National Institute for Health and Care Excellence

Polycystic Ovary Syndrome

Adaptation report 4 – Management of non-fertility features

NICE guideline [NGXX]

July 2026

Draft for Consultation

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The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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1

Contents

4 Management of non-fertility features

The adaptation reports were produced using the reviews from the International Guideline (IG). Any further details can be found in the technical report from the IG, including results of the analyses and full study references.

4.1 Pharmacological treatment principles in PCOS

4.1.1 Recommendations from the International evidence-based guideline for PCOS*

Practice points:

- Shared decision making between the patient (and parent/s or guardian/s, if the patient is a child) and the healthcare professional is required.
- An individual's characteristics, preferences and values must be elicited and considered when recommending any intervention alone or in combination.
- Understanding how individual adults and adolescents value treatment outcomes is essential when prescribing medications.
- Medical therapy is generally not approved for use specifically in PCOS and recommended use is therefore evidence-based, but off-label. Healthcare professionals need to inform adults, adolescents and their parents/s or guardian/s and discuss the evidence, possible concerns and side-effects. Regulatory agencies should consider approval of evidence-based medications for use in PCOS.

IG clinical evidence

There was no evidence review for these clinical practice points, therefore there is no ROBIS assessment for this review.

IG economic evidence

No health economic evidence was identified in the IG for review question 4.1 on pharmacology treatment principles in PCOS.

4.1.2 NICE economic evidence

Included studies

A single health economic search was performed by NICE to identify published economic evaluations of relevance to all review questions in this guideline. See the literature search strategy in Appendix A.

No economic studies were identified which were applicable to this review question (see economic study selection flow chart in Appendix B)

Excluded studies

No economic studies were reviewed at full text and excluded from this review.

Economic model

No original health economic modelling was conducted for review question 4.1 as the committee agreed that pharmacological treatment principles are already covered in NICE's existing guidelines (such as patient experience and shared decision making).

4.1.3 NICE recommendations

No recommendations have been contextualised from this section of the IG.

4.1.4 The committee's discussion and interpretation of the evidence

Clinical evidence

The committee agreed that recommendations would be contextualised into one overall section on management of PCOS. This would be consistent with other NICE guidelines where the guideline is structured to follow the patient pathway.

Health economic

No health economic evidence was identified in the IG, or as part of NICE's original health economic literature search for review question 4.1 on pharmacology principles in PCOS.

The committee acknowledged that the majority of the practice point recommendations listed in the IG recommendations for section 4.1 are already covered by existing NICE guidance. This guidance was cross-referred and none of the IG's recommendations were contextualised. As no recommendations were contextualised there are no health economic implications associated with this review question.

4.2 Oral contraceptive pill alone or in combination

Review question 4.2: Is the oral contraceptive pill alone or in combination effective for management of hormonal and clinical PCOS features in adolescents and adults with PCOS?

4.2.1 Recommendations from the International evidence-based guideline for PCOS*

Evidence-based recommendation:

4.2.1 The combined oral contraceptive pill (COCP) could be recommended in reproductive age adults with PCOS for management of hirsutism and/or irregular menstrual cycles.

4.2.2 The COCP could be considered in adolescents at risk or with a clear diagnosis of PCOS for management of hirsutism and/or irregular menstrual cycles.

4.2.3 Health professionals could consider that there is no clinical advantage of using high dose ethinylestradiol (≥ 30 µg) versus low dose ethinylestradiol (< 30 µg) when treating hirsutism in adults with PCOS.

4.2.4 General population guidelines should be considered when prescribing COCP in adults and adolescents with PCOS as specific types or doses of progestogens, estrogens or combinations of COCP cannot currently be recommended.

4.2.5 The 35 µg ethinyl estradiol plus cyproterone acetate preparations should be considered as second-line therapy over other COCPs, balancing benefits and adverse effects, including venous thromboembolic risks.

4.2.6 Progestogen only oral contraceptives may be considered for endometrial protection, based on general population guidelines, acknowledging that evidence in women with PCOS is limited.

Practice points:

4.2.7 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.

IG clinical evidence

Critical Appraisal - ROBIS systematic review checklist

Section	Question	Answer
Study eligibility criteria	Did the review adhere to pre-defined objectives and eligibility criteria?	Probably yes *(Unclear if protocol is published prior to review but the protocol has well-defined criteria).*
Study eligibility criteria	Were the eligibility criteria appropriate for the review question?	Yes *(Detailed eligibility criteria appropriate for the question).*
Study eligibility criteria	Were eligibility criteria unambiguous?	Yes *(There was no ambiguity in the criteria).*
Study eligibility criteria	Were all restrictions in eligibility criteria based on study	Yes *(As it was pharmacological intervention,*

Section	Question	Answer
	characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	*they limited the date of searches to the last 20 years 'given change in doses and progestogens over time.' High quality studies were included (RCTs, SRs and evidence-based guidelines), which is appropriate for pharmacological interventions).*
Study eligibility criteria	Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Yes *(Only limit was on English language, which is appropriate).*
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low *(All questions scored as yes and one as probably yes, eligibility criteria was clear, detailed and appropriate)*.
Identification and selection of studies	Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Probably no *(Some suitable databases used, additional references harvested from other SRs. However, lack of inclusion of trial registries).*
Identification and selection of studies	Were methods additional to database searching used to identify relevant reports?	Yes *(Reference list checking present).*
Identification and selection of studies	Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	No *(Drugs were searched for at class level (e.g. "oral contraceptive") but terms for individual agents (e.g. oestrogen, progestogen) were absent, RCT filter missing truncation on "random").*
Identification and selection of studies	Were restrictions based on date, publication format, or language appropriate?	Probably Yes *(English language limit applied, lack of information regarding search dates, only referencing 2017 search strategies)*
Identification and selection of studies	Were efforts made to minimise error in selection of studies?	Yes *(Study selection was carried out by two reviewers)*.
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	High *(RCT filter is inaccurate, individual drug terms missing, lack of clear information for databases other than Medline).*

Section	Question	Answer
Data collection and study appraisal	Were efforts made to minimise error in data collection?	Probably yes *(Selection and appraisal was conducted by two independent reviewers – it does not clearly state who carried out data extraction).*
Data collection and study appraisal	Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Probably yes *(There were no study extractions within the report but there is a summary of studies included that gives basic details of the studies. The results are provided for each study).*
Data collection and study appraisal	Were all relevant study results collected for use in the synthesis?	Yes *(PRISMA diagram states 85 included studies and references show 85 included, whereas the text states 84 RCTs included. Table of included studies also has 85 listed studies so assume the 84 in the text is a typo).*
Data collection and study appraisal	Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	No information *(The GRADE tables show risk of bias was assessed but there are no risk of bias extractions shown for the individual studies, so we do not know what was used to assess risk of bias).*
Data collection and study appraisal	Were efforts made to minimise error in risk of bias assessment?	Yes *(Two independent reviewers appraised the studies).*
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Unclear *(Most of the questions scored yes or probably yes. Risk of bias was assessed but we do not know how or why studies may have been downgraded because there are no study extractions).*
Synthesis and findings	Did the synthesis include all studies that it should?	Yes *(All studies were included in the analysis based on the comparisons reported).*
Synthesis and findings	Were all pre-defined analyses reported or departures explained?	Probably yes *(All analyses mentioned and addressed in the results section. All necessary analysis (narrative analyses and meta-analyses) were carried out to include all of the studies).*

Section	Question	Answer
Synthesis and findings	Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Yes *(The synthesis was appropriate. Only RCTs were included, they were analysed according to the appropriate comparison and individual outcome).*
Synthesis and findings	Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Probably yes *(Random effects model is used for all meta-analysed comparisons. The authors state subgroup analysis was also conducted where possible, with adults, smokers, and adolescents being pre-specified subgroups).*
Synthesis and findings	Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Yes *(Funnel plots are given for all of the meta-analysed comparisons).*
Synthesis and findings	Were biases in primary studies minimal or addressed in the synthesis?	Probably yes *(GRADE was carried out).*
Synthesis and findings	Concerns regarding the synthesis and findings	Low *(Most questions scored yes or probably yes).*
Judging risk of bias	Concerns regarding specification of study eligibility	Low *(All questions scored as yes and one as probably yes, eligibility criteria was clear, detailed and appropriate).*
Judging risk of bias	Concerns regarding methods used to identify and/or select studies	High *(RCT filter is inaccurate, individual drug terms missing, lack of clear information for databases other than Medline).*
Judging risk of bias	Concerns regarding methods used to collect data and appraise studies	Unclear *(Most of the questions scored yes or probably yes. Risk of bias was assessed but we do not know how or why studies may have been downgraded because there are no study extractions).*
Judging risk of bias	Concerns regarding the synthesis and findings	Low *(Most questions scored yes or probably yes).*
Overall review ratings	Overall risk of bias	Low *(Some issues with risk of bias due to unclear reporting of downgrading and issues with search strategy).*

Section	Question	Answer
Overall review ratings	Applicability as a source of data	Fully applicable

IG evidence to recommendations justification: 84 studies were included in this new systematic review. Thirty-two comparisons were undertaken comparing the combined oral contraceptive pill (COCP) with a variety of other medications such as progestogen, lifestyle factors and anti-obesity treatment, and metformin.

The following comparisons had a GRADE evidence certainty of very low:

- Comparison 3: COCP with 1st vs. COCP with 3rd generation progestogen
- Comparison 4: COCP with 1st vs. COCP with 4th generation progestogen
- Comparison 5: COCP with 2nd vs. COCP with 3rd generation progestogens
- Comparison 6: COCP with 2nd vs. COCP with 4th generation progestogens
- Comparison 7: COCP with 3rd vs. COCP with 4th generation progestogens
- Comparison 9: COCP vs. progestogen
- Comparison 10: COCP vs. controls
- Comparison 11: COCP vs. placebo
- Comparison 12: COCP vs lifestyle
- Comparison 13: COCP vs. lifestyle +/- anti-obesity treatment
- Comparison 14: COCP vs. combination of COCP and lifestyle with/without anti-obesity treatment
- Comparison 15: lifestyle +/- anti-obesity treatment vs. combination of COCP and lifestyle +/- anti-obesity treatment
- Comparison 16: COCP vs. anti-obesity
- Comparison 17: COCP vs. COCP + anti-obesity
- Comparison 18: COCP + metformin vs. COCP + anti-obesity
- Comparison 19: COCP vs. COCP + metformin + anti-obesity
- Comparison 20: COCP vs. metformin (also incl. in Q4.3)
- Comparison 22: COCP vs. anti-androgen (also in Q4.6, but their time limit 6 m treatment)

- Comparison 23: COCP vs. COCP + antiandrogen androgen (also in Q4.6, with time limit of 6m)
- Comparison 24: COCP vs. metformin +anti-androgen androgen (also in Q4.6, with time limit of 6m)
- Comparison 25: COCP +anti-androgen vs. metformin androgen (also in Q4.6, with time limit of 6m)
- Comparison 26: COCP + anti androgen vs. COCP + anti androgen + metformin + androgen
- Comparison 27: COCP + anti-androgen vs. COCP + metformin androgen
- Comparison 28: COCP vs. COCP + metformin + anti-androgen androgen (also in Q4.6)
- Comparison 29: COCP vs. SPIOMET (=metformin + anti-androgen + glucose sensitizer) (also in Q4.6)
- Comparison 32: COCP + met vs. EE/CPA + met

The following comparisons had a GRADE evidence certainty of low:

- Comparison 1: COCP with high vs. COCP with low levels of estrogen
- Comparison 8: COCP vs. EE/CPA
- Comparison 21: COCP vs. COCP + metformin

The following comparison had a GRADE evidence certainty of moderate:

- Comparison 23: COCP vs. COCP + antiandrogen androgen (also in Q4.6, with time limit of 6m)

The following comparison had no evidence available:

- Comparison 2: COCP with 1st vs. COCP with 2nd generation progestogen

The outcomes for these comparisons were reported elsewhere in the guideline:

- Comparison 30: COCP + AA1 vs. COCP + AA2 (reported in Q4.6)

- Comparison 31: Metformin vs COCP + metformin (reported in Q4.3)

The evidence from review question 4.2 formed six evidence-based recommendations. All were conditional weak recommendations for the option. Recommendation 4.2.3 was made based on two RCTs that took place over a 12-month period and had a low risk of bias, this comparison found that there was no significant difference for outcomes including hirsutism with high or low levels of oestrogen. This supports the recommendation which highlights to healthcare professionals that there is no clinical advantage of using a higher dose oestrogen.

Recommendation 4.2.4 was based on evidence from comparison 5, which looked at 2nd and 3rd generation progestogens, levonorgestrel and desogestrel. The crossover study found a greater decrease in free androgen index (FAI) and an increase in sex hormone-binding globulin (SHBG) after desogestrel use, however it had a very low certainty of evidence. There was no difference between groups for any other outcomes including hirsutism, side effects of the medication were also not reported on. Comparison 6 compared 2nd generation progestogens (levonorgestrel) with 4th generation progestogens (drospirenone) however, as in comparison 5, evidence was very low quality, and the studies did not report on side effects. Comparison 7 looked at 3rd versus 4th generation progestogens, despite some slight improvements noted with 4th generation progestogens, none of these were clinically significant and had very low certainty of evidence. As such the IG made a recommendation that stated general population guidelines should be followed when prescribing COCP for adults with PCOS as there was insufficient evidence to make recommendations on the use of specific types of progestogens.

Comparison 8 provided evidence for recommendation 4.2.5, which states that ethinyl oestradiol (EE) plus cyproterone acetate (CPA) should be considered second line therapy over other COCPs. This comparison included 10 RCTs, covering time periods between 3 and 12 months, with 2 studies including adolescents. The meta-analysis found the combination of EE/CPA had a beneficial effect with lower BMI and total testosterone; however, it resulted in higher LDL levels and higher cholesterol

levels. This was very low certainty evidence. In a subgroup analysis in adults, lower total testosterone levels were seen. This was not seen in adolescents. No difference in SHBG levels was seen between treatments for either adults or adolescents. All evidence was either low or very low certainty. Side effects were reported in some of the studies. As such the recommendation was made to use EE/CPA as a second line treatment, bearing in mind the potential adverse effects.

Comparison 10 provided evidence for recommendations 4.2.1 and 4.2.2 which state that COCP could be recommended in women and adolescents with PCOS for management of hirsutism and/or irregular menstrual cycles. This was based on evidence from 3 RCTs where COCP was superior to controls in 301 subjects. Improvements were seen in cycle regularity, health-related quality of life, weight, testosterone and insulin levels. Less adverse effects were reported with COCP than controls, however adolescents reported an increase in weight. Comparison 11 also looked at COCP versus placebo in adolescents and found lower levels of testosterone, higher SHBG and lower FAI with only mild side effects reported. As such the IG considered this evidence to be sufficient to recommend the use of COCP in women with PCOS for either hirsutism and/or irregular menstrual cycles, which seems appropriate.

Comparison 17 covers the use of EE+ CPA + orlistat, there were 3 RCTs, with a total of 349 participants. Results showed lower dehydroepiandrosterone sulphate (DHEAS), free androgen index (FAI) and homeostatic model assessment of insulin resistance (HOMA-IR) with no difference for all other outcomes. The evidence was of low/very low certainty. The data from comparison 17 did not contribute to the evidence-based recommendations.

The IG noted that the availability of different COCP combinations could be aa potential barrier to implementation. They also state that metabolic risk monitoring should be considered. Large scale studies for side effects in women with PCOS with COCP should be considered for future research, as should use and dose of

progestogens, efficacy of COCP on acne, hair loss and psychological outcomes should also be considered for research priorities.

IG economic evidence

No health economic evidence was identified in the IG on the combined oral contraceptive pill (COCP).

The IG noted that costs for the COCP vary according to preparation. The IG also noted that there is no evidence on the cost effectiveness of the COCP for management of PCOS but acknowledged that the cost of the COCP is generally low.

4.2.2 NICE economic evidence

Included studies

A single health economic search was performed by NICE to identify published economic evaluations of relevance to all review questions in this guideline. See the literature search strategy in Appendix A.

No economic studies were identified which were applicable to this review question (see economic study selection flow chart in Appendix B)

Excluded studies

No economic studies were reviewed at full text and excluded from this review.

Economic model

No original health economic modelling was conducted for review question 4.2 on the oral contraceptive pill as other areas were identified as a higher priority. The committee also noted that the recommendations in the IG were largely reflective of UK current practice.

Unit costs

Table 1: Unit costs for the combined oral contraceptive pill

Resource	Unit costs per unit
Ethinylestradiol 30 microgram, Levonorgestrel 150 microgram	£0.04
Drospirenone 3 mg, Estetrol (as Estetrol monohydrate) 14.2 mg	£0.31
Estradiol (as Estradiol hemihydrