope but can be considered in the next iteration. The language statement upfront seeks to address this issue around gender. On wide consultation across the GDGs, the consensus was that gender inclusive and not gender neutral language was preferred as the vast majority of those of female sex, who are assigned female at borth identify as women and the desire to avoid erasure of that identity guided the consensus to include a gender inclusive statement and several strategies to enhance inclusion without moving to gender neutral language.

91	We were particularly happy to see more inclusive language that accounts for all patients and how they may identify and the recognition of bias in care, including in addressing weight and gender. A new feature of the updated guideline is introductory material explaining the inclusive use of language and stigma. We appreciate the acknowledgment of gender-diverse individuals with PCOS and the recognition that PCOS occurs in those who identify as cisgender and transgender/nonbinary. The introductory material on inclusive language is a welcomed addition to the guideline; however, the retention of the word 'woman' to represent all regardless of how they identify is counter to the focus on inclusion. While we do not want or intend to erase women from the conversation, there are several instances in the guidelines where the word woman could be omitted, and the guideline would retain its meaning. In other instances, the word "woman" can easily be replaced by "person," and the word "women" can be replaced with "people," where person or people refers to those who were assigned female at birth to increase inclusion.	We aim to be inclusive, however as 98% of those assigned female at birth identify as women, after long consideration and consultation, the decision was made to be gender inclusive rather than gender neutral. Subsequent research in this will explore the broader preferences for how this is best represented.
105	There is no mention or discussion regarding the ontogeny of PCOS and the novel notion that PCOS -at least in adolescent girls- may not be a post-menarcheal disorder, but a pre-menarcheal disorder that manifests after menarche. This notion may obviously influence the therapeutic options (doi: 10.1159/000479371; doi: 10.1016/j.tem.2018.09.005; doi: 10.1002/oby.21935).	As this is a clinical guideline, genetics and ontogeny are not covered and are considered out of scope. They were also not prioritised by the partners, experts or consumers in this guideline.
105	Cut-off values should be given for androgen levels and FAI (despite the methodological considerations that have been raised). Methodological considerations for defining ovulatory dysfunction and polycystic ovarian morphology are also discussed and yet the guideline provides detailed descriptions of these additional diagnostic criteria.	Evidence was explored on this topic, but was not adequate for a consistent international cut off value. Cut offs are influenced by lab method and assay which is a central issue for all hormonal assays and is not an issue for ovulatory dysfunction and follicle number
105	A section of acne and its treatment is lacking, despite the fact that it may be a major cause of psychological distress in these women.	The guideline was not able to cover all areas of PCOS and areas prioritised by consumers took priority. Acne was stated for consideration in the next guideline update.

ID	Guideline recommendation	Comments	Guideline development group consensus response
12	1.1.3 PP In adolescents with irregular menstrual cycles, the value and optimal timing of assessment and diagnosis of PCOS should be discussed with the patient and their parent/s or guardian/s, considering diagnostic challenges at this life stage and psychosocial and cultural factors.	Consider emphasising importance of FSH/LH/oestradiol measurement in patients with primary amenorrhoea due to wide differential diagnosis	We are unable to specify investigations for the breadth of presentations here. We rely on clinical interpretation for other differentials. We have added a section in the guideline document on differentials to recommend referring to guidelines on other relevant differential diagnoses.
12	1.1.5 PP Ovulatory dysfunction can still occur with regular cycles and if anovulation needs to be confirmed serum progesterone levels can be measured.	Should the guideline stipulate the timing of progesterone measurement to confirm or refute ovulation?	As women with PCOS are oligoanovulatory we cannot stipulate this accurately
12	1.2.9 PP If androgen levels are markedly above laboratory reference ranges, causes of hyperandrogenaemia other than PCOS, including ovarian and adrenal neoplastic growths, congenital adrenal hyperplasia, Cushing's syndrome, ovarian hyperthecosis (after menopause), iatrogenic causes, and syndromes of severe insulin resistance, should be considered. However, some androgen-secreting neoplasms are associated with only mild to moderate increases in androgen levels. The clinical history of time of onset and/or rapid progression of symptoms is critical in assessing for an androgen-secreting tumour.	This is an important practice point as it alerts the clinician to think of other causes of PCOS when the presentation is atypical. As is suggested, it is difficult to be too prescriptive on what concentration of androgen equates to ¯markedly elevated", and clinical judgement is as important as the absolute androgen value in this setting. Should guidance be offered on "red flag" symptoms to consider when the clinical history is obtained?	We are unable to specify investigations for the breadth of presentations here and need to rely on clinical interpretation for other differentials. We have added a section in the differentials to recommend referring to guidelines on other relevant differential diagnoses.
12	1.2.11 PP Laboratories involved in androgen measurements in females should consider: •Determining laboratory normal values by either the range of values in a well characterised healthy control population or by cluster analysis of the values of a large general population. •Applying the most accurate methods where available •Using extraction/chromatography immunoassays as an alternative to mass spectrometry only where adequate expertise is available. •Future improvements may arise from measurement of 11-oxygenated androgens, and from establishing cut off levels or thresholds based on large-scale validation in populations of different ages and ethnicities	We welcome comments on future biochemical developments, including the potential value of measuring 11-oxygenated androgens. Is there value in commenting on the potential utility of steroid metabolomic measures in the future?	As yet, there is inadequate evidence to support these measures but we look forward to reviewing relevant evidence in the next guideline update.
12	1.2.2 EBR If testosterone or free testosterone is not elevated, healthcare professionals could consider measuring androstenedione and dehydroepiandrosterone sulfate (DHEAS), noting their poorer specificity and the greater age associated decrease in DHEAS.	Is there a reason why A4 and DHEAS should not be recommended for measurement "up front" with testosterone to reduce future venepuncture, particularly given the relative ease and low cost of assaying with serum T?	The false positive rate and lack of specificity of these tests will have significant consequences for women including potential overdiagnosis
12	1.2.9 PP If androgen levels are markedly above laboratory reference ranges, causes of hyperandrogenaemia other than PCOS, including ovarian and adrenal neoplastic growths, congenital adrenal hyperplasia, Cushing's syndrome, ovarian hyperthecosis (after menopause), iatrogenic causes, and syndromes of severe insulin resistance, should be considered. However, some androgen-secreting neoplasms are associated with only mild to moderate increases in androgen levels. The clinical history of time of onset and/or rapid progression of symptoms is critical in assessing for an androgen-secreting tumour.	1.2.9: Reasonable to apply a cut off here for serum T? consider 5nmol/l?	The expert GDG committee considered this during recommendation development, however laboratory values vary depending on individual assays and the population and a set level could not be determined from the evidence.
12	1.3.5 CR A modified Ferriman Gallwey score (mFG) of ≥ 4 - 6 indicates hirsutism, acknowledging that self-treatment is common and can limit clinical assessment.	We would question the usefulness of the modified Ferriman-Gallwey scoring system in clinical practice since the majority of patients will be self-treating (and inter-observer variation is likely to be high). There may be a danger that the mFG assessment may under-recognise the presence and/or severity of hirsutism in these circumstances. The patients view of the extent of hirsutism is likely to be as informative, or more so than the clinicians.	The importance of patient perception is recognised in the practice points with a focus on this being the key priority.
12	1.3.7 PP Healthcare professionals should: •Be aware that standardised visual scales are preferred when assessing hirsutism, such as the mFG scale in combination with a photographic atlas •Consider the Ludwig or Olsen visual scales for assessing female pattern hair loss •Note that there are no universally accepted visual instruments for assessing the presence of acne •Recognise that women commonly treat clinical hyperandrogenism cosmetically, diminishing their apparent clinical severity •Appreciate that self-assessment of unwanted excess hair growth, and possibly acne and female pattern hair loss, has a high degree of validity and merits close evaluation, even if overt clinical signs of hyperandrogenism are not readily evident on examination •Only terminal hairs need to be considered in defining hirsutism, and these can reach >5 mm if untreated, vary in shape and texture and are generally pigmented •Note that new-onset severe or worsening hyperandrogenism, including hirsutism, requires further investigation to rule out androgen-secreting tumours and ovarian hyperthecosis •Monitor clinical signs of hyperandrogenism, including hirsutism, acne and female pattern hair loss, for improvement or treatment adjustment during therapy	Consider including statement that overt virilisation is not consistent with a diagnosis of PCOS	This was considered and was added to the background section of the guideline
12	1.5.5 PP Healthcare professionals need to be aware of factors that influence AMH including: •Age: Serum AMH generally peaks between the age of 20-25 years •Body mass index (BMI): Serum AMH is lower in those with higher BMI •Ethnicity: Serum AMH may be influenced by ethnicity •COCP: Serum AMH may be suppressed by current or recent COCP use •Menstrual cycle day: Serum AMH may vary across the menstrual cycle	Data on serum AMH across cycle is contentious "clinical experience would suggest that variability is minimal" when do the authors recommend it is measured in cycle?	1.5.5 The GDG has considered this comment and confirmed evidence that AMH variation across the cycle is dependent on the assay and the recommendation wordings are retained. Also as most individuals PCOS are oligo-anovulation, the specific timing of the cycle is not clinically recommended.
12	1.8.3 CR All women with PCOS, regardless of age and BMI, should have a fasting lipid profile (cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol and triglyceride level) at diagnosis. Thereafter, frequency of measurement should be based on the presence of hyperlipidaemia and additional risk factors or global cardiovascular risk.	Whilst we support the importance of addressing cardiovascular risk factors, including fasting lipids, at baseline and follow-up, prescription of lipid-lowering therapy will need to consider the desire for fertility in addition to lipid levels.	The GDG agrees hence no recommendations on the use of lipid lowering therapy has been made here.
12	1.8.5 CR Funding bodies should recognise that PCOS is highly prevalent with multisystem effects including cardiometabolic disease, and should diversify and increase research support accordingly.	Research funding statement is very much welcome	Nil needed
12	1.9 Impaired glucose tolerance and type 2 diabetes risk	Ethnicity, a family history of type 2 diabetes and a personal history of gestational diabetes are important risk factors to capture at assessment, and help in stratifying frequency of screening for dysglycaemia. Should there be a practice point in section 1.9 to emphasise the importance of capturing these risk factors at the outset?	1.9.3 has already indicated that individual risk factors for diabetes should be taken into account.

12	1.9.11 EBR An OGTT should be offered to all women with PCOS and without pre-exiting diabetes, when planning pregnancy or seeking fertility treatment, given the high risk of hyperglycaemia and the associated comorbidities in pregnancy. If not performed preconception, an OGTT should be offered at the first prenatal visit and all women with PCOS should be offered the test at 24-28 weeks gestation.	Typographical error. Change "without pre-exiting diabetes" to "without pre-existing diabetes"	This typographical error was corrected
12	1.10.1 EBR Healthcare professionals should be aware that women with PCOS have significantly higher prevalence of obstructive sleep apnea compared to women without PCOS.	Is the higher prevalence of obstructive sleep apnoea independent of weight? Should a symptom-enquiry be prioritised (or confined) to higher-weight patients?	This is independent of BMI and this detail has now been added to the recommendation and evidence summary.
12	1.10.3 PP Simple obstructive sleep apnea screening questionnaires (such as the Berlin questionnaire, validated in the general population) can assist in identifying obstructive sleep apnea in women with PCOS.	Recommend including a statement that referral for formal sleep studies is advised based on cut offs in screening assessment " sleep scores in isolation cannot diagnose sleep apnoea"	Wordings of the recommendation are changed.
12	1.11.1 EBR Healthcare professionals should be aware that premenopausal women with PCOS have markedly higher risk of developing endometrial hyperplasia and endometrial cancer.	We agree that the relative risk of endometrial cancer may be higher but the absolute risk is still low in a pre-menopausal population and are pleased to see that practice point 1.11.2 recognises this. The benefits of addressing risk factors (obesity, amenorrhoea) and introducing preventative strategies (cyclical progestogens, progesterone-releasing IUD, COCPs) needs to be balanced against the potential to increase health anxiety if this difference between relative and absolute risk isn't appreciated.	The recommendation is clear that the overall risk of endometrial cancer is low. The translation tools developed for the consumer will clear explain the difference between relative and absolute risk for consumers.
12	1 Screening, diagnostic and risk assessment and life-stages	The risk of NAFLD is not discussed. Was this considered? We accept that formal screening for NAFLD may not be justified in the absence of specific therapies and in line with other recommendations (e.g. NICE). However, should clinicians have a heightened awareness of an increased risk of NAFLD in PCOS, and if detected/suspected refer accordingly?	NAFL was not prioritised in the guideline and as such is out of scope. The reasons for this in part relate to the factors raised by the reviewer, that this is a manifestation of obesity and that there are no specific therapies that are effective above recommended weight loss.
17	1.3.6 CR The prevalence of hirsutism is similar across ethnicities, yet the severity of hirsutism varies by ethnicity.	mFG/Hirsutism scores appear to vary significantly between various ethnic groups Data (N>10,000) from various collaboration centres including China, Italy, USA, Nigeria, Russia, South Korea, Turkey and Iran show that mFG varies significantly between ethnic groups from these countries. These findings are pending confirmation after accounting for inter-observer variation.	Based on the evidence available, we have insufficient evidence to suggest that mFG scores vary significantly between various ethnic groups. This has been identified as a priority area for future research by the guideline group.
18		Serum AMH as one of the diagnostic criteria Not all laboratories have standardised methods for AMH. This might lead to false diagnosis (most likely over diagnosis) If only two laboratory markers are positive e.g. hyperandrogenism andAMH, it will make a diagnosis of PCOS. Having diagnosis based on only biochemical parameters (without lab/ USG) might overdiagnose PCOS.	The substitution of ultrasound for biochemical markers is no different to the current scenario where women may be diagnosed based on non clinical parameters. Either PCOM or AMH alone result in similar rates of diagnosis, however doing both may over diagnose. It is now clarified that either and not both tests can be performed to identify PCOM.
31		There was a lot of concern is that these guidelines expand the definition of PCOS. Six editors agreed with this concern. This will inevitably lead to more women being diagnosed with a disease that potentially has serious short and long-term health consequences. https://pubmed.ncbi.nlm.nih.gov/28814559/. Tessa Copp has done a lot of work in this area, and I understand that 16% of reproductive age women will meet the new diagnostic criteria for PCOS if this guidance is implemented. This has the potential to do harm. Concerningly, women newly diagnosed with PCOS were 3.4x more likely to stop using contraception! https://pubmed.ncbi.nlm.nih.gov/32003425/. Jenny Doust has published on expanding disease diagnostic criteria, including the potential risks of changing disease classifications https://pubmed.ncbi.nlm.nih.gov/32031569/. Those considering widening disease definitions should consider: How many people will this affect? What is the risk that patients diagnosed using this new testing guideline or disease definition will develop more severe disease or complications? What is the evidence that early treatment will prevent serious disease or complications? What are the potential harms of diagnosis and treatment? Also in JAMA there is a published a checklist for those planning to modify the definition of a disease https://pubmed.ncbi.nlm.nih.gov/28505266/ We dont think this process was followed when the diagnostic criteria for PCOS were expanded and there is already evidence of potential harm (psychological effects, stopping contraception etc).	The issue of accurate diagnosis was a key objective of the guideline. Prior the 2018 guidelines, each component of the diagnostic criteria were relatively poorly defined based on consensus. In 2018 these were updated to evidence- based criteria and more clearly defined for each individual component of the diagnostic criteria. Overall, the diagnostic criteria were significantly narrowed in the 2018 guideline with ultrasound no longer recommended in adolescents and tighter follicle count and menstrual cycle cut offs in adults. These recommendations persist in the current guideline, and have been shown to markedly reduce PCOS prevalence in adolescents (Tay et al 2021). In the systematic review associated with this guideline, prevalence is around 7-8% in adolescents and 10 -13% in adults. Here, diagnostic criteria are not expended per se but rather AMH can now be substituted in adults only, instead of ultrasound to identify PCOM, with similar sensitivity and specificity. This has been shown not to increase diagnosis, over the application of PCOM. Tessa Copps work has had a focus on women who do not have clinical features of PCOS nor an established diagnosis, but are given hypothetical scenarios of symptoms. In a large community based study, distress was higher in those with PCOS but a diagnosis of PCOS did not increase this distress in those with the condition. Overwhelmingly women with this condition report extensive and unacceptable delays in diagnosis and missed diagnoses. Publications by Copp et al have recommended that even in women with the diagnosis, clinicians should not inform women. This was seen as unacceotable to consumers groups and as patronising and paternalistic as per the published response to Copp et al in the BMJ. The key problems with overdiagnosis occurs with the use of ultrasound in adolescents (now not recommended in the guideline) and to a lesser extend in adults. Ultrasound is now not recommended routinely in diagnosis in adolescents and collaborations with the Ultrasound Society of Australia will lead to implementation of reporting requirements to limit inappropriate over diagnosis, should an ultrasound occur. Phenotypes captured under Rotterdam criteria have very significant long term health implications as clearly outlined in the guideline. Indeed the long term natural history especially in terms of infertility and pregnancy complications indicates the significant need to avoid both over and underdiagnoses.
51		RE: Page 44 The narrative review details that polycystic ovary morphology (PCOM) alone is not diagnostic for PCOS, and this requires correlation with serum androgens/ovulatory dysfunction. PCOM is often incidentally noted on ultrasound whilst investigating other symptoms unrelated to PCOS (such as pelvic pain). This may increase over diagnosis. Given the risk of over diagnosis, in addition to this PP 1.4.9, a recommendation for clinicians on the implication of PCOM noted on ultrasound would be very helpful (e.g. PCOM on ultrasound should prompt serum androgen assessment etc). It was reassuring to note that most ultrasonograohers know the key features of PCOS on US. Some of the suggestions in the manuscript noted here do not align to PCOS clinically such as day of the cycle as these women have oligoanovulation. The suggestion on what to do if isolated PCOM is detected ??practice point	Individuals with isolated PCOM do not have PCOS and the current guideline will not apply to them.

35		Page 14, prelude to the guideline: further evaluation recommended in those with amenorrhea and more severe clinical features including consideration of hypogonadotropic hypogonadism, Cushings disease, or suspected androgen producing tumours. PCOM is a frequent finding in FHA (see Makoll et al for review1). Its signification is unclear but this association is confusing since it includes 2 out of the 3 items of the Rotterdam classification. They therefore must be differentiated from PCOS phenotype D. Patients history and assays of serum testosterone, SHBG and LH may help2.	PCOS is a diagnosis of exclusion, hence having two features of PCOS criteria in FHA does not allow a diagnosis of PCOS. These can be difficult to differentiate, however evidence is inadequate currently on the optimal way to differentiate these. Detailed recommendations on differentiation from FHA, Cushing's and other differentials was out of scope in the current guideline.
20	1.4.3 CR PCOM criteria should be based on either follicle excess (FNPO, FNPS) and/or ovarian enlargement (OV).	PCOM criteria should be based on either follicle excess (FNPO, FNPS) and/or ovarian enlargement (OV). The use of and/ or in the 2018 guidelines created confusion as to whether one of the features was sufficient or both FNPO and increased ovarian volume were necessary. I think the word on this 2023 update is clearer (specifying either) but I would suggest further spelling out of this to remove any ambiguity. We conducted a survey of Australasian sonographers in 2022. We gave respondents several clinical scenarios as asked them to say whether these would indicated PCOM or not. Initially, only 15% of respondents got all four of these correct. After being supplied the guidelines, only 29% of respondents could accurately report. We thought this indicated that there were issues interpreting the guidelines.	Encouragingly the references study showed that ultrasonographers can detect the two main features of PCOS over 90% of the time. The accuracy of diagnosis on clinical scenarios is perhaps of less concern in those doing the ultrasound, however this highlights an opportunity for education with plans to undertake this in dissemination. Wordings of the recommendations in 1.4 are also amended now.
20	1.4.7 PP When an ultrasound is indicated, if sexually active and/or acceptable to the individual, the transvaginal approach is the most accurate for the diagnosis of PCOM.	Sexual activity (or lack thereof) is not a contraindication for performing TVUS if the person is comfortable with this technique. Whilst I appreciate this is an international guideline, and cultural norms vary greatly across the world, not offering a medical examination to an adult woman strips her of her own agency- something I feel we need to strongly avoid in healthcare. I would suggest rewording to When an ultrasound is indicated, the transvaginal approach is the most accurate for the diagnosis of PCOM, unless contraindicated€➢This then leaves the option open for people not to proceed with TVUS id they feel this is inappropriate in their culture but not deny others an important medical examination. There is limited evidence behind this. The British Society of Ultrasound in Medicine last year produced a contemporary guideline on this topic which is a helpful reference.	Wordings of the recommendation are changed.
20	1.4.9 PP In patients with irregular menstrual cycles and hyperandrogenism, an ovarian ultrasound is not necessary for PCOS diagnosis.	The narrative review details that PCOM alone is not diagnostic for PCOS and this requires correlation with serum androgens/ ovulatory dysfunction. PCOM is often incidentally noted on ultrasound whilst investigating other symptoms unrelated to PCOS (such as pelvic pain). In my personal opinion, this is a large cause of over diagnosis. Given the risk of over diagnosis from this, in addition to this PP 1.4.9, a recommendation for clinicians on the implication of PCOM noted on ultrasound would be very helpful (e.g. PCOM on ultrasound should prompt serum androgen assessment etc). No additional evidence is required. Your review has covered this evidence well. I would just consider adding this specifically as it's own recommendation.	Nil needed
27	1.6.2 EBR Healthcare professionals should be aware that PCOS prevalence is similar across ethnicities, for each diagnostic criteria.	I am the lead for the systematic review of this topic. The recommendation says PCOS prevalence is similar across ethnicities. However, the original meta-analysis grouped by ethnicity (including all criteria) shows that confidence intervals do not overlap for some groups, e.g. North African and Middle Eastern 0.13 (0.10, 0.15) versus American 0.07, 0.09, or Australian Indigenous 0.16 (0.11, 0.20) versus most of the ethnicity groups. This is still the case after the sensitivity analysis, whereby only Rotterdam or NIH prevalence was selected when studies reported according to several criteria. For NIH, this is the case for Australian indigenous versus most other groups. For Rotterdam, this is the case for North African and Middle Eastern 0.17 (0.15, 0.19) versus all the other groups. When confidence intervals do not overlap, we can be fairly confident there is a difference between groups. Furthermore, we have been able to include a number of additional studies after contacting corresponding authors and meta-analysis has now been undertaken, which will be included in a research paper. When including all criteria, confidence intervals do not overlap for e.g. North African and Middle Eastern 12.02 (10.01, 14.02) versus South/North East Asian 7.15 (5.91, 8.38). This is still the case when reporting according to NIH or Rotterdam only. See above. Further evidence and results of the updated meta-analysis is available upon request.	The GDG reviewed the additional evidence added to the guideline systematic review after contacting authors and the background section of 1.6 have been updated. Wordings of the recommendation are amended accordingly.
29	1.9.1 EBR Healthcare professionals and women with PCOS should be aware that, regardless of age and BMI, women with PCOS have an increased risk of impaired fasting glucose, impaired glucose tolerance and type 2 diabetes.	Should be looking at glucose and impaired insulin sensitivity. It is also insulin, not only impaired glucose, that links with testosterone function	No additional evidence was provided for the GDG members to assess. Insulin is a well established driver of hyperandrogenism, however as per prior responses: insulin resistance cannot yet be accurately assessed in clinical practice and is not recommended.
29	1.9.9 EBR Healthcare professionals and women with PCOS should recommend the 75-g oral glucose tolerance test (OGTT) as the most accurate test to assess glycaemic status in PCOS.	OGTT including insulin testing to see both the glucose and insulin response. Insulin and glucose tolerance are important to understand in PCOS, not glucose only	No additional evidence was provided for the GDG members to assess. As per prior responses: insulin resistance cannot yet be accurately assessed in clinical practice and is not recommended.
32	1.5.1 EBR Serum AMH could be used for assessing antral follicle excess in adults.	Would it be possible to state that it may be used as a surrogate marker for follicle number per ovary (FNPO) excess?	The included studies have used AMH as a predictor for either PCOS or PCOM, both defined categorically. Follicle number as a continuous measure was not analysed separately. The comment has been considered by the GDG. 1.5.1 is amended to "Serum AMH could be used for defining PCOM in adults" without specifying FNPO.

32		One aspect that is not mentioned in Chapter 1 is an estimate of the current delay for PCOS diagnosis. Indeed, often women report delayed diagnosis and inadequate information. I believe that these gaps in diagnosis, education, and support are clear opportunities for improving patient experience and general awareness and they should be included in this document Delay in diagnosis is reported in many papers but opportunities for improving gaps not provided. Early predictors are not addressed as actionable items	The GDG would agree as do the involved consumers and extensive evidence review and recommendations are dedicated to this in section two of the guideline. In addition extensive consumer resources are expected to add value here. The delays in diagnosis are noted throughout many sections of the guideline and are cited as a key stimulus for this work.
33	1.5.5 PP Healthcare professionals need to be aware of factors that influence AMH including: •Age: Serum AMH generally peaks between the age of 20-25 years •Body mass index (BMI): Serum AMH is lower in those with higher BMI •Ethnicity: Serum AMH may be influenced by ethnicity •COCP: Serum AMH may be suppressed by current or recent COCP use •Menstrual cycle day: Serum AMH may vary across the menstrual cycle	Body mass index (BMI): Serum AMH is lower in those with higher BMI Menstrual cycle day: Serum AMH may vary across the menstrual cycle I do not agree with the sentences above. For the BMI, serum AMH levels are very variable from one study to another. Not all of them find a decrease in AMH associated with obesity. Moreover, no study has shown that specific thresholds should be used for non obese/obese patients. Kloos J, Coyne K, Weinerman R. The relationship between anti-MÃ¼llerian hormone, body mass index and weight loss: A review of the literature. Clin Obese. 2022 Dec;12(6):e12559. -Oldfield AL, Kazemi M, Lujan ME. Impact of Obesity on Anti-Mullerian Hormone (AMH) Levels in Women of Reproductive Age. J Clin Med. 2021 Jul 20;10(14):3192. Concerning the second point, AMH variations according to the menstrual cycle, this is very disputed and with very modest variations of circulating AMH documented in the literature. I personally would not include this sentence at all.	The majority of studies show an influence of BMI. The evidence were reviewed by the GDG and the recommendation wordings in 1.5.5 regarding BMI is retained The potential variations of AMH in the menstrual cycle (recent meta-analysis shows differences of AMH throughout the menstrual cycle) and in relation to BMI, have been observed, however given the strength of that evidence, some nuances have been made in the formulation of the practice points. Does Anti-Müllerian hormone vary during a menstrual cycle? A systematic review and meta-analysis - PubMed (nih.gov) Khodavirdilou J Ovarian Res 2022 Jul. (Women with regular cycle. The results showed that the AMH level in the follicular phase was significantly higher than in the luteal phase (95% CI = 0.11 [0.01 to 0.21]; p < 0.05) and it varies about 11.5% from the luteal phase.) The review by Oldfield et al on BMI and AMH concludes that studies may point to the existence of a negative relationship between BMI and AMH. Overall, 11 studies were included in this review, 8 show a negative correlation between BMI and AMH, 3 show no significant relationship. 2 of these 3 included less than 50 patients, the remaining other study included 293 PCOS women, all with an BMI below 32.
34		PCOS is associated with both CVD and venous thromboembolism (VTE). However, this aspect has not been mentioned in this chapter. A recent meta-analysis found an odds ratio of 1.44 (1.13-1.84) for coronary heart disease in women with PCOS vs non-PCOS and a cohort study, which included 87,000 participants, found 1.5-fold higher risk for VTE in women with PCOS than in controls. In general, cardiovascular events are rare in premenopausal women, which is why markers of low-grade inflammation and endothelial dysfunction could be included as measurement of CVD risk in PCOS. If space allows, this could be discussed in the introductory paragraph. Bird ST, et al (2023). Risk of venous thromboembolism in women with polycystic ovary syndrome: a population-based matched cohort analysis. CMAJ 2013. 185 E115-E120 (10.1503/cmaj.120677)	Venous thromboembolism was not prioritised for inclusion in this guideline update by consumers or health professionals however it is a relevant consideration and will be considered for inclusion in the next guideline update. Risk of CVD is covered in 1.8.
35	1.5.1 EBR Serum AMH could be used for assessing antral follicle excess in adults.	We would add : It may be used as a surrogate for excess FNPO, providing the use of a sensitive and specific cut-off that must be defined in-house since there is no international consensus for the moment. Defining PCOS by using either PCOM or AMH as one of the 3 Rotterdam items does not change significantly the prevalence of PCOS. Using both markers (PCOM and/or increased AMH level), the prevalence is significantly increased. Fraissinet A, Robin G, Pigny P, Lefebvre T, Catteau-Jonard S, Dewailly D. Use of the serum anti-MÃ¼llerian hormone assay as a surrogate for polycystic ovarian morphology: impact on diagnosis and phenotypic classification of polycystic ovary syndrome. Hum Reprod. 2017 Aug 1;32(8):1716-	This point is well made and the algorithm for diagnosis clarifies this. Wordings of the recommendation are also changed now.
35	1.4.3 CR PCOM criteria should be based on either follicle excess (FNPO, FNPS) and/or ovarian enlargement (OV).	I would add: Other measures have not proven superiority• This is well discussed in the review evidence.	Nil needed
35	1.5.5 PP Healthcare professionals need to be aware of factors that influence AMH including: •Age: Serum AMH generally peaks between the age of 20-25 years •Body mass index (BMI): Serum AMH is lower in those with higher BMI •Ethnicity: Serum AMH may be influenced by ethnicity •COCP: Serum AMH may be suppressed by current or recent COCP use •Menstrual cycle day: Serum AMH may vary across the menstrual cycle	Serum AMH is lower in those with higher BMI. This statement is a little bit peremptory and is not supported by the recent literature. No study has shown that specific thresholds should be used for non obese/obese patients. Kloos J, Coyne K, Weinerman R. The relationship between anti-MÃ¼llerian hormone, body mass index and weight loss: A review of the literature. Clin Obes. 2022 Dec;12(6):e12559. -Oldfield AL, Kazemi M, Lujan ME. Impact of Obesity on Anti-Mullerian Hormone (AMH) Levels in Women of Reproductive Age. J Clin Med. 2021 Jul 20;10(14):3192.	**See response above about AMH and BMI.** **The majority of studies show an influence of BMI. The evidence were reviewed by the GDG and the recommendation wordings in 1.5.5 regarding BMI is retained**
37	1.2.1 EBR Healthcare professionals should use total testosterone, free testosterone or calculated free androgen index to assess biochemical hyperandrogenism in the diagnosis of PCOS.	Total testosterone on the same line, with the same importance, with free testosterone or calculated free androgen index, is not the right message to convey. Total testosterone is very much insensitive. So, it should be mentioned separately (when costs are an issue). In page 41 on the Guideline, it is clearly stated that Meta-analyses results showed that calculated free testosterone and calculated FAI had the best sensitivity and specificity to diagnose biochemical hyperandrogenism compared to all other tests. However, it is not reflected in the recommendation.	Wordings of the recommendation are changed.
37	1.6.3 PP Healthcare professionals should be aware that the presentation of PCOS may vary across ethnic groups.	This sentence is convoluted. There is no comment on what the variability in different ethnic group might be. This is left up to an individual HCP to determine what is normal and what is abnormal. It will help the users to know what are the variability in clinical presentation in different ethnicity	As above this has now been clarified in the recommendations.

37	1.8.3 CR All women with PCOS, regardless of age and BMI, should have a fasting lipid profile (cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol and triglyceride level) at diagnosis. Thereafter, frequency of measurement should be based on the presence of hyperlipidaemia and additional risk factors or global cardiovascular risk.	This wording is based on the use of the non-fasted state to detect aberrations in lipid metabolism in TG, apoB and non-HDL-C (as a markers of atherogenic remnant cholesterol). This recommendation is based on international cardiovascular risk and dyslipidaemia guidelines including 2021 Canadian Cardiovascular Society Guidelines. (Can J Cardiol.Â 2021 Aug;37(8):1129-1150. Â doi: 10.1016/j.cjca.2021.03.016.Â Epub 2021 Mar 26. Table 2). and Eur Heart J. 2020 Jan 1;41(1):111-188. doi: 10.1093/eurheartj/ehz455. ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (5.4.3 Fasting or non-fasting?â€‚130) Traditionally, blood sampling for lipid analyses has been recommended in the fasting state. Recent systematic studies comparing fasting and non-fasting samples have suggested that the difference is small for most lipid parameters. Non-fasting sampling has been used in large population-based studies. In most studies, non-fasting samples display a higher TG level. On average, and for most individuals, this increment will be of no clinical significance. Indeed, a number of guidelines recommend non-fasting sampling. It is also easier for patients to do non fasting samples.	This was considered and the GDG has reworded the recommendation.
37		1 is missing from 1.8.3 so written as .8.3	This typographical error was corrected
37	1.9.9 EBR Healthcare professionals and women with PCOS should recommend the 75-g oral glucose tolerance test (OGTT) as the most accurate test to assess glycaemic status in PCOS.	We suggest to mention somewhere (recommendation or justification) that the OGTT should be recommended independent of BMI, since this is a change from the previous guideline. This should be highlighted clearly since overall results suggest that FPG or HbA1C cannot replace OGTT	This has been added to the practice point
37		First paragraph- there are places where the font for T2D looks bigger or bolded. It is unlike that was intentional.	Formatting will be revised in the final guideline production after responses to public consultation and all fonts will be revised.
37		Note for future Consideration in Recommendations. Are women with PCOS at increased risk for cardiovascular disease (CVD)? The technical report only investigates CVD outcomes in PCOS not the usefulness of assessment of primary risk factors such as atherogenic dyslipidaemia, blood pressure, ACVD in those at different ages with PCOS: adolescents, young women, menopause. There is new recommendations and new and revised concept for on cardiovascular imaging for patients with dyslipidaemia. (Eur Heart J. 2020 Jan 1;41(1):111-188. doi: 10.1093/eurheartj/ehz455. ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk).	Lipid profiles, glycaemic status and BP are all recognised in the guideline with recommendations on screening. Once a woman has dyslipidaemia, the management for this is outside the scope for the guidelines and clinicians would be expected to defer to other guidelines on lipid management.
42		Happy to endorse	Nil needed
44	1.5 Anti- Müllerian Hormone (AMH)	In light of the increased online direct-to-consumer sales of AMH tests, should there be a caution to inform women that this test cannot predict current or future fertility and that levels can be affected by PCOS? https://doi.org/10.1016/j.fertnstert.2020.09.134 Markers of ovarian reserve have been shown to be good predictors of oocyte yield, but poor independent predictors of reproductive potential. See link to article above	This important point will be picked up in the translation resources. The heading of 1.5 is also changed to indicate the recommendations are regarding PCOS diagnosis.
45	1.5.1 EBR Serum AMH could be used for assessing antral follicle excess in adults.	AMH should not be used as an alternative to PCOM The review has examined measures of diagnostic accuracy comparing the sensitivity and specificity of AMH against the reference standard of polycystic ovarian morphology. However, this is not the appropriate method to determine if a test should be incorporated into the definition of a disease. The test should be examined to determine that it is able to group patients with similar prognosis or response to treatment. See Doust J, Vandvik PO, Qaseem A, Mustafa RA, Horvath AR, Frances A, Al-Ansary L, Bossuyt P, Ward RL, Kopp I, Gollogly L, Schunemann H, Glasziou P; Guidelines International Network (G-I-N) Preventing Overdiagnosis Working Group. Guidance for Modifying the Definition of Diseases: A Checklist. JAMA Intern Med. 2017 Jul 1;177(7):1020-1025. doi: 10.1001/jamainternmed.2017.1302. PMID: 28505266. This recommendation would also increase the number of women diagnosed with PCOS: Bell RJ, Islam RM, Skiba MA, Herbert D, Martinez Garcia A, Davis SR. Substituting serum anti-MÃ¼llerian hormone for polycystic ovary morphology increases the number of women diagnosed with polycystic ovary syndrome: a community-based cross-sectional study. Hum Reprod. 2021 Dec 27;37(1):109-118. doi: 10.1093/humrep/deab232. PMID: 34741176.	The specific terms used were considered by the GDG and the wordings are retained. An increase in women diagnosed would not be a problem if it would lead to a more precise identification of PCOS women. Defining PCOS by using either PCOM or AMH as one of the 3 Rotterdam items does not change significantly the prevalence of PCOS. Using both markers (PCOM and/or increased AMH level), the prevalence is significantly increased.
45	1.7.1 CR Healthcare professionals should be aware that a diagnosis of PCOS should be considered as enduring / lifelong.	The uncertainty of this statement needs to be included in the recommendation. There is no strong longitudinal evidence that a diagnosis of PCOS is enduring/lifelong and the statement in the recommendation is not evidence based.	The evidence here supports that the risk of features of PCOS including diabetes, CVD and non fertility related issues is increased and as such this genetic condition which is recognised to manifest beyond reproductive features, is considered to be enduring.
45		The caveat that is used for endometrial cancer should be included in the recommendation acknowledging that the risk of CVD in premenopausal women is low. The uncertainty of this recommendation should be highlighted. The studies that have investigated the risk of CVD in women with a history of PCOS have generally been done in younger women with a very low absolute risk of disease. The studies frequently group inappropriate outcomes, such as grouping venous thrombotic disease with ischaemic heart disease and generally have a high risk of bias. Higher quality studies, and particularly in the age group where CVD assessment should be considered, have generally not shown an increased risk of CVD.	The caveat for premenopausal women is added to the recommendation. No additional evidence is presented to refute the recommendation and the guideline outlines the limitations in quality studies in the appropriate age groups.
45	1.8.4 CR All women with PCOS should have blood pressure measured annually and when planning pregnancy or seeking fertility treatment, given the high risk of hypertensive disorders in pregnancy and the associated comorbidities.	The risk of hypertension in women with PCOS who are premenopausal remains low. Blood pressure in women with PCOS should be done according to the CVD risk guidelines and in consideration of all potential risk factors. This is a consensus recommendation, but should be better aligned with the overall population guidelines	No evidence was provided to refute or alter the recommendations. This recommendation is carried over from the last guidelines and is based on risk of hypertension, hypertensive disorders in pregnancy, type II diabetes, hyperlipidaemia, obesity and ultimately CVD in this condition. There is no consistent recommended age to start screening across guidelines and most do not specify. Once CV risk factors emerge, then annual screening is recommended.
45	1.8.6 CCR Cardiovascular general population guidelines should consider the inclusion of PCOS as a cardiovascular risk factor.	This is a consensus statement that is not supported by evidence The current evidence does not support the inclusion of PCOS as a cardiovascular risk factor	The evidence was reviewed and the term "should" was revised to be "considered"

45	1.9.9 EBR Healthcare professionals and women with PCOS should recommend the 75-g oral glucose tolerance test (OGTT) as the most accurate test to assess glycaemic status in PCOS.	The guidelines recommend a different test for testing for type 2 diabetes in women with PCOS than in the general population. This recommendation should be changed. It is now recommended that HbA1c be used to diagnose type 2 DM. This is on the basis that HbA1c is able to predict microvascular and macrovascular complications of type 2 DM at least as well as the OGTT and has better biochemical predictability. The review has used the OGTT as a reference standard in determining the diagnostic accuracy of HbA1c. This will artificially make it appear as though HbA1c is an inferior test, whereas it is more likely to be a superior test.	The results of the extensive studies reviewed here support the lack of accuracy of HbA1C in this population. Estrogen status in premenopausal women generates sex and life stage effects which alter the results of glycaemic testing and the aetiology of IR in PCOS likely differs to that of type II diabetes. No evidence was provided to the GDG to refute or alter the recommendation.
45	1.12.1 EBR Healthcare professionals should be aware that fathers and brothers of women with PCOS may have an increased prevalence of metabolic syndrome, type 2 diabetes, and hypertension.	The usual caveats about population screening should apply to this recommendation. Also the magnitude of the increased risk should be highlighted. Although there is an increased risk of the risk factors described above, from the papers included here the risk is primarily mediated through BMI.	The awareness of increased risk did not extend to routine screening which should rely on the composite of risk factors present. A note to this effect was added to the guideline justification to focus on composite risk. Magnitude of increased risk is captured in the guideline main text
20	1.4.3 CR PCOM criteria should be based on either follicle excess (FNPO, FNPS) and/or ovarian enlargement (OV).	The use of and/ or in the 2018 guidelines created confusion as to whether one of the features was sufficient or both follicle number per ovary (FNPO) and increased ovarian volume were necessary. The wording on this 2023 update is greatly improved from the previous guideline. However, further clarity will remove any ambiguity.	Wordings are changed.
20	1.4.7 PP When an ultrasound is indicated, if sexually active and/or acceptable to the individual, the transvaginal approach is the most accurate for the diagnosis of PCOM.	Sexual activity (or lack thereof) is not a contraindication for performing trans vaginal ultrasound (TVUS) if the person is comfortable with this technique. Whilst this is an international guideline, and cultural norms vary greatly across the world, not offering a medical examination to an adult woman strips her of her own agency. Consider rewording. The British Medical Ultrasound Society last year produced a contemporary guideline on this topic: https://www.bmus.org/static/uploads/resources/Transvaginal_Ultrasound_Guidance_Final_With_Front_Cover_MesUP8a.pdf	This is an international guideline and needs to consider cultural factors. However this is a very valid point and has now been noted in the justification/ implementation section.
55	1.5 Anti- Müllerian Hormone (AMH)	While I agree with the conclusion that the evidence shows that women with PCOS have a distribution of AMH that is shifted to the right relative to the distribution of AMH for women without PCOS, I wonder whether the specific recommendation to use AMH as a proxy for PCOM may be premature. My main concern relates to the use of lab-specific cut-offs (recommendation 1.5.6). While this approach is generally reasonable for hormonal assays, the strong age-dependency of AMH and the lack of sufficiently detailed age-specific distributions of AMH across the life course make me wonder if rather than recommending AMH as a clinically useful marker, filling the knowledge gaps should be prioritized prior to solidifying this recommendation. The issues mentioned above in my comments are all part of the discussion of the draft guideline and the technical report of the guideline as it relates to this question. There is no disagreement on the evidence or the grading of the evidence, only on whether or not the evidence as of today raises to the point where it can be clinically actionable as opposed to an area of need for research.	This aligns to the extensive discussion in the GDG and evidence teams. To overcome the most controversial and unresolved area here, AMH is only recommended in adults and not adolescents. No further evidence was provided to refute or alter the recommendation.
56	1.10.2 EBR Healthcare professionals should assess women with PCOS for symptoms of obstructive sleep apnea (i.e. snoring in combination with waking unrefreshed from sleep, daytime sleepiness or fatigue) and if present, screen with validated tools or refer for assessment.	Could this include recognition of fatigue as often reported symptom - may be linked with insulin resistance.	Fatigue was not explored as a feature of PCOS other than in relation to sleep apnoea. As such it wasn't prioritised by health professionals or consumers.
56	1.11.5 PP When excessive endometrial thickness is detected, a progestogen-induced withdrawal bleed is indicated, and further follow-up is required.	Why is monitoring for excessive endometrial thickness not advised as routine?	The overall prevalence of abnormalities is very very low and the down sides of excess screening are important to consider. Overall routine screening is not warranted.
67	1.1.1 CR Irregular menstrual cycles are defined as: •Normal in the first year post menarche as part of the pubertal transition • 1 to < 3 years post menarche: < 21 or > 45 days • 3 years post menarche to perimenopause: < 21 or > 35 days or < 8 cycles per year • 1 year post menarche > 90 days for any one cycle •Primary amenorrhea by age 15 or > 3 years post thelarche (breast development) When irregular menstrual cycles are present a diagnosis of PCOS should be considered and assessed according to these PCOS Guidelines.	For EBR 1.1. Androstenedione assay may provide an equally specific diagnosis of PCOS as testosterone. Therefore the guideline should include an option between testosterone and androstenedione. From an internal meta-analysis on various studies performed with an aim to analyse the hormone profiles in PCOS women, we found that androstenedione and testosterone both show equally significant changes in the different populations Study link https://pubmed.ncbi.nlm.nih.gov/125040/ https://pubmed.ncbi.nlm.nih.gov/1740195/ https://academic.oup.com/humrep/article/12/5/905/665451?login=false https://pubmed.ncbi.nlm.nih.gov/10545743/ https://www.fertstert.org/article/S0015-0282(05)00885-X/fulltext#tbl1 https://pubmed.ncbi.nlm.nih.gov/17760884/ https://pubmed.ncbi.nlm.nih.gov/18549684/ https://pubmed.ncbi.nlm.nih.gov/20303485/ https://eje.bioscientifica.com/view/journals/eje/162/3/611.xml https://pubmed.ncbi.nlm.nih.gov/22144419/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4195601/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5460696/ https://www.hindawi.com/journals/ije/2020/6237141/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7258370/ https://pubmed.ncbi.nlm.nih.gov/17895317/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7816782/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5016474/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4845525/ https://pubmed.ncbi.nlm.nih.gov/21193545/	The systematic review and meta analysis performed for the guideline and focused on accuracy, as noted in the technical report, shows a lack of specificity for androstenedione with a risk of overdiagnosis.

67	1.5.1 EBR Serum AMH could be used for assessing antral follicle excess in adults.	I would add : It may be used as a surrogate for excess FNPO, providing the use of a sensitive and specific cut-off that must be defined in-house since there is no international consensus for the moment.	Unfortunately, data is lacking to include an age-specific recommendation for the cut-off of AMH as a predictor for PCOS or PCOM. It is unclear as yet whether international applicable cut offs can be developed and hence no specific cut-off is mentioned in the guideline.
67	1.2.9 PP If androgen levels are markedly above laboratory reference ranges, causes of hyperandrogenaemia other than PCOS, including ovarian and adrenal neoplastic growths, congenital adrenal hyperplasia, Cushing's syndrome, ovarian hyperthecosis (after menopause), iatrogenic causes, and syndromes of severe insulin resistance, should be considered. However, some androgen-secreting neoplasms are associated with only mild to moderate increases in androgen levels. The clinical history of time of onset and/or rapid progression of symptoms is critical in assessing for an androgen-secreting tumour.	ESHRE Members commented on specifics of lab techniques. If androgen levels are markedly above laboratory reference ranges, causes of hyperandrogenaemia other than PCOS, including ovarian and adrenal neoplastic growths, congenital adrenal hyperplasia, Cushing's syndrome, ovarian hyperthecosis (after menopause), iatrogenic causes, and syndromes of severe insulin resistance, should be considered Is there any standard reference laboratory levels? It is important to set a laboratory reference range to delineate between PCOS vs other causes of raised androgen levels.	Androgen cut offs are very assay and lab influenced and specific cut offs were not deemed evidence based or appropriate
67	1.3.7 PP Healthcare professionals should: •Be aware that standardised visual scales are preferred when assessing hirsutism, such as the mFG scale in combination with a photographic atlas •Consider the Ludwig or Olsen visual scales for assessing female pattern hair loss •Note that there are no universally accepted visual instruments for assessing the presence of acne •Recognise that women commonly treat clinical hyperandrogenism cosmetically, diminishing their apparent clinical severity •Appreciate that self-assessment of unwanted excess hair growth, and possibly acne and female pattern hair loss, has a high degree of validity and merits close evaluation, even if overt clinical signs of hyperandrogenism are not readily evident on examination •Only terminal hairs need to be considered in defining hirsutism, and these can reach >5 mm if untreated, vary in shape and texture and are generally pigmented •Note that new-onset severe or worsening hyperandrogenism, including hirsutism, requires further investigation to rule out androgen-secreting tumours and ovarian hyperthecosis •Monitor clinical signs of hyperandrogenism, including hirsutism, acne and female pattern hair loss, for improvement or treatment adjustment during therapy	Note that there are no universally accepted visual instruments for assessing the presence of acne• There is good evidence on assessing the presence of acne. If we can modify that we do not have any reference acne scoring in PCOS then the sentence might sound acceptable. https://jamanetwork.com/journals/jamadermatology/fullarticle/2759750 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5023002 https://onlinelibrary.wiley.com/doi/full/10.1111/j.1600-0846.2011.00542.x https://onlinelibrary.wiley.com/doi/full/10.1111/j.1600-0846.2011.00542.x https://link.springer.com/referenceworkentry/10.1007/978-3-319-32383-1_96	Reviews and appraisal of instruments for measuring acne severity identifies concerns regarding the quality of published measures. It highlights the need for a valid and reliable acne severity scale, especially for use in research and evaluation. The ideal scale would demonstrate adequate validation and reliability and be easily implemented for third-party analysis. We agree regarding the lack of accepted and validated acne scoring as per current recommendation.
67	1.4.3 CR PCOM criteria should be based on either follicle excess (FNPO, FNPS) and/or ovarian enlargement (OV).	PCOM criteria should be based on either follicle excess (FNPO, FNPS) and/or ovarian enlargement (OV). I would add: Other measures have not proven superiority This is well discussed in the review evidence. No need to add further references	nil needed
67	1.4.1 EBR Follicle number per ovary (FNPO) should be considered the most effective ultrasound marker to detect polycystic ovarian morphology (PCOM) in adults.	Thresholds for PCOM should be revised regularly with advancing ultrasound technology Follicle number per ovary are most effective marker of PCOM then changes in USG machine as a criteria to revise the threshold might not be a great option to revise. Moreover, how regularly the criteria should be revised if machines changes very often or do not change. This could be considered, even if the reviewers consider the evidence for this section is well discussed	This will be addressed in each guideline update every 5 years
67	1.5.5 PP Healthcare professionals need to be aware of factors that influence AMH including: •Age: Serum AMH generally peaks between the age of 20-25 years •Body mass index (BMI): Serum AMH is lower in those with higher BMI •Ethnicity: Serum AMH may be influenced by ethnicity •COCP: Serum AMH may be suppressed by current or recent COCP use •Menstrual cycle day: Serum AMH may vary across the menstrual cycle	Serum AMH is lower in those with higher BMI This statement is a little bit peremptory and is not supported by the recent literature. No study has shown that specific thresholds should be used for non obese/obese patients. Another reviewer commented that there is no need to talk about it or put more nuance. It is very variable from one study to another, not all of them find a decrease in AMH in case of obesity and if there is a decrease, it is minor. Kloos J, Coyne K, Weinerman R. The relationship between anti-Mullerian hormone, body mass index and weight loss: A review of the literature. Clin Obes. 2022 Dec;12(6):e12559. -Oldfield AL, Kazemi M, Lujan ME. Impact of Obesity on Anti-Mullerian Hormone (AMH) Levels in Women of Reproductive Age. J Clin Med. 2021 Jul 20;10(14):3192.	**See response above about AMH and BMI.** **The majority of studies show an influence of BMI. The evidence were reviewed by the GDG and the recommendation wordings in 1.5.5 regarding BMI is retained**
67	1.11.5 PP When excessive endometrial thickness is detected, a progestogen-induced withdrawal bleed is indicated, and further follow-up is required.	When excessive endometrial thickness is detected, consideration of a biopsy with histological analysis and withdrawal bleed is indicated. Is there any age cut off to offer endometrial biopsy along with the other risk factors that are present? It also did not mention the ET thickness cut off to offer biopsy. Recommendation is differently formulated in main guideline versus summary version ESHRE suggests adding the reference to the Green-top Guideline (available via https://www.rcog.org.uk/guidance/browse-all-guidance/green-top-guidelines/management-of-endometrial-hyperplasia-green-top-guideline-no-67/)	The GDG have considered the comment but this is out of the scope of the guideline and other endometrial hyperplasia and endometrial cancer guidelines are available.
70		Full form of EBR not included in Table 3	This error was corrected in the final guideline
70	1.5.5 PP Healthcare professionals need to be aware of factors that influence AMH including: •Age: Serum AMH generally peaks between the age of 20-25 years •Body mass index (BMI): Serum AMH is lower in those with higher BMI •Ethnicity: Serum AMH may be influenced by ethnicity •COCP: Serum AMH may be suppressed by current or recent COCP use •Menstrual cycle day: Serum AMH may vary across the menstrual cycle	Age: Serum AMH generally peaks between the age of 20-25 years. Change to Age: Serum AMH is thought to peak between the age of 25-30 years, and declines thereafter until menopause (Bonifacio et al, 2015). In addition, although there is an overall good concordance between serum AMH concentrations and antral follicle count, AMH concentrations are known to decline faster with age in comparison to antral follicle count (Arvis et al, 2022). Antral follicle excess should therefore be interpreted in relation to age-specific reference ranges, and it is important to be aware that lower AMH concentrations may represent antral follicle excess in older populations.	Age specific reference range would be ideal, however, because of the lack of these data we cannot give age-specific recommendations. The reference is a study not specific for PCOS. Longitudinal data in PCOS shows that the decrease in follicle number and ovarian volume is less pronounced in women with PCOS compared to controls. The wordings in the recommendation are retained.

70	1.5.5 PP Healthcare professionals need to be aware of factors that influence AMH including: •Age: Serum AMH generally peaks between the age of 20-25 years •Body mass index (BMI): Serum AMH is lower in those with higher BMI •Ethnicity: Serum AMH may be influenced by ethnicity •COCP: Serum AMH may be suppressed by current or recent COCP use •Menstrual cycle day: Serum AMH may vary across the menstrual cycle	Body mass index (BMI): Serum AMH is lower in those with higher BMI. Change to Body mass index (BMI): There is some evidence that obesity is associated with lower AMH concentrations (Kriseman et al, 2015, Zhang et al, 2023). However, serum AMH concentrations should not be interpreted in relation to BMI as more research is required to understand the effect of PCOS, insulin resistance and obesity on AMH concentrations, as well as the effect of weight loss and/or bariatric surgery (Kataoka et al, 2022, Nguyen et al, 2023, Zhao et al, 2023).	**See response above about AMH and BMI.** **The majority of studies show an influence of BMI. The evidence were reviewed by the GDG and the recommendation wordings in 1.5.5 regarding BMI is retained**
70	1.5.5 PP Healthcare professionals need to be aware of factors that influence AMH including: •Age: Serum AMH generally peaks between the age of 20-25 years •Body mass index (BMI): Serum AMH is lower in those with higher BMI •Ethnicity: Serum AMH may be influenced by ethnicity •COCP: Serum AMH may be suppressed by current or recent COCP use •Menstrual cycle day: Serum AMH may vary across the menstrual cycle	Ethnicity: Serum AMH may be influenced by ethnicity. Change to There is some evidence that different ethnic groups have different serum AMH concentrations, however, these studies are small and there are no conclusive findings (Bhide et al, 2014, Bleil et al, 2014, Elchuri et al, 2014, Gromski et al, 2022, Iglesias et al, 2014, Marsh et al, 2016, Melado et al, 2021, Nelson et al, 2020, Olcha et al, 2016, Pinheiro et al, 2005, Schuh-Huerta et al, 2016). Ethnicity should therefore not be used to interpret serum AMH concentrations or rule out serum AMH concentrations which are suggestive of antral follicle excess.	The GDG agreed that the data for ethnicity is still inconclusive and has deleted the sentence from 1.5.5.
70	1.5.5 PP Healthcare professionals need to be aware of factors that influence AMH including: •Age: Serum AMH generally peaks between the age of 20-25 years •Body mass index (BMI): Serum AMH is lower in those with higher BMI •Ethnicity: Serum AMH may be influenced by ethnicity •COCP: Serum AMH may be suppressed by current or recent COCP use •Menstrual cycle day: Serum AMH may vary across the menstrual cycle	COCP: Serum AMH may be suppressed by current or recent COCP use. Change to Hormonal contraception, medication, pre-existing diagnoses and surgeries: Serum AMH may be temporarily suppressed by both oestrogen-containing and progesterone-only hormonal forms of contraception (Nelson et al, 2023). If testing serum AMH in patients who have recently stopped using hormonal contraception, it is important to be aware that AMH concentrations can take up to a year to return to what is normal for that person depending on the contraception type (Amer et al, 2020). Other medications, such as chemotherapy and biological therapies have been known to lower serum AMH concentrations (Iwase et al, 2015). Medications which may be used as part of fertility treatment, including Metformin and Clomiphene Citrate, have also been shown to temporarily reduce AMH concentrations in people with PCOS (Yin et al, 2022). Suboptimal serum Vitamin D concentrations have been associated with higher AMH concentrations, however this effect is not significant (Yin et al, 2022). There is evidence that pre-existing conditions, including autoimmune conditions and endometriosis (if endometriomas are present or endometriosis is present in or around the ovaries) (Tian et al, 2021). In addition, surgery on or around the ovaries may lower serum AMH concentrations (Huang et al, 2023, Kobayashi et al, 2022, Morena-Sepulveda et al, 2022).	Wordings are changed.
70	1.5.5 PP Healthcare professionals need to be aware of factors that influence AMH including: •Age: Serum AMH generally peaks between the age of 20-25 years •Body mass index (BMI): Serum AMH is lower in those with higher BMI •Ethnicity: Serum AMH may be influenced by ethnicity •COCP: Serum AMH may be suppressed by current or recent COCP use •Menstrual cycle day: Serum AMH may vary across the menstrual cycle	Menstrual cycle day: Serum AMH may vary across the menstrual cycle. Change to There is currently little evidence on the intracycle variability of AMH concentrations that represent antral follicle excess.	1.5.5 The GDG has considered this comment and confirmed evidence that AMH variation across the cycle is dependent on the assay and the recommendation wordings are retained. Also as most individuals PCOS are oligo-anovulation, the specific timing of the cycle is not clinically recommended.
70	1.5.6 PP Laboratories should use assay specific cut-offs.	Laboratories should use assay specific cut-offs. Change to: Serum AMH reference ranges will be specific to the population, assay, instrument used for measurement and the laboratory protocol itself. However, it is important to be aware that many reference ranges that laboratories have created for AMH include participants with antral follicle excess in their healthy reference population, meaning that some AMH concentrations that fall within the reference range may be indicative of antral follicle excess. Therefore, it is important that serum AMH concentrations are interpreted based on a specific antral follicle excess or PCOM upper limit, rather than an assay-specific upper limit or reference range upper limit which has been provided by the laboratory.	The recommendation wordings has been modified.
70	1.6.1 EBR Healthcare professionals should be aware of the high prevalence of PCOS among adults and adolescents across different ethnicities, ranging from 8-10% globally.	Change to: Global prevalence is quoted as 6-20% depending on the diagnostic guideline used (Escobar.,2018)	The extensive evidence here across ethnic groups in non-selected populations shows a prevalence of 10% as noted in the technical report with further details now added from updated meta analysis.
70	1.7.1 CR Healthcare professionals should be aware that a diagnosis of PCOS should be considered as enduring / lifelong.	Change to: Healthcare professionals should be aware that a diagnosis of PCOS can impact someone throughout their life	The wording on this recommendation was endorsed by all GDG members, went out to public consultation and has not raised concerns. It also aligns to evidence and hence wording has not been changed here.
70	1.7.2 CR Healthcare professionals should be aware that both clinical and biochemical hyperandrogenism can persist in the postmenopause for women with PCOS.	Change to: Healthcare professionals should be aware that both clinical and biochemical hyperandrogenism can persist in post menopause in those with PCOS	Wordings of the recommendation are changed.
70	1.9.1 EBR Healthcare professionals and women with PCOS should be aware that, regardless of age and BMI, women with PCOS have an increased risk of impaired fasting glucose, impaired glucose tolerance and type 2 diabetes.	This is the only point where it says HCP and women should be aware. Is there a reason this is specifically something they should tell women?	As glycaemic abnormalities require regular screening and need prevention, women should be aware of these increased risk to support self care.
70	1.9.11 EBR An OGTT should be offered to all women with PCOS and without pre-exiting diabetes,	Typo - correct pre-exiting diabetes to pre-existing diabetes	This typographical error was fixed
70	1.11.3 PP Long-standing untreated amenorrhea, higher weight, type 2 diabetes and persistent thickened endometrium are additional to PCOS as risk factors for endometrial hyperplasia and endometrial cancer.	Specifying medication such as tamoxifen, oestrogen only HRT	This is beyond the scope of the current guideline
70	1.2.6 PP It is very difficult to reliably assess for biochemical hyperandrogenism in women on the combined oral contraceptive pill (COCP) as the pill increases sex hormone-binding globulin and reduces gonadotrophin-dependent androgen production. If already on the COCP, yet assessment of biochemical androgens is imperative, the pill should be withdrawn for a minimum of three months and contraception should be managed otherwise during this time.	While this is clinically sound, I would argue that withdrawing the COCP could be detrimental for a 3-month period. Personally, when I was on the COCP, it was quite effective in managing my acne and hirsutism and I'm not sure how I would've felt if it were withdrawn. In my opinion, it should only be conducted when there are little to no signs of clinical hyperandrogenism as stated in 1.2.5	This is addressed in the algorithm and recommendations to use clinical hyperandrogenism first and only use biochemical tests if hirsutism is not present.
70	1.3.5 CR A modified Ferriman Gallwey score (mFG) of ≥ 4 - 6 indicates hirsutism, acknowledging that self-treatment is common and can limit clinical assessment.	Based on the audit I have been conducting as well as personal experience, the FG scoring system does not seem to be used that often. As stated, self-management can obscure the extent of hair growth so a belief in what the patient is saying is important. After all, her personal experience of hair growth and its discomfort is what is most important to assess.	This is an important point and is reflected in the practice point to prioritise patient concerns.

70	1.3.6 CR The prevalence of hirsutism is similar across ethnicities, yet the severity of hirsutism varies by ethnicity.	While this is true, I have personally felt dismissed about the severity of my symptoms due to my ethnicity. It is important for HCPs to recognise the difference between idiopathic hair growth and male pattern terminal hairs, and not simply put it down to ethnicity.	This was considered by the GDG and we agreed that the potential negative psychosocial impact of clinical hyperandrogenism is high. This is covered in CR 1.3.4
70	1.6- Ethnic Variation	There is some evidence to suggest rates are higher in South Asian and Black women, however this is not conclusive in the slightest.(1,2)It is however important for HCPs to consider the pre existing higher rates of insulin resistance and risk of cardiovascular complications in BAME individuals and pay more attention to monitoring and management in these populations,.(3)	Further evidence on ethnic differences has since emerged, sparked by the guideline questions. This section and recommendations have been updated.
106		I didn't see anything about NAFLD. The prevalence in women with PCOS is actually quite high – at an earlier age and seems to be more advanced seems like screening with ALT/AST is fairly inexpensive	Non alcoholic fatty liver disease (NAFLD) and non alcoholic steatohepatitis (NASH) were not prioritised for this update. Whilst NAFL is prevalent (24%US population has NAFL based on 5% of liver fatty infiltration), NASH is uncommon (1-5% of NAFL) and cirrhosis extremely uncommon and most with NASH die of CVD and not liver disease itself. We understand that both NASH and NAFLD are prevalent in PCOS because their main risk factor is obesity. However, the only treatment available now is weight loss and weight management is already highlighted in the guideline. The guideline development group feels that 1) separating the diagnosis of NAFLD/ NASH is difficult and expensive; and 2) the benefit of widespread screening for NASH/NAFLD in women with PCOS, over obesity, remains unclear at this time. They may be prioritised in the next guideline update when more is known.
24	1.5 Anti- Müllerian Hormone (AMH)	In light of the increased online direct-to-consumer sales of AMH tests, should there be a caution to inform women that this test cannot predict current or future fertility and that levels can be affected by PCOS?	This was not the scope of this PICO. 1.5 subject heading is changed to reflect the use of AMH in the diagnosis of PCOS
12	Abstract. Page 1.	Whilst it is important to acknowledge a relatively increased risk of endometrial cancer (and to prevent endometrial hyperplasia accordingly), the absolute risk in the premenopausal population is low. The guideline may benefit from a small adjustment in the wording to acknowledge this (although in fairness this is considered later).	As stated, absolute risk is considered in the recommendation wordings.
67	Page 14, prelude to the guideline: "further evaluation recommended in those with amenorrhea and more severe clinical features including consideration of hypogonadotropic hypogonadism, Cushing's disease,or suspected androgen producing tumors."	I would add" a Functional Hypothalamic Amenorrhea can also occur in PCOS women in the case of strict weight control with food restriction and/or excessive exercise and stress. The prevalence of this association is probably underestimated. Another reviewer stated I would add "in case of amenorrhea in a context of recent weight loss and/or psychological distress and/or eating disorder, a Functional Hypothalamic Amenorrhea should be ruled out even in the presence of polycystic ovaries on ultrasound. This can be confirmed by a low serum LH level." Justification: Unrecognition of FHA may lead to inappropriate care. Those patients should be treated as "regular" FHA, in particular for ovulation induction. It has been effectively reported that pulsatile GnRH therapy is a more successful and a safer treatment for ovulation induction than gonadotropins (1-2). 1.Dubourdieu S, Freour T, Desolle L, Barriere P. Prospective randomized comparison between pulsatile GnRH therapy and combined gonadotropin 5FSH+LH) treatment for ovulation induction in women with hypothalamic amenorrhea and underlying polycystic ovary syndrome. Eur J Obstet Gynecol reprod Biol. 2013;168:45-8 2.DumontA, Dewailly D, Plouvier P, Catteau-Jonard S, Robin G. Comparison between pulsatile GnRH therapy and gonadotropins for ovulation induction in women with both functional hypothalamic amenorrhea and polcystic ovarian morphology. Gynecol Endocrinol. 2016 Dec;32(12):999-1004. The order of steps in Formulate guidance and Disseminate, implement, update is reader difficult so if we can 11-15 and 16-22 PCOM is a frequent finding in FHA (see Makollé et al for review1). Its signification is unclear but this association is confusing since it includes 2 out of the 3 items of the Rotterdam classification. Those patients must therefore be differentiated from PCOS phenotype D. Patient's history and assays of serum testosterone, SHBG and LH may help2. Unrecognition of FHA may lead to inappropriate care of patients who need psychological/nutritional support. Those patients should be treated as "regular" FHA, in particular for ovulation induction. It has been effectively reported that they most often respond to pulsatile GnRH therapy3,4. 1-Makolle S, Catteau-Jonard S, Robin G, Dewailly D. Revisiting the serum level of anti-Müllerian hormone in patients with functional hypothalamic anovulation. Hum Reprod. 2021 Mar 18;36(4):1043-1051	This guideline applies to women with PCOS and it has been stated in the population section in p9 that the recommendations exclude those with hypogonadotropic or hypergonadotropic ovulatory dysfunction.
105	1.1.8 Irregular cycles and ovulatory dysfunction	The first and second year after menarche is too early to consider menstrual irregularities as a PCOS feature. It may result in overdiagnosis, and certainly in overtreatment. Menstrual irregularities & anovulatory cycles are not uncommon up to 2-3 yr post-menarche (doi: 10.4158/EP15748.DSC). Accordingly, the definition of "irregular menstrual cycles" for the diagnosis of PCOS should not be considered before at least 2 yr post-menarche at any age.	This recommendation is retained from 2018, where it was endorsed by all 40 collaborating societies. It has since been validated in one of the longest running cohort studies on PCOS from in utero to the early 30s (Tay et al 2021). The only reference provided here is a consensus based guideline from 8 years ago, with superseding research that confirms the 2018 recommendations and as such the GDG recommendations were not altered. The duration of normal cycles is varied by gynaecological age, based on direct evidence on menstrual cycle length in the general population as per the 2018 guidelines.
105	1.1.8 Irregular cycles and ovulatory dysfunction	Please define in detail what is considered to be a girl "at risk".	The concept of "at risk" is clarified in the guideline as referring to an adolescent with either hyperandrogenism or irregular cycles who then warrants later evaluation to avoid both overdiagnosis and a potential missed diagnosis. This was prioritised strongly by consumer groups with many women / studies highlighting the challenges of missed and delayed diagnoses.

105	1.2.2 EBR If testosterone or free testosterone is not elevated, healthcare professionals could consider measuring androstenedione and dehydroepiandrosterone sulfate (DHEAS), noting their poorer specificity and the greater age associated decrease in DHEAS.	Explain the rationale for considering androstenedione and DHEAS measurements as a substitute of testosterone for PCOS diagnosis when the latter happens to be within normal limits. The evidence is very low. GDG1	No evidence was provided to reconsider the recommendation. Up to 15% of women may have hyperandrogenism that is only detected on these assays. We also do note the issue of specificity here. Overall, the GDG considered that the current recommendation should be retained.
105	1.2.8 PP In most adolescents, androgen levels reach adult ranges at the age of 12-15 years.	The statement that in most adolescents, androgen levels reach adult ranges at the age of 12-15 yrs should take into consideration gynecological age, not chronological age. GDG1 PAEDS	This was addressed and endorsed in the last guideline and was derived from evidence on age range and not gynaecological age (Salameh 2010). As such this point has not be altered. Salameh WA, Redor-Goldman MM, Clarke NJ, Reitz RE, Caulfield MP. Validation of a total testosterone assay using high-turbulence liquid chromatography tandem mass spectrometry: total and free testosterone reference ranges. Steroids. 2010 Feb;75(2):169-75. doi: 10.1016/j.steroids.2009.11.004. Epub 2009 Nov 17. PMID: 19925815.
105	1.3 Clinical hyperandrogenism	"Androgen related alopecia" vs "female pattern hair loss". The latter concept should be defined.	The definition for female pattern hair loss was added to the glossary
105	page 44, line 6:	Should read 10 ml (not 10 cm)	Thank you, this mistake was corrected.
105	1.9 Impaired glucose tolerance and type 2 diabetes risk	Impaired glucose tolerance and type 2 diabetes risks. Comment: should also mention if there is higher risk for gestational diabetes.	Gestational diabetes is dealt with in the section on pregnancy risk in GDG4.
105	1.10.1 EBR Healthcare professionals should be aware that women with PCOS have significantly higher prevalence of obstructive sleep apnea compared to women without PCOS.	It should state whether this is independent from the co-presence of obesity (as mentioned for eating disorders)	Thank you for this comment, the evidence supports an increased risk of sleep apnoea independent of obesity and hence this change has been made to note this is "independent of BMI".

ID	Guideline recommendation to which feedback is targeted.	Comments	Guideline development group consensus response
12	Section 2	We endorse the importance of screening for psychological features and any adverse impact on quality of life as these are frequently under-recognised in clinical practice.	Nil needed
12	2.6.1 Information needs	We are pleased to see the importance of information needs being recognised in the updated guideline given the high priority for patients.	Nil needed
29	2.5 Eating disorders	Add to Justification: increased risk of blood sugar dysregulation. Blood sugar dysregulation also plays a role in how eating disorder manifest in the individual.	Blood sugar regulation is not a clinically defined term and there is no current evidence to support inclusion of this term in the current guidline
29	2.5 Eating disorders	PCOS patients have a higher risk of disordered eating, health professionals should be aware of this before asking, mentioning or recommending weight loss. Weight loss can be a sensitive and stress inducing topic for PCOS patients, particularly those with disordered eating.	The guideline is very sensitive to the issues around weight and as such covers weight related stigma. It also recommends asking permission to weigh women and consideration of eating disorders prior to addressing weight related issues. We take a holistic approach to PCOS care in which weight management is one option. We also highlight the options around weight inclusive care.
56	2.6.1.1 EBR Healthcare professionals should provide tailored information, education and resources that are high-quality, culturally appropriate and inclusive to all with PCOS.	Could guidelines mention difficulties around existance of resources and so recommend them in appendix	Extensive resources will be codeveloped and linked in the final guideline with all available from the ASK PCOS app in multiple languages.
65	2.2.2 EBR Healthcare professionals should be aware of the high prevalence of moderate to severe anxiety symptoms and anxiety disorders in adults and should screen for anxiety in all adults with PCOS, using regionally validated screening tools.	In 2.2 Depressive and anxiety symptoms, it is unclear in the summary of systematic review if 7 or 4 studies were low risk of bias. Is EBR 2.2.2 referring to "all" adults when noting the high prevalence of severe anxiety symptoms and disorders or adults with PCOS as for 2.2.1? data missing/clarification needed	The background section in these areas were clarified as suggested
65	2.6.1.1 EBR Healthcare professionals should provide tailored information, education and resources that are high-quality, culturally appropriate and inclusive to all with PCOS.	In 2.6 Information resources, are the Quality-of-Life data from adolescents included in this summary in the right place? I expected broader narrative data from CALD groups. In addition, given that "unavailability of female physicians" was identified as a barrier to accessible and culturally appropriate information, should recommendations toward global entities responsible for health professional education be targeting greater equity and support in training female physicians? Clarification of recommendation intent	As an international guideline, we acknowledge that this issue is of greater relevance to some cultures. This is noted in the background of the information section and will require local application for some cultures, and in 2.6.1.4 we recommend considering the diversity of the population they serve when adapting practice paradigms.
65	2.1.1 EBR Healthcare professionals and women should recognise the adverse impact of PCOS and/or PCOS features on quality of life in adults.	While relative prevalence of various psychological features are compared with the general population and odds ratios indicate relative risk, actual prevalence figures or estimates for these features in women with PCOS are missing from the summaries. Could not find this in the summary	This was revised to include prevalence information in the summary sections where prevalence could be reliably reported.
65	2.1.1 EBR Healthcare professionals and women should recognise the adverse impact of PCOS and/or PCOS features on quality of life in adults.	In 2.1 Quality of life, the meta-analysis results in the Summary of systematic review evidence should be re-written for clarity. This was quite difficult to follow	This was revised for clarity.
73	2.4 Body Image	What is the recommended approach to body image concerns? What should the professional do about it? How does one screen for it? I.e. how to discuss the impact of hirsutism if a woman is comfortable with her facial/body hair without making it sound like the clinician thinks it's a problem. Providers should consider their own biases around ideal body image and body size and consider taking a weight bias tool through Harvard. https://implicit.harvard.edu/implicit/takeatest.html	It is recognised that body image is often dismissed. We highlight the importance of body image in the guideline and we recommed that cognitive behavioural therapy is the recommended approach. We have also covered health professional awareness, empathy and education as important throughout the guideline and we recognise that patient concerns are paramount.
73	2.4 Body Image	There needs to be more of an emphasis on how negative body image impacts health outcomes and overall well-being with PCOS. We cite some PCOS-specific research, but it is worthwhile to reference research done on body image in general since PCOS research is so limited Body image impacts sleep - https://pubmed.ncbi.nlm.nih.gov/31630370/ Body impacts depression and anxiety - https://pubmed.ncbi.nlm.nih.gov/31395311/ https://pubmed.ncbi.nlm.nih.gov/24639704/	It is recognised that body image is often dismissed. We highlight the importance of body image in the guideline. As this is an evidence based guideline we can only rely on evidence that is available but we have highlighted this as a research gap.
70	2.6.1 Information needs	More can be put in the education section, educating patients of their condition, potential symptoms to look out for and the long-term implications. This education should also be extended to those in schools and colleges as failure to recognise symptoms was one of the leading barriers to delays in a PCOS diagnosis according to our research (Ali et al.,2022). According to the study, mental health issues were consistently not addressed and although mental health risks are included, screening and management recommendations are not clear. Due to the existing evidence of increased risk of mental health conditions in PCOS, Depression and anxiety should be screened in all patients with PCOS. Additionally, the prevalence of eating disorders and low QoL is also very high in PCOS patients, more should be included along with screening and management options.	This feedback was considered and has helped to inform the translation tools which currently are not included in the guideline. We do recommend a lifelong reproductive health plan which begins in adolesence. Regional approches to school education may faciliate integration into local education programs. Our screening recommendations also highlight screening in depression (2.2.1) however data in adolescence is more limited and only adult screenign is recommended (2.2.2 and 2.2.3). A balance between the prevalence of conditions and the ability to screen in clinical care and in areas such as QoL or eating disorders the evidence was not strong enough to recommend routine screening. Management options were also covered in the recommendations.
70	2.1.1 Healthcare professionals and women should recognise the adverse impact of PCOS and/or PCOS features on quality of life in adults.	Change to: Healthcare professionals and women should recognise the adverse impact of PCOS and/or PCOS features on quality of life in adults and adolescents.	The evidence for adolescents is not currently available but this is captured as a research priority.
70	2.2.2 Healthcare professionals should be aware of the high prevalence of moderate to severe anxiety symptoms and anxiety disorders in adults and should screen for anxiety in all adults with PCOS, using regionally validated screening tool	Change to: Healthcare professionals should be aware of the high prevalence of moderate to severe anxiety symptoms and anxiety disorders in adults and adolescents should screen for anxiety in PCOS patients, using regionally validated screening tools.	The evidence for adolescents is not currently available but this is captured as a research priority.
70	2.2.4 PP Severity of symptoms and clinical diagnosis of depression or anxiety should guide management. The optimal interval for anxiety and depression screening is not known. A pragmatic approach could include screening at diagnosis with repeat screening based on clinical judgement, risk factors, comorbidities and life events, including the perinatal period. Screening for mental health disorders comprises assessment of risk factors, symptoms, and risk of deliberate self-harm and suicidal intent.	Screening for mental health disorders comprises assessment of risk factors, symptoms, and risk of deliberate self-harm and suicidal intent. - this wording could be considered as stigmatising towards mental health issues.	It is appreciated that language is important however these are vital to screen to avoid missing those who may need the greatest help. The language in consumer reseources will be adapted. The term deliberate was removed from this recommendation.

70	2.3 Psychosexual function	Healthcare professionals should be aware of the multiple factors that can influence psychosexual function in PCOS including infertility, higher weight, hirsutism, mood disorders and PCOS medications. - it would be better to rearrange this list as the focus appears to be only on infertility, whereas people could be facing issues much before they are trying to conceive.	The order was considered by the GDG and we have now immersed infertility as one of the factors but not listed it first.
70	2.3 Psychosexual function	They should refer patients or reassess treatment options depending on the trigger.	Our guiding princples include person centred care which is relevant here. There is inadequate evidence for psychosexual dysfunction in PCOS which limits recommendatiosn to screen or refer over and above the general population
70	2.3 Psychosexual function	Appropriate contraception advice is important if deemed appropriate.	The point here was unclear
70	2.4 Body Image	Specify what aspects might be affecting patients. Ask the patient and refer based on the cause of concerns.	This is addressed under recommendations to ascertain and address patient concerns. Our guiding princples include person centred care which is relevant here. See 2.6.4
70	2.6.1 Information needs	People might have differing views about the best types and sources of information. Some research has indicated people might prefer digital sources. Health care professionals should refer to up to date, scientifically accurate and culturally appropriate information sources.	Evidence on information needs has informed the dissemination strategies.
70	2.6.1 Information needs	Health care professionals should be aware that there are increased reports of patients being reliant on unregulated information sources such as social media for health related information and they should counsel them about the pros and cons about this and guide them to appropriate resources.	This is important and a practice point on reliable sources was added to the guideline around evidence based information and limiting the imapct of misinformation.
70	2.6.1 Information needs	Information provided should be tailored based on the patients concerns and life stage.	This is dealt with in some of the recommendations (2.6.1) and will be covered in the dissemination section and added to the justification section of the guideline . This also is covered under patient centred care.
70	2.6.3 Support to manage PCOS	Define public health actors.	Added to glossary - Public health actors: those who influence or determine health policy and practice. Examples may include but are not limited to policy makers (inlcuding politicians, health professional/medical societies, non-government organisationswho are in a position to influence policy and health system design.
70	2.6.3 Support to manage PCOS	Information regarding PCOS should be provided during menstrual health education to improve awareness and support.	This is encompassed in the reproductive lifeplan recommendation and can be addressed in regional adaptation.
70	2.8 Psychological therapy	Section 2.8 on psychological therapy should come before 2.7 or combine it into one section	We have reordered the sections as suggested.
70	2.8.2 - Women with PCOS with disordered eating, body image distress, low self-esteem, problems with fitting with social norms, or psychosexual dysfunction should be offered evidence-based treatments (e.g., cognitive behaviour therapy) where appropriate.	Problems with feminine identity can be a controversial statement, I would avoid this to be gender inclusive.	Feminine identity is irrespective of sex and gender. This relates to social and cultural norms and hence we have altered the terminology around feminine identity to social and cultural norms.
70	2.1 Health related Quality of Life	These are much welcomed interventions. There must be a much higher focus on quality of life from HCPs. However, given funding cuts and long waiting times for psychotherapy I am not sure how well this will play out in practice. The first HCP a patient meets is generally a GP, and patients do not feel that their GP is adequately informed about the psychosocial complications of PCOS. Referral to charities and CBT resources may be a first step for women suffering with psychological symptoms unable to get therapy on the NHS. Psychosocial concerns vary by ethnicity. For example, this study concluded that Non-white women and women born in India reported higher emotional and sexual dysfunction, whereas white women and women born in the UK reported higher body image concerns and weight stigma. Ethnicity and birthplace need to be considered for tailored, multidisciplinary care.(4)	CBT based edcuation and strategies will be included in the PCOS resrouces. Ethnicity is also being considered in the translation tools and in the provision of resources, which also consider lack of access

ID	Guideline recommendation to which feedback is targeted.	Comments	Guideline development group consensus response
12	3.1.10 PP Insulin resistance is a pathophysiological factor in PCOS, however, clinically available insulin assays are of limited clinical relevance and should not be used in routine care.	3.1.10. We endorse the limited value of insulin measurement in the clinical setting but wonder whether this biochemical recommendation is better made in the relevant section on diagnosis (or additionally there).	We have kept the practice point in Chapter 3 as well as now adding it to Chapter 1.
22		Many physicians and the public are unfamiliar with healthy eating guidelines. It may be more helpful to include descriptions of a healthy diet which can lower insulin resistance and strengthen the gut microbiome such as a plant forward, whole food diet, decreased heavily processed foods, decreased sugary foods and beverages, and decreased red and processed meats.	The detailed reference to specific diets is managed in the translation tools.
29	3.1.9 PP In those who are not overweight, in the adolescent and at key life points, the focus should be on healthy lifestyle and the prevention of excess weight gain.	Look to reword as lean PCOS can still have insulin resistance, it is not only about weight again. Lifestyle should not focus solely on weight management but on insulin management.	The wording in the recommendation is focused separately for healthy lifestyle AND prevention of weight gain as two separate points here. Lifestyle is not instituted to directly target insulin resistance which cannot be reliably measured in clinical practice. There is also no evidence based approach to optimising insulin levels through diet. Hence the GDG after considering this feedback did not alter the recommendations. Also detailed reference to specific diets is managed in the translation tools.
29	3.1.10 PP Insulin resistance is a pathophysiological factor in PCOS, however, clinically available insulin assays are of limited clinical relevance and should not be used in routine care.	Insulin Assays are of good clinical relevance, especially for those who do not present with signs of insulin resistance e.g. hip to waist ratio, and HbA1c is normal. Can provide further critical data on the patient and their insulin status to better inform practitioners for personalised treatment.	Insulin resistance is key to pathophysiology on PCOS however there are no accurate assays as opposed to clamp studies that can be applied in clinical practice in diabetes or PCOS. No evidence was provided in the feedback for the GDG to review the current recommendations.
29	3.2.2 PP Behavioural support could include: goal setting, problem solving, self-monitoring and reviewing, or SMART goals (Specific, Measurable, Achievable, Realistic and Timely)	PP: We have found that SMART goals need to be based on behaviour/habit change rather than on an outcome. Outcomes can be out of the patient's control e.g. the amount of weight they want to lose. The goal should be linked to the behaviour change rather than the outcome which is within control of the patient. Based on clinical observations and experience.	The PP does not specify either behaviour or health outcomes, rather the point is for behavioural support.
29	3.3.2 CR Any diet composition consistent with population guidelines for healthy eating will have health benefits, and within this, healthcare professionals should advise sustainable healthy eating tailored to individual's preferences and goals.	Population guidelines include 4-6 servings of carbohydrates and grains. May need to be tailored to the patient. RDI for nutrients are not PCOS specific Cannot guarantee health benefits just by following population guidelines. E.g. following guidelines does not mean a patient may achieve weight loss or the goals of the patient.	Please refer to the PP above regarding diet plans for cardiovascular disease and diabetes population. There is no additional evidence provided to alter the GDG recommendations.
29	3.3.3 PP Tailoring of dietary changes to food preferences, allowing for a flexible, individual and co-developed approach to achieving nutritional goals and avoiding unduly restrictive and nutritionally unbalanced diets, are important, as per general population guidelines.	Tailoring of dietary changes to food preference and clinical markers of the individual. PP: personal carbohydrate tolerances differ within individuals hence it is critical to find what is the best for the particular patient.	We have already recommended that diet advice should be provided based on personal preferences and goals in 3.3.2 and 3.3.3.
29	3.4.3 CR Healthcare professionals should encourage and advise the following in concordance with general population physical activity guidelines: ●All adults should undertake physical activity as doing some physical activity is better than none. ●Adults should limit the amount of time spent being sedentary (e.g. sitting, screen time) as replacing sedentary time with physical activity of any intensity (including light intensity) provides health benefits. For the prevention of weight gain and maintenance of health, adults (18-64 years) should aim for a minimum of 150 to 300 minutes of moderate intensity activities or 75 to 150 minutes per week of vigorous intensity aerobic activity or an equivalent combination of both spread throughout the week, plus muscle strengthening activities (e.g. resistance/flexibility) on two non-consecutive days per week. For promotion of greater health benefits including modest weight-loss and prevention of weight-regain, adults (18-64 years) should aim for a minimum of 250 min/week of moderate intensity activities or 150 min/week of vigorous intensities or an equivalent combination of both, plus muscle strengthening activities (e.g. resistance/flexibility) on two non-consecutive days per week. Adolescents should aim for at least 60 minutes of moderate- to vigorous-intensity physical activity per day including activities that strengthen muscle and bone, at least three times per week.	"Strength training on-consecutive days": It might suit the routine and lifestyle of the patient to do 2 days back to back to strength training. Adequate time for recovery with 2 strength based exercise sessions on consecutive days.	We have adopted the WHO guidelines which recommended 2 non-consecutive days due to research showing 48 hours of recovery post muscle strengthening exercise. However, we have now amended the wordings in 3.4.3 to reflect that muscle strengthening activities (e.g.resistance/flexibility) on two non-consecutive days per week is ideal but not compulsory.
29	3.6.4 PP Healthcare professionals should be aware of weight-inclusive practices which promote acceptance of and respect for body size diversity and focus on improvement of health behaviours and health outcomes for people of all sizes. In PCOS this includes: ●Acknowledging that whilst higher weight is a risk factor for PCOS and its complications, it is only one indicator of health and broader factors should be assessed. ●Asking permission to discuss and measure weight and using strategies to minimise discomfort (e.g. blind weighing). ●Recognising that the terms "overweight" and "obese/obesity" can be stigmatising with suggested alternatives including "higher weight" ●If weighing, explaining how weight information will be used to inform risks, prevention and treatment and how not knowing may impact on recommendations. ●Ensuring appropriate equipment is available for women of all sizes. ●Offering options of weight-centric care (promoting intentional weight loss) or weight-inclusive care (promoting healthy lifestyle change without focusing on intentional weight loss) tailored to individual goals and preferences. ●Offering all women best-practice assessment, treatment and support regardless of weight, acknowledging that weight may be a non-modifiable risk factor when using lifestyle modification alone.	"Higher weight is a risk factor for PCOS" - wording indicates that PCOS has been developed from weight gain/being overweight. Whereas should be worded that weight gain can exacerbate PCOS symptoms and its underlying cause. Weight is a symptom of PCOS. While weight loss may improve symptoms, weight gain is not the cause of PCOS and it is not the fault of the patient.	As outlined in the technical report, the evidence supports that the relationship between weight and PCOS is bidirectional. In susceptible individual, higher weight increases the risk of PCOS and symptom severity, and PCOS increases propensity to weight gain, whilst weight loss reduces PCOS features. No evidence was provided for GDG consideration to alter this recommendation.

29	3.6.4 PP Healthcare professionals should be aware of weight-inclusive practices which promote acceptance of and respect for body size diversity and focus on improvement of health behaviours and health outcomes for people of all sizes. In PCOS this includes: ●Acknowledging that whilst higher weight is a risk factor for PCOS and its complications, it is only one indicator of health and broader factors should be assessed. ●Asking permission to discuss and measure weight and using strategies to minimise discomfort (e.g. blind weighing). ●Recognising that the terms “overweight” and “obese/obesity” can be stigmatising with suggested alternatives including “higher weight” ●If weighing, explaining how weight information will be used to inform risks, prevention and treatment and how not knowing may impact on recommendations. ●Ensuring appropriate equipment is available for women of all sizes. ●Offering options of weight-centric care (promoting intentional weight loss) or weight-inclusive care (promoting healthy lifestyle change without focusing on intentional weight loss) tailored to individual goals and preferences. ●Offering all women best-practice assessment, treatment and support regardless of weight, acknowledging that weight may be a non-modifiable risk factor when using lifestyle modification alone.	Practitioners should query if weight really needs to be known and would change the treatment plan for the patient. Would body composition be a better measure to take over body weight? Progress can be tracked via clothes feel, how is the patient feeling, body comp measurements etc, rather than body weight. Where is the value in knowing body weight? Does this alter the treatment plan for the patient (e.g. may be needed for medication dose, if not, then is weight relevant?). No need to cause unnecessary stress to the patient.	This was debated at length by the GDG however weight is a very strong predictor of complications and in some cases of response to treatment. Permission to weigh and justification for weighing is recommended. There is no evidence that supports body composition is a better measure in PCOS.
29	3.1.1 EBR Lifestyle intervention (exercise alone or multicomponent diet combined with exercise and behavioural strategies) should be recommended for all women with PCOS, for improving metabolic health including central adiposity and lipid profile.	3.1.1: states 'exercise alone or multicomponent'. ¨Diet alone" should also be considered. And why is the focus exercise alone if not multicomponent? Exercise can be a barrier for many and diet/healthy eating changes can be an easier entry.	The recommendation directly reflects the evidence in the literature and no additional evidence for provided to alter the GDG recommendation.
29	3.4 Exercise Intervention	Patients with PCOS who are not currently exercising really struggle with the barrier to begin exercising. Health practitioners should start with a smaller goal and build up to 75 mins. Health practitioners should ask first what the patient is currently doing for exercise and give recommendations based on this. Meet the client where they are at.	This is covered by 3.4.2 and 3.4.3, and is based on general population guidelines.
29	3.6 Weight Stigma	Awareness of weight bias is great to see, but also including education in tertiary settings of what is causing the weight bias to break the cycle. Need more than just awareness to address and lower weight bias in PCOS	The guideline group agrees and it is already stated in 3.6.3 that health policy makes, managers and educators should all promote and invest in weight stigma education and minimisation strategies.
35	3.3.1 EBR Healthcare professionals and women should be aware that there is no evidence to support any one type of diet composition over another for anthropometric, metabolic, hormonal, reproductive or psychological outcomes.	Healthy lifestyle for PCOS patients may also try to avoid endocrine disruptors exposure (food chain, food containers and packaging, food preservatives and dyes) because of their harmful effect on steroidogenesis and on glucose metabolism 1 -Polycystic Ovary Syndrome: An Evolutionary Adaptation to Lifestyle and the Environment. Int. J. Environ. Res. Public Health 2022, 19, 1336. 2-The association between the environmental endocrine disruptor bisphenol A and polycystic ovary syndrome: a systematic review and meta-analysis. gynaecological endocrinology, 2018, 34: 3-BPA and PCOS: a review of the literature., Rev Environ Health 2020 Jul 14;35(4):323-331	The impact of endocrine disruptors was not prioritised by consumers and multidisciplinary health professionals for the guideline update and was out of scope, but may be considered in future.
35	3.3.1 EBR Healthcare professionals and women should be aware that there is no evidence to support any one type of diet composition over another for anthropometric, metabolic, hormonal, reproductive or psychological outcomes.	considering the type of diet, shouldn't we recommend a diet helping to improve insulin sensitivity and lower inflammation? 1 - Low glycaemic index diet improves insulin sensitivity in women with polycystic ovary syndrome. BarrS, et al, Acad Nutr Diet. 2013 Nov;113(11):1523-1531 2 - Effect of a low glycaemic index compared with a conventional healthy diet on polycystic ovary syndrome. Marsh K.A. et al, Am J Clin Nutr. 2010 Jul;92(1):83-92	Our extensive systematic review and meta-analysis did not find any evidence to support any one type of diet over the other. The references provided in the comment were already considered by the guideline group (see technical report).
37	3.5.2 PP Whilst the specific mechanisms are unclear, it is recognised that many women with PCOS will have underlying mechanisms that drive greater longitudinal weight gain and higher BMI which may: ●Underpin greater challenges with weight management. ●Highlight the importance of lifelong healthy lifestyle strategies and prevention of excess weight gain. ●Assist women with PCOS and healthcare professionals in forming realistic, tailored lifestyle goals.	"it is recognized that many women with PCOS will have underlying mechanisms that drive greater longitudinal weight gain and higher BMI• this sentence is confusing. There is insufficient evidence to state that women with PCOS may have underlying mechanisms driving greater weight gain that are due to PCOS per se. Suggestion is to remove or temper this sentence, such as "it is recognized that many women with PCOS will have underlying mechanisms, related or not to PCOS, that drive greater longitudinal weight gain and higher BMI. This observation might only be due to a selection bias, since these individuals have developed PCOS that is a weight-related condition. Also, most outcomes are self-reported and prone to recall bias and misreporting, as mentioned in page 77.	Unselected population based studies confirmed that women with PCOS have higher longitudinal weight gain as per referenced studies.
73		Language About Weight and Lifestyle; We were pleased to see that weight stigma was included in the guideline, and recognition of the terms “overweight,” “obese,” and “obesity” and their potential to be stigmatizing. We also appreciate the suggestion to use alternative language, including “higher weight”. Additionally, it was good to highlight the benefits of a healthy lifestyle, even without the emphasis on weight loss. However, the lifestyle section still lacks specific nutrition recommendations. Also, while there is a progression in thought and practice, the overall emphasis is still on controlling weight, even when referring to weight maintenance.	We have now added specific exemplars of healthy diet and more details will be provided in the translation tools. Biologically, weight is a key determinant of health, and of complication prevention and treatment hence to not mention weight maintenance denies women accurate information. This was debated for a long time, however given weight is the number one concern raised by women and that it is the key determinant of fertility, response to treatment and pregnancy health, the decision to retain a reference to weight was made with consumer input.

ID	Guideline recommendation to which feedback is targeted.	Comments	Guideline development group consensus response
4	4.7 Inositol (P90) in guideline.	1) The sentence is proposed that hyperinsulinemia in PCOS enhances MI to DCI conversion and impacts the ratio which is 100:1 generally but in PCOS may be 0.2:1 needs some clarifications, as it is misleading. 2) The sentence MI may also enhance androgen production is false. No publication has ever reported this information, least of all the reference indicated in the text. 3) The sentence "there is considerable misinformation on efficacy" is quite outdated. Justification: 1) Under insulin stimulation, epimerase enzyme converts myo-inositol (myo-Ins) into its stereoisomer D-chiro-inositol (D-chiro-Ins). This unidirectional reaction allows each organ and tissue to benefit from a specific and proper balance between myo-Ins and D-chiro-Ins content, ensuring the correct metabolic functions and consequent physiological status. In some pathological conditions, the decreased insulin sensitivity in many tissues leads to reduced epimerase activity and lower D-chiro-Ins production [1]. However, ovaries can maintain normal insulin sensitivity, despite the presence of insulin resistance. Indeed, according to the so-called 'ovarian paradox', ovaries never become insulin resistant, and therefore, the compensatory hyperinsulinemia overstimulates the ovarian epimerase, causing excessive D-chiro-Ins synthesis at the expense of myo-Ins concentration [2]. So, while healthy women's ovaries show higher myo-Ins levels and lower concentrations of D-chiro-Ins, with a ratio around 100:1; on the contrary, ovaries in PCOS patients proved to have marked myo-Ins depletion and increased D-chiro-Ins content, with a ratio dropping to 0.2:1 [3]. The resultant impaired ovarian myo-Ins to D-chiro-Ins ratio may account for PCOS pathogenesis in insulin resistant patients. In fact, the increase in D-chiro-Ins concentration promotes androgen synthesis, meanwhile myo-Ins depletion worsens FSH signalling and oocyte quality. The ovarian paradox hypothesis may help to explain why supplementation with D-chiro-Ins alone, especially at high doses and for a prolonged time, cannot be considered an effective approach to manage PCOS. In contrast, several lines of evidence proved myo-Ins efficacy and safety in managing PCOS symptoms and improving outcomes [4], with the most promising clinical results observed in obese, insulin-resistant PCOS women, when combining myo-Ins and D-chiro-Ins in a 40:1 ratio. The 40:1 ratio which may appear arbitrary, actually is similar to the plasma ratio reported in healthy women [5], thus supporting its supplementation to restore the physiological concentrations of myo-Ins and D-chiro-Ins. In this case, the small quantity of D-chiro-Ins reduces systemic insulin levels, leading to an increase in intraovarian myo-Ins, which improved FSH sensitivity and restored ovulation. 2) Actually, it is well known that research on inositols demonstrated that D-chiro-Ins, and not myo-Ins, stimulates the ovarian production of androgens by thecal cells [6].	We have amended the sections: 1) It is proposed that hyperinsulinemia in PCOS enhances ovarian epimerase activity which enhances D-Chiro-Inositol synthesis at the expense of myo-inositol concentration. In women without PCOS, the ratio of MI to DCI is 100:1 in follicular fluid whereas in women with PCOS, this ratio drops to 0.2:1. (Unfer 2014) 2) MI is also postulated to enhance aromatase synthesis in granulosa cells and therefore reducing androgen production 3) "However, there are concerns about misinformation and potential conflict of interest and these supplements come at high cost, with a priority to ensure evidence based information on inositol
12	4.2 Combined Oral Contraceptive Pills (COCP)	It is surprising that there is not as stronger statement on the risks of COCP prescription in those with BMI >35, particularly given prevalence of obesity in this condition	We have already recommended that general guidelines should be taken into account when prescribing the OCP. BMI in itself is not a contraindication.
12	4.6.1 EBR In combination with effective contraception, anti-androgens could be considered to treat hirsutism in women with PCOS, if there is a suboptimal response after a minimum of six months of COCP and/or cosmetic therapy.	Should the guideline be more explicit in defining ¨effective contraception"? Which methods would be considered effective and which not? Should anti-androgens be avoided when barrier methods alone are in use?	Effective contraception is not specific to women with PCOS and contraception efficacy would be similar between with PCOS and without. Extensive discussion occurred in the GDG regarding this issue and this was the consensus wording.
12	4.6.1 EBR In combination with effective contraception, anti-androgens could be considered to treat hirsutism in women with PCOS, if there is a suboptimal response after a minimum of six months of COCP and/or cosmetic therapy.	4.6.1: "or in patients in whom COCPs are contraindicated"	This is covered in 4.6.4
12	4.6.5 PP When prescribing anti-androgens, based on general population recommendations, healthcare professionals should consider that: •Spironolactone at 25-100mg / day appears to have lower risks of adverse effects. •Cyproterone acetate at high doses (≥ 10mg) is not advised due to an increased risk including for meningioma. •Flutamide and bicalutamide have an increased risk of severe liver toxicity. •The relatively limited evidence on anti-androgens in PCOS needs to be appreciated with small numbers of studies and limited numbers of participants.	Consider brief mention of finasteride	A statement on finasteride is added as suggested.
12	4.8	4.8. This needs a section heading.	It is not clear where the heading is recommended, however detailed final formatting will be completed in the final guideline version.
12	4.8.6 PP Policy makers should consider funding this evidence-based effective therapy for women with PCOS to alleviate distressing symptoms of hirsutism, and related negative impact on quality of life, body image and psychological health.	4.8.6. We strongly endorse the call for healthcare providers to fund laser therapy, as patients have difficulty in accessing this in many healthcare economies (including the UK). This creates a societal divide, with privately-accessed treatment being confined to those patients who can afford it.	Nil needed
12	4.11.1 EBR Metformin should not be routinely used in pregnant women with PCOS as it has not been shown to prevent: •Gestational diabetes •Late miscarriage (12 weeks+1 day to 21 weeks +6 days gestational age) •Hypertension in pregnancy •Pre-eclampsia •Macrosomia or birthweight ≥ 4000 g	4.11.1: What is the consensus on use of metformin in women with PCOS during the first trimester of pregnancy?	This is addressed in 4.11 as not being routinely recommended and only considered in certain circumstances.
29	4.2 Combined Oral Contraceptive Pills (COCP)	Education needed on how COCP gives a regular bleed and this is not regular ovulation. When coming off COCP, periods may be just as or more so irregular due to the suppressed ovulation. Further education needed on a regular bleed compared to regular ovulation.	This is covered in patient related translation material from the guideline. The COCP is also often prescribed continuously or at least for multiple months before a withdrawal bleed. This is also covered in translation resources.
29	4.2.1 EBR The COCP should be recommended in reproductive age adults with PCOS for management of hirsutism and/or irregular menstrual cycles.	COCP is not the only way to achieve a regular bleed. A regular bleed is not the same as a regular cycle.	We were not inferring regular cycles, but were referring to cycle regulation. No change required.
29	4.3 Metformin	Missing: use and safety during pregnancy. This medication does cross the placenta. There should be more informed decision making.	There is a separate section in 4.11 on metformin in pregnancy

29	4.2.7 PP When prescribing COCPs in adults and adolescents with PCOS, and adolescents at risk of PCOS •It is important to address main presenting symptoms and consider other treatments such as cosmetic therapies •Shared decision-making (including accurate information and reassurance on the efficacy and safety of COCP) is recommended and likely to improve adherence •Natural estrogen preparations and the lowest effective estrogen doses (such as 20-30 micrograms of ethinyl estradiol or equivalent), need consideration, balancing efficacy, metabolic risk profile, side effects, cost and availability •The relatively limited evidence on COCPs specifically in PCOS needs to be appreciated with practice informed by general population guidelines •The relative and absolute contraindications and side effects of COCPs need to be considered and be the subject of individualised discussion •PCOS specific features such as higher weight and cardiovascular risk factors, need to be considered	Shared decision making: discussion and education needed on potential side effects, method of action, and also having informed consent from the patient. Reassurance can be pressure, rather than consent. Justification: To achieve informed consent from the patient	Initiating any medication requires discussion of risks and benefits. This was considered by the GDG, however there was no specific differences to practice for COCPs or PCOS that differ to other medications, hence this was not altered.
35	4.7 Inositol	Several false statements, some data out of date and some recommendations to amend. This sentence needs some clarifications. Under insulin stimulation, epimerase enzyme converts myo-inositol (myo-Ins) into its stereoisomer D-chiro-inositol (D-chiro-Ins). This unidirectional reaction allows each organ and tissue to benefit from a specific and proper balance between myo-Ins and D-chiro-Ins content, ensuring the correct metabolic functions and consequent physiological status. In some pathological conditions, the decreased insulin sensitivity in many tissues leads to reduced epimerase activity and lower D-chiro-Ins production [1]. However, ovaries can maintain normal insulin sensitivity, despite the presence of insulin resistance. Indeed, according to the so-called ovarian paradox, ovaries never become insulin resistant, and therefore, the compensatory hyperinsulinemia overstimulates the ovarian epimerase, causing excessive D-chiro-Ins synthesis at the expense of myo-Ins concentration [2]. So, while healthy women's ovaries show higher myo-Ins levels and lower concentrations of D-chiro-Ins, with a ratio around 100:1; on the contrary, ovaries in PCOS patients proved to have marked myo-Ins depletion and increased D-chiro-Ins content, with a ratio dropping to 0.2:1 [3]. The resultant impaired ovarian myo-Ins to D-chiro-Ins ratio may account for PCOS pathogenesis in insulin resistant patients. In fact, the increase in D-chiro-Ins concentration promotes androgen synthesis, meanwhile myo-Ins depletion worsens FSH signalling and oocyte quality. The ovarian paradox hypothesis may help to explain why supplementation with D-chiro-Ins alone, especially at high doses and for a prolonged time, cannot be considered an effective approach to manage PCOS. In contrast, several lines of evidence proved myo-Ins efficacy and safety in managing PCOS symptoms and improving outcomes [4], with the most promising clinical results observed in obese, insulin-resistant PCOS women, when combining myo-Ins and D-chiro-Ins in a 40:1 ratio. The 40:1 ratio that may appear arbitrary, actually is similar to the plasma ratio reported in healthy women [5], thus supporting its supplementation to restore the physiological concentrations of myo-Ins and D-chiro-Ins. In this case, the small quantity of D-chiro-Ins reduces systemic insulin levels, leading to an increase in intraovarian myo-Ins, which improved FSH sensitivity and restored ovulation. Page 90 MI may also enhance androgen production. This sentence is false. No publication has ever reported this information, least of all the reference indicated in the text. Actually, it is well known that research on inositols demonstrated that D-chiro-Ins, and not myo-Ins, stimulates	The background section of inositol has been reviewed and amended.
70		There are lots of alternative therapies targeted for PCOS management and it might be beneficial to Include a section on alternative therapies with current evidence	Alternative therapies were not identified as a key priority by women or health professionals and hence are out of scope. Evidence for most alternative therapies is very limited. The guidelines do include recommendations on inositol.
67	SECTION: 4.7 Inositol	The physiological MI:DCI ratio is 40:1, not 100:1. There are lots of alternative therapies targeted for PCOS management and it might be beneficial to Include a section on alternative therapies with current evidence. Please see the following international Position Statement summarizing the available pieces of evidence: https://pubmed.ncbi.nlm.nih.gov/32396844/ https://pubmed.ncbi.nlm.nih.gov/32129111/	The background section of inositol has been reviewed and amended.
67	P 90 MI may also enhance androgen production	This is not correct. DCI (not MI) was found to act as modulator of aromatase activity (see: https://pubmed.ncbi.nlm.nih.gov/27582109/). For this reason, high levels of DCI inhibit the aromatase activity, so the production of estradiol from testosterone and, in this way, increases the circulating levels of androgens and decrease the circulating levels of estrogens (for the reduced rate of their production). This modulator activity on aromatase was found only for DCI, not for MI, so MI does not enhance androgen production. For more information, please refer to: https://pubmed.ncbi.nlm.nih.gov/32998310/ https://pubmed.ncbi.nlm.nih.gov/32552009/ https://pubmed.ncbi.nlm.nih.gov/32396844/	The background section of inositol has been reviewed and amended.

67	4.7.1 to 4.7.6 Inositol	Several false statements, some data out of date and some Recommendations to amend (see my suggestions below). Please see the argument below that has been posted by Dr Simona Dinicola on the CREWHIRL site. I fully agree with this argument. Comments on Sections 4.7 and 5.8 about Inositols of the International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome 2023. Page 90 It is proposed that hyperinsulinemia in PCOS enhances MI to DCI conversion and impacts the ratio which is 100:1 generally but in PCOS may be 0.2:1. This sentence needs some clarifications. Under insulin stimulation, epimerase enzyme converts myo-inositol (myo-Ins) into its stereoisomer D-chiro-inositol (D-chiro-Ins). This unidirectional reaction allows each organ and tissue to benefit from a specific and proper balance between myo-Ins and D-chiro-Ins content, ensuring the correct metabolic functions and consequent physiological status. In some pathological conditions, the decreased insulin sensitivity in many tissues leads to reduced epimerase activity and lower D-chiro-Ins production [1]. However, ovaries can maintain normal insulin sensitivity, despite the presence of insulin resistance. Indeed, according to the so-called "ovarian paradox", ovaries never become insulin resistant, and therefore, the compensatory hyperinsulinemia overstimulates the ovarian epimerase, causing excessive D-chiro-Ins synthesis at the expense of myo-Ins concentration [2]. So, while healthy women's ovaries show higher myo-Ins levels and lower concentrations of D-chiro-Ins, with a ratio around 100:1; on the contrary, ovaries in PCOS patients proved to have marked myo-Ins depletion and increased D-chiro-Ins content, with a ratio dropping to 0.2:1 [3]. The resultant impaired ovarian myo-Ins to D-chiro-Ins ratio may account for PCOS pathogenesis in insulin resistant patients. In fact, the increase in D-chiro-Ins concentration promotes androgen synthesis, meanwhile myo-Ins depletion worsens FSH signalling and oocyte quality. The "ovarian paradox hypothesis" may help to explain why supplementation with D-chiro-Ins alone, especially at high doses and for a prolonged time, cannot be considered an effective approach to manage PCOS. In contrast, several lines of evidence proved myo-Ins efficacy and safety in managing PCOS symptoms and improving outcomes [4], with the most promising clinical results observed in obese, insulin-resistant PCOS women, when combining myo-Ins and D-chiro-Ins in a 40:1 ratio. The 40:1 ratio that may appear arbitrary, actually is similar to the plasma ratio reported in healthy women [5],	The background section of inositol has been reviewed and amended.
70	Section 4. Management of non-fertility features	Sexual health and mental health needs should be addressed in this section	This has been covered in Chapter 2 in detail
70	4.2.1 EBR The COCP should be recommended in reproductive age adults with PCOS for management of hirsutism and/or irregular menstrual cycles.	While COCP is effective, HCP should explain properly. Women have expressed frustration with the use of long term medication without other forms of support.(6) I remember feeling that I was being ignored and sent away with a one size fits all solution, when if the HCP had explained the mechanism of action to me, I would have walked away satisfied.	Working in partnership with patients and shared decision making have been discussed in detail elsewhere in the guideline
70	4.3.1 EB Metformin alone should be considered in adults with PCOS and a BMI ≥ 25 kg/m2 for anthropometric, and metabolic outcomes including insulin resistance, glucose, lipid profiles and androgen levels.	There is growing evidence that metabolic risk varies across different ethnicities and hence the current practice for ethnicity-based cut-off for treatment recommendation.	Metformin is not an anti-obesity medication. There is insufficient evidence for metformin for different ethnic BMI cut offs to provide ethnicity specific recommendations
70	4.7.4 PP Specific types, doses or combinations of inositol cannot currently be recommended in adults and adolescents with PCOS, due to a lack of quality evidence.	While this is generic, I wonder if there is merit to address the combination of metformin and inositol which appears to be common practice these days.	The comparison was considered in the evidence synthesis and covered in the background section of inositol.
70	4.8.1 EBR Mechanical laser and light therapies should be considered for reducing facial hirsutism and for related depression, anxiety and quality of life in women with PCOS.	This is extremely welcome, but again I wonder how much it will be prescribed in practice.	No response required

73	4.7 Inositol	Our group consensus is that this section is written in such a definitive and negative way towards inositol, especially when compared to other sections of this guideline where recommendations are made with low evidence (for example, section 5.4) without the same tone. Inositol is widely used as an alternative to metformin for those who desire an option with fewer GI side effects, and this document should encourage additional research. The outline gives a negative narrative of inositol. This may dissuade doctors from being open-minded to their patients taking inositol. There are many studies to consider which may not have been reviewed in consideration of drafting Section 4.7. The following is an outline of studies from 2007-2023: https://www.tandfonline.com/doi/abs/10.1080/09513590.2021.1981282?journalCode=igye20 https://www.tandfonline.com/doi/abs/10.1080/09513590.2020.1810657 https://www.ncbi.nlm.nih.gov/pubmed/30614289 https://journals.lww.com/ebjwh/Abstract/2015/08000/Inositol_versus_Metformin_administration_in.2.aspx%20 https://www.ncbi.nlm.nih.gov/pubmed/20222840 https://rbej.biomedcentral.com/articles/10.1186/s12958-023-01055-z https://www.ncbi.nlm.nih.gov/pubmed/30570133 https://www.ncbi.nlm.nih.gov/pubmed/30078122 https://www.ncbi.nlm.nih.gov/pubmed/28544572 https://www.ncbi.nlm.nih.gov/pubmed/29245250 https://www.ncbi.nlm.nih.gov/pubmed/27795706 https://www.europeanreview.org/wp/wp-content/uploads/5512-5521.pdf https://pubmed.ncbi.nlm.nih.gov/28277112/ https://www.ncbi.nlm.nih.gov/pubmed/27635136%20 https://pubmed.ncbi.nlm.nih.gov/26507336/ https://www.ncbi.nlm.nih.gov/pubmed/26067283 https://www.ncbi.nlm.nih.gov/pubmed/25259724%20 https://www.ncbi.nlm.nih.gov/pubmed/23708322 https://www.ncbi.nlm.nih.gov/pubmed/23336594%20 https://www.ncbi.nlm.nih.gov/pubmed/21744744 https://www.ncbi.nlm.nih.gov/pubmed/21608442%20 https://www.ncbi.nlm.nih.gov/pubmed/18462730	The recommendations have been based on the limited evidence in this area, that met the rigorous data integrity requirements for inclusion. Our research recommendations have suggested this as a priority area for high quality evidence in future. Strong consumer representation was present and was an integral part of the formation of the recommendations.
73	Section 4. Management of non-fertility features	Management of Non-Fertility Features Our group appreciated the inclusion of shared decision-making and taking the individual patient into account, which is crucial. It was also noted and appreciated that the guideline included support, education and lifestyle; however, some sections seemed to be heavily pro-metformin and therefore need to include more emphasized discussion on metformin intolerance and other management techniques. Many clinicians, including our own who participated in this review, recognize many PCOS patients don't tolerate metformin well. Patients should be informed that diet and active lifestyle interventions have similar efficacy to metformin. The outline gives a negative narrative of inositol. This may dissuade doctors from being open-minded to their patients taking inositol. While bariatric surgery is an option for some patients, it's not a one-and-done situation and needs to address the psychological component as well as continue to pay attention to nutrition/lifestyle after/before surgery.	We agree that these are important as part of shared decision making. Reference to sections in guideline, e.g. metformin adverse effects. See above regarding inositol. 4.7.6
75		Could you consider "preterm birth" instead of "preterm delivery" in all sections - for instance this section as well as 4.10.2 refers to preterm delivery but 4.10.3 uses preterm birth. Also, is there a reason why 4.10 appears after 4.11	Wordings are change to preterm birth. The order of 4.10 and 4.11 is also changed as suggested.
79	4.3.2 EBR Metformin alone could be considered in adolescents at risk of or with PCOS for cycle regulation, acknowledging limited evidence.	Why do the authors consider metformin and not progesterone for cycle regulation?	The evidence for metformin is stronger. Progesterone therapy was not prioritised as a clinical question and the GDG considered that adherence might be a factor to consider also. We acknowledge that cyclical progesterone is a potential medical therapy for endometrial protection.
79	4.6.5 PP When prescribing anti-androgens, based on general population recommendations, healthcare professionals should consider that: •Spironolactone at 25-100mg / day appears to have lower risks of adverse effects. •Cyproterone acetate at high doses (≥ 10mg) is not advised due to an increased risk including for meningioma. •Flutamide and bicalutamide have an increased risk of severe liver toxicity. •The relatively limited evidence on anti-androgens in PCOS needs to be appreciated with small numbers of studies and limited numbers of participants.	The authors could mention that measuring kaliemia is not necessary when prescribing spironolactone in young women. The authors mention cyproterone acetate (CPA) at a high dose > 10 mg. A high dose of CPA is usually higher than 50 mg. The duration of treatment is a major issue.	Wordings on cyproterone acetate are changed.
80	4.3.4 PP Where metformin is prescribed the following need to be considered: •Shared decision making needs to consider feasibility and effectiveness of active lifestyle intervention. Women should be informed that metformin and active lifestyle intervention have similar efficacy. •Mild adverse effects, including gastrointestinal side-effects are generally dose dependent and self-limiting •Starting at a low dose, with 500mg increments 1-2 weekly and extended-release preparations may minimise side effects and improve adherence. •Suggested maximum daily dose is 2.5g in adults and 2g in adolescents. •Use appears safe long-term, based on use in other populations, however indications for ongoing requirement needs to be considered •Use may be associated with low vitamin B12 levels, especially in those with risk factors for low vitamin B12 (e.g. diabetes, post bariatric / metabolic surgery, pernicious anaemia, vegan diet etc.), where monitoring should be considered	Important suggestions about the management and use of metformin	Nil action required

80	4.6.3 PP Whenever pregnancy is possible, healthcare professionals must educate and counsel women and adolescents, parents/s or guardian/s, regarding the risks of incomplete development of external genital structures of male fetuses (undervirilisation) when anti-androgens are used. To prevent this, women who can get pregnant should be strongly counseled to use effective contraception (e.g. Intrauterine device or COCPs).	Important principles	Nil action required
84	4.3 Metformin	Metformin- Mild adverse effects, including gastrointestinal side-effects are generally dose dependent and self-limiting, but can be decreased by changing to extended release formulations. Metformin intolerance is not insignificant. Switching to the sustained release formation is often needed, and this option should be made clear to the practitioner. SR is also dose once a day, rather than twice a day, which can improve adherence. In the original diabetes prevention program study, 16% of adults in the metformin group did not reach the full dose of 1700 mg a day due to side-effects/intolerance, and rather were treated with 850 mg once a day. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1370926/?report=reader In the TODAY study, the largest study in youth with type 2 diabetes, of those randomized to metformin alone 56% percent reported GI distress and in the metformin + lifestyle 58% reported GI distress. https://www.nejm.org/doi/full/10.1056/nejmoa1109333 GI distress reduced after changing to SR in adult with type 2 diabetes https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5463552/ https://www.frontiersin.org/articles/10.3389/fendo.2022.975912/full recent meta-analysis From a personal clinical perspective, approximately 20 % the teens with obesity and PCOS do not tolerate regular metformin. Of these, most tolerate a change to either 1500 or 2000 mg a day of extended release, although some patients do not tolerate either one.	These points were acknowledged by the GDG, however side effects are noted in the current recommendations on metformin. The evidence provided here is largely in non PCOS populations and the efficacy (versus the side effects) of the slow release preparation in PCOS is not yet clear. The practice point already included ways to reduce GI adverse effects in 4.3.4 including consideration of extended release preparations. No changes were made to the guideline wording.
84	4.5 Anti-obesity pharmacological agents	anti-obesity pharmacologic agents- Consider including phentermine/topiramate. I realize that right now phentermine/topiramate is only approved in the US and Korea. However, it is included in many other guidelines regarding obesity, and is a very effective therapy- twice the efficacy of liraglutide. 4.5.1 CR Anti-obesity medications including liraglutide, semaglutide, both glucagon-like peptide-1 (GLP-1) receptor agonists, orlistat and phentermine/topirimate, could be considered, in addition to active lifestyle intervention, for the management of higher weight in adults with PCOS as per general population guidelines. â¦â¦â¦ 4.5.2 PP Healthcare professionals should ensure concurrent effective contraception when pregnancy is possible, for women who take GLP1 receptor agonists, as pregnancy safety data are lacking and phentermine/topiramate is associated with a higher risk of congenital abnormalities. 4.5.3 PP Gradual dose escalation for GLP-1 receptor agonists is recommended to reduce gastrointestinal adverse effects. (Is 4.5.3 PP needed. All the medications are prescribed with a dose titration?) 4.5.4 PP Shared decision making, when discussing GLP-1 receptor agonist use with women with PCOS, needs to consider side effects, and the potential need for long-term use in weight management, given the high risk for weight regain after discontinuation, and the lack of long-term safety data. Only agents approved for use by multiple regulatory agencies in weight management were the subject of recommendations here including exenatide, liraglutide, semaglutide and orlistat.â€• Phentermine/topiramate first FDA approved weight loss in 2012. Currently approved in South Korea (2018). It is listed as the most cost-effective weight loss medication: https://icer.org/news-insights/press-releases/icer-publishes-evidence-report-on-treatments-for-obesity-management/ Phentermine/topiramate is part of other association guidelines and is much more effective than liraglutide. Included in 2016 Endocrine Society pharmacologic options for obesity: https://academic.oup.com/jcem/article/100/2/342/2813109 2023 American Gastroenterology Association - note- they do not recommend Orlistat - see figure below https://www.gastrojournal.org/article/S0016-5085(22)01096-4/fulltext From a professional perspective, in adolescent obesity we rarely recommend Orlistat. The side-effects are intolerable, with minimal weight loss. If you do get higher weight loss, there is an increased risk of cholelithiasis. Liraglutide is also only moderately effective for the cost and burdensome with a requirement for daily injections.	There is insufficient evidence at present to recommend phenterminate/topiramate in women with PCOS. We acknowledge that there is some evidence in the general population for use of these medications in the management of obesity.
105	4.2 Combined Oral Contraceptive Pills (COCP)	The authors recommend almost universally the use of combined oral contraceptive pills (COCPs) including in very young girls and in girls only “at risk”, and suggest that the authorities should officially approve the use of COCPs as “the” treatment for PCOS. Given the very low evidence for this recommendation, it makes little sense (see Specific Comments below), and accordingly, we disagree.	The wording in the guideline does not recommend universal use of COCP, rather it is recommended as first line medical treatment with specific indications. COCP is an evidence based treatment for clinical features of PCOS including hyperandrogenism and cycle regulation, with more limited specific information in PCOS. There was no evidence provided here to support reconsideration of the recommendations.
105	4.1 Treatment	The authors should at least mention the existence of novel treatment options in adolescent girls addressed at reducing ectopic fat excess and not at masquerading the symptoms (doi: 10.1210/jendso/bvaa032).	The question of the novel treatments was not addressed in the guideline as they were not prioritised by the GDG experts or consumers. Furthermore, the evidence provided here was two small pilot trials in a single centre and would not have been adequate evidence to inform recommendations here.

105	4.2 Combined Oral Contraceptive Pills (COCP)	Their use was recommended with evidence quality of GRADE 2 (⊕⊕OO = low quality) in the 2018 guideline. In the revised guideline version, evidence quality was decreased to "(⊕OOO = very low quality"). Likewise, recommendation was changed from ****Strong recommendation (2018) to ***Conditional recommendation" (2023), for adult women.	This is an important point and has now been explained In the guideline justification section. The evidence is not of lower quality than the 16 comparisons covered in the 2018 guidelines, however since then many more comparisons have been trialled (32) and these new comparisons have lower level evidence. However convention dictates that the lowest evidence rating needs to be reported and hence adding in new comparisons results in a lower evidence certainty, despite the original evidence remaining the same since 2018. We have now clarified this overall under the section on certainty of evidence and in the justification section of the individual relevant clinical questions in the guideline where relevant. Furthermore, recommendation for use is informed by use in the general population and effects on hyperandrogenism and cycle control. We also added to the Interpreting the recommendations section in p15. Aligned to Cochranes methods, certainty of evidence varies significantly across outcomes for each clinical questions. In this guideline, the recorded evidence certainty reflects the lowest certainty for the top three critical outcomes for each question. Hence evidence was often stronger for the most critical outcome and often high quality RCT addressed an individual question, but multiple additional low quality studies may have resulted in low certainty evidence overall. These nuances in the evidence were considered for every clinical question and are outlined in the technical report and GRADE tables. Hence, an apparent discrepancy may be observed between the strength of the recommendation and the certainty of the evidence. Where this occurs, a justification is added to the guideline under the relevant clinical question..
105	4.2.2 EBR The COCP should be considered in adolescents at risk or with a clear diagnosis of PCOS for management of hirsutism and/or irregular menstrual cycles.	Regarding this statement, there is no evidence in the technical report supporting that COCPs SHOULD be used in adolescents at risk for PCOS. Additionally, although the recommendation grade became "very low quality" instead of "low quality", the authors state that COCPs "SHOULD be considered in adolescents at risk"; however in the 2018 guideline, their statement read: "COULD be considered in adolescents who are deemed 'at risk'". This makes indeed no sense. What is the rationale for such a recommendation?	Additional information on interpreting the recommendations is now added upfront in the guideline as per above. After GDG consideration the wording was altered to "could be considered"
105	4.2.7 PP When prescribing COCPs in adults and adolescents with PCOS, and adolescents at risk of PCOS • It is important to address main presenting symptoms and consider other treatments such as cosmetic therapies • Shared decision-making (including accurate information and reassurance on the efficacy and safety of COCP) is recommended and likely to improve adherence • Natural estrogen preparations and the lowest effective estrogen doses (such as 20-30 micrograms of ethinyl estradiol or equivalent), need consideration, balancing efficacy, metabolic risk profile, side effects, cost and availability • The relatively limited evidence on COCPs specifically in PCOS needs to be appreciated with practice informed by general population guidelines • The relative and absolute contraindications and side effects of COCPs need to be considered and be the subject of individualised discussion • PCOS specific features such as higher weight and cardiovascular risk factors, need to be considered	When prescribing COCPs, "adolescents at risk of PCOS" should not be categorized within the same group as "adults and adolescents with PCOS". Along the same lines, not all adolescents of the "at risk" group are using COCPs on a routine basis for contraceptive purposes, at least this is not the case in many countries.	This point was considered by both the GDG4 and the paediatric expert group. Wording was altered in the related clinical question, however all practice points here under 4.2.7 were still considered relevant to all those in whom the COCP was being considered.
105	4.3.1 EBR Metformin alone should be considered in adults with PCOS and a BMI ≥ 25 kg/m2 for anthropometric, and metabolic outcomes including insulin resistance, glucose, lipid profiles and androgen levels.	The underlined text does not align well with other parts in the guideline, such as: OC is preferred for hirsutism treatment (4.2.1). When OC may not be given for hirsutism, other interventions (not metformin) are suggested (4.4.5).	The androgen levels section was deleted.
105	4.3.2 EBR Metformin alone could be considered in adolescents at risk of or with PCOS for cycle regulation, acknowledging limited evidence.	The underlined text is not defined and is therefore unclear. Moreover, this sentence is consistent with the previous guideline version although the recommendation grade became "very low quality" instead of "low quality". On the other hand, the recommendation in adolescents focuses solely on cycle regulation, but not on BMI and metabolic outcomes as in adults. Indeed, the data regarding the effect of metformin on BMI in adolescents is limited. In contrast, in the draft guideline of 172 pages, it is stated that: "There was inadequate evidence to make a recommendation about the use of metformin for irregular menstrual cycles". So, the pertinence of this recommendation (4.3.2) exclusively for irregular cycles is -in the best of cases- debatable. In addition, the use of metformin for irregular menstrual cycles, in case the COCPs are contraindicated or not tolerated, is mentioned elsewhere (section 4.4.5). In the draft of the full guideline (172 pages), in page 85 (Justification section) there is another statement that we consider inappropriate and with which we totally disagree: "Women should be informed of the benefits and risks and the regulation status of metformin could be revised. Regulatory agencies should also consider approving COCP for use in PCOS." This is a way of saying that metformin has risks, so that COCPs should be approved without having the evidence to make this statement.	Over the past 5 years all major statements in adolescents have followed the "at risk terminology" and it was the strong position of the GDG and consumers before and during the guideline process that this terminology should be retained. We have removed the reference to the COCP in this section of the guideline as actually relates to metformin. This has resolved the issues raised here in per review

ID	Guideline recommendation to which feedback is targeted.	Comments	Guideline development group consensus response
1	General comment	In PCOS PTS under Ov.stimulation could be use both urinary and recombinant gonadotropin as well metformin to reduce eventually OHSS risk that however reduce by antagonist. Asking you evidence in the LETROZOL use to reduce OHSS risk Off label letrozol use confirmation by you if possible	The GDG considered the comment but unfortunately was unclear of the key recommendations this comment was on. As such the GDG decided to stay onto our original wordings.
12	5.2.1 CR In women with PCOS and infertility due to anovulation alone with normal semen analysis, the risks, benefits, costs and timing and techniques of tubal patency testing in relation to the cost and complexity of the treatment, should be discussed on an individual basis, depending on personal history and population prevalence, prior to starting ovulation induction with timed intercourse or intrauterine insemination.	40.5.2.1: Important to mention 1% risk of pelvic infection with HSG in consideration of decision to investigate tubal patency	Specific adverse effects of all therapies are not listed in the guideline.
14	5.5.1 EBR Gonadotrophins alone could be considered rather than clomiphene citrate in therapy naïve women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, clinical pregnancy and live birth rates.	Is it the recommendation that gonadotropins be first line agents for ovulation induction? This appears to be the conclusion of the statement above. Can this be clarified? Did not see a cost benefit analysis related to use of a more expensive regimen with increased risk of multiple gestation particularly in low resource countries.	This is a very legitimate point and was considered by the GDG. It is stated in 5.3.1 that letrozole is first line for ovulation induction in PCOS. In 5.5.1 gonadotrophins can be used in preference to clomiphene citrate in therapy naive women with PCOS according to the recommendation. The algorithm will clarify this. The points of consideration of cost and expertise is covered in PP 5.5.6
14	5.5.2 EBR Gonadotrophins combined with clomiphene citrate is not recommended over gonadotrophins alone in women with PCOS who are anovulatory and infertile with clomiphene citrate resistance or failure, and no other infertility factors.	see prior comment section 5.5.1	5.5.2 This recommendation applies to women with clomiphene citrate resistance or failure, and hence not first line.
14	5.5.6 PP Where gonadotrophins are to be prescribed, the following should be considered: •Cost of the intervention for ovulation induction. •Expertise required for the use of the intervention for ovulation induction. •The degree of intensive ultrasound monitoring that is required. •A low dose gonadotrophin protocol should be used to optimise the chance of monofollicular development. •Implications of potential multiple pregnancy.	should this be stated a "low dose step up gonadotropin protocol"? Most of the provided literature utilizes a step up protocol	5.5.6 The GDG considered and have amended the PP to "A low dose step up gonadotrophin protocol should be used..."
14	5.6.2 PP When using laparoscopic ovarian surgery, the following should be considered: •Comparative cost of the intervention for ovulation induction •Expertise required for the safe use of the intervention for ovulation induction •Both intraoperative and postoperative risks, which are higher in women who are above healthy weight •Multiple pregnancy in women who are above higher weight may exacerbate poor obstetric outcomes	Bullet point 3 and 4 appear to indicate opposite recommendations. The first suggests LOD is riskier in women above healthy weight and 4 suggests that LOD is better for women above healthy weight due to reduced multiple gestation. Is this the intention of bullet point 4? Clarification of language for recommendation of LOD needed	The interpretation of point 3 is correct. The GDG considered the comment and decided to delete bullet point 4.
35	5.4 Clomiphene citrate and Metformin	For Clomiphene Citrate, what about mentioning the potential oncological risks of many repeated cycles? Risk of cancer after assisted reproduction: a review of the available evidences and guidance to fertility counselors . Del Pup L. Eur Rev Med Pharmacol Sci. 2018 Nov;22(22):8042-8059.	The algorithm recommends to consider IVF after 6 cycles of ovulation induction and this will avoid the risk of cancer. More than 12 cycles of clomiphene citrate does not reflect modern practise. We have noted this in a PP
35	5.4.2 Clomiphene citrate vs metformin	For Clomiphene Citrate, what about mentioning the potential risk of many repeated cycles? Risk of cancer after assisted reproduction: a review of the available evidences and guidance to fertility counselors . Del Pup L. Eur Rev Med Pharmacol Sci. 2018 Nov;22(22):8042-8059.	The algorithm recommends to consider IVF after 6 cycles of ovulation induction and this will avoid the risk of cancer. More than 12 cycles of clomiphene citrate does not reflect modern practise. We have noted this in a PP
35	5.4.2.1 EBR Clomiphene citrate could be used in preference to metformin in women with PCOS with anovulatory infertility and no other infertility factors, to improve ovulation, clinical pregnancy and live birth rates.	For Clomiphene Citrate, what about mentioning the potential risk of many repeated cycles? Risk of cancer after assisted reproduction: a review of the available evidences and guidance to fertility counselors . Del Pup L. Eur Rev Med Pharmacol Sci. 2018 Nov;22(22):8042-8059.	The algorithm recommends to consider IVF after 6 cycles of ovulation induction and this will avoid the risk of cancer. More than 12 cycles of clomiphene citrate does not reflect modern practise. We have noted this in a PP
35	5.4.2.2 PP The risk of multiple pregnancy is increased with clomiphene citrate use and therefore clomiphene cycles will require ultrasound monitoring.	Previous comment	The algorithm recommends to consider IVF after 6 cycles of ovulation induction and this will avoid the risk of cancer. More than 12 cycles of clomiphene citrate does not reflect modern practise. We have noted this in a PP
40	5.4.3.1 EBR Clomiphene citrate combined with metformin could be used rather than clomiphene citrate alone in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation and clinical pregnancy rates.	Since ultrasound monitoring is recommended for clomiphene citrate induced cycles in 5.4.2.2 and 5.4.4.2, would you think it also needs to be mentioned here as 5.4.3.2 since the recommendation is about clomiphene and metformin vs clomiphene alone comparison. Both sides of the comparison involve clomiphene so mentioning ultrasound monitoring to avoid multiples would be relevant here as well.	We have modified PP 5.4.2.2 to "The risk of multiple pregnancy is increased with clomiphene citrate use (alone or in combination with metformin) and therefore clomiphene cycles will require ultrasound monitoring."
40	5.5.1 EBR Gonadotrophins alone could be considered rather than clomiphene citrate in therapy naïve women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, clinical pregnancy and live birth rates.	In countries where letrozole cannot be used for ovulation induction clomiphene is the default first line choice. While the guideline makes it clear that oral antiestrogens are the first line before gonadotropins, this recommendation when read in isolation sounds like gonadotropin should/could be the first choice if letrozole is not available.	It is stated in 5.3.1 that letrozole is first line for ovulation induction in PCOS. In 5.5.1 gonadotrophins can be used in preference to clomiphene citrate in therapy naive women with PCOS according to the recommendation. The algorithm will clarify this. The points of consideration of cost and expertise is covered in PP 5.5.6. A reference to 5.5.6 PP is added at the end of recommendation 5.5.1
40	5.5.5 EBR Gonadotrophins could be second line pharmacological therapy for women with PCOS who are anovulatory and infertile, with no other infertility factors and who have failed first line oral ovulation induction.	This follows my former comment on 5.5.1. The guideline is clear in overall recommendations, but when these are read in isolation, I suspect that 5.5.1 and 5.5.5 do not seem to reconcile. Maybe can be phrased differently. I have to say English is not my first language, and there is a chance that I may be missing a nuance.	5.5.1 refers to therapy naive women whereas 5.5.5 refers to those who had failed firstline ovulation induction, i.e. clomiphene resistance or failure
44	PP Prenatal vitamins supplementation should be commenced with ovulation induction therapy aligned to routine prenatal care	Should prenatal care be changed to pre-conception care, as folic acid needs to be started before conception. Dorney E, Black KI. Preconception care. Aust J Gen Pract. 2018 Jul;47(7):424-429. doi: 10.31128/AJGP-02-18-4485. PMID: 30114868. The addition of a 400-500 Âµg folic acid supplement in the preconception period has been shown to effectively prevent neural tube defects such as spina bifida and anencephaly.	Wordings are changed to "preconception care" as suggested.

44	PP There should be ongoing monitoring of patients for adverse effects and infants for congenital anomalies in all studies conducted with ovulation induction agents and these should be reported in any published papers	Should this specify the need to monitor for multiple follicle development and risk of multiple birth if more than one oocyte is ovulated? doi: 10.31128/AJGP-08-22-6512 see table 2 ovulation induction risks	PP in p34 - The wordings are deliberately broad to cover all types of adverse effects and not just multiple birth/pregnancies.
44	5.1.2 CR Consistent with routine preconception care, in women with PCOS planning pregnancy, weight, blood pressure, smoking, alcohol, nutritional status, exercise, sleep and mental, emotional and sexual health should be considered and optimised to improve reproductive and pregnancy outcomes and overall health.	Add diet and nutritional status Diet is the food consumed and nutrition is what comes from the food we eat. May be easier for patients to understand if the word diet is used inconjunction with nutrition.	Agree. Wordings in 5.1.2 are changed.
54	5.7.3.1 CR Either urinary or recombinant FSH can be used in women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, with insufficient evidence to recommend a particular type of FSH preparation.	It is a minor comment. According to ICMART Glossary, it is not recommended to use the term "controlled" ovarian "hyper" stimulation but just ovarian stimulation. I see you have them in parenthesis and I do not know what it signifies, so possibly my comment could be superfluous. ICMART Glossary	The GDG has considered the comment. The added parenthesis cover all ways of saying COH in the literature including ICMART definition.
105	5.9 Anti-obesity pharmacological agents	liraglutide is already discussed above (4.5.1).	This section in Chapter 5 focuses on anti-obesity agents and reproductive outcomes.
105	5.8. Inositol	Already discussed above (4.7).	This section in Chapter 5 focuses on inositol and reproductive outcomes.
107	5.1.2 CR Consistent with routine preconception care, in women with PCOS planning pregnancy, weight, blood pressure, smoking, alcohol, nutritional status, exercise, sleep and mental, emotional and sexual health should be considered and optimised to improve reproductive and pregnancy outcomes and overall health.	Please consider adding in a recommendation for using folate 5mg for women with BMI > 30 kgm2	Wordings in 5.1.2 are changed.
107	5.1.5 PP Chronic conditions such as diabetes, high blood pressure, anxiety, depression and other mental health conditions, should be optimally managed and women should be counseled regarding the risk of adverse pregnancy outcomes.	Please consider adding in a comment guiding 'optimally managed' diabetes. For example, HbA1c < 6.0%	The GDG has considered the comment but this is out of the scope of the PCOS guideline.
107	5.2.1 CR In women with PCOS and infertility due to anovulation alone with normal semen analysis, the risks, benefits, costs and timing and techniques of tubal patency testing in relation to the cost and complexity of the treatment, should be discussed on an individual basis, depending on personal history and population prevalence, prior to starting ovulation induction with timed intercourse or intrauterine insemination.	Not checking tubal patency before ovulation induction regimens and costs to the patient both in dollars and angst seems leaving both the clinician and the patient open to regret.	This is already taken into account in the recommendation. No wordings are changed.
107	5.3 Aromatase Inhibitors	The heading in the main body of the guideline should be Aromatase Inhibitors and not Letrozole (as it is in the title of the recommendations)	The heading is changed to "Letrozole"
107	5.3 Aromatase Inhibitors in the background section in p103	The comment that the action of Letrozole is unknown seems surprising when considering the physiological actions of aromatase inhibitors	The wording is altered to "not fully eluciadated"
107	5.3.1 EBR Letrozole should be considered the first line pharmacological treatment for ovulation induction in infertile anovulatory women with PCOS, with no other infertility factors.	Letrozole is considered the superior oral ovulation induction agent, yet there are a lot more subheadings for clomiphene	The format of the guideline is framed around the clinical questions and the interventions being compared.
107	5.3.1 EBR Letrozole should be considered the first line pharmacological treatment for ovulation induction in infertile anovulatory women with PCOS, with no other infertility factors.	It might be more useful to have the one subheading "oral ovulation induction agents" and then list: Letrozole superior Off-label and may not be available Clomiphene an alternative Clomiphene +/- metformin etc etc Metformin alone	The format is related to the clinical questions and the interventions being compared. This is also covered in the algorithm
107	5.4.1.1 EBR Metformin could be used alone, in women with PCOS with anovulatory infertility and no other infertility factors, to improve clinical pregnancy and live birth rates, although women should be informed that there are more effective ovulation agents.	There is evidence that metformin reduces the risk of early miscarriage, as well as other benefits. (Ref Zhao Gynecol Endocrinol 202238:7, 558-568) which might support its use during pregnancy	Extensive evidence synthesis as outlined in the guideline and technical report, overall did not support the general use of metformin in pregnancy and is covered in GDG4.
107	5.5 Gonadotrophins	This section is not concise enough and not in the correct order	Format is determined by the clinical questions.
107	5.5 Gonadotrophins	Clinicians may not be aware of the difference between low dose ovulation induction with gonadotrophins aiming for monofollicular growth vs higher dose gonadotrophins in controlled ovarian hyperstimulation prior to IVF/ICSI (Ref van der Meer M et al, Fertil Steril. 1996 Oct;66(4):571-6) An option would be changing the subheading to Gonadotrophins for ovulation induction (Mon-follicular growth). This will set it apart from IVF/IVM sections which use higher dose gonadotrophin for controlled ovarian hyperstimulation	Considered by the GGD and no change made
107	5.5 Gonadotrophins	Gonadotrophins alone could be considered rather than clomiphene citrate in therapy naïve women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, clinical pregnancy and live birth rates.	Considered by the GDGD and no change made
107	5.5 Gonadotrophins	Why is there no comparison of Gonadotrophins to letrozole which is the "gold standard" oral option?	Where no studies comparing two agents, it is not noted here. This is detailed in the technical document where all comaprisons are noted in pages 5258 onwards
107	5.5.5 EBR Gonadotrophins could be second line pharmacological therapy for women with PCOS who are anovulatory and infertile, with no other infertility factors and who have failed first line oral ovulation induction.	This should be the first statement in this section, followed by Point 5.5.6. It would flow more logically Subsequent order 5.5.2, 5.5.3, 5.5.4 – can these be condensed these to one point?	This was reviewed by the GDG and was retained as format is determined by the clinical questions
107	5.5.8 PP When using gonadotrophins, best clinical practice is to avoid multiple pregnancy. Considerations here include cancelling cycles when there is more than a total of two follicles greater than 14mm in diameter and advising avoidance of unprotected intercourse.	This is essentially a repeat point from 5.5.6 – perhaps state in dot point 4 of 5.5.6 to "...optimise monofollicular development and cancel cycle if this is not achieved" and delete 5.5.8	This was reviewed by the GDG and was retained
107	5.5.9 PP Live birth rate, clinical pregnancy rate per patient and ovulation rate per cycle are higher with gonadotrophins than with clomiphene citrate	This is essentially repeating point 5.5.1	This was reviewed by the GDG and was retained
107	5.5.10 PP A low dose gonadotrophin protocol should be used to optimise the chance of monofollicular growth and multiple pregnancy	• Again repeating 5.5.8 and 5.5.6 regarding monofollicular growth • Should it read minimise multiple pregnancy??	5.5.10 has been modified to " A low dose gonadotrophin protocol should be used to optimise the chance of monofollicular growth and minimise multiple pregnancy.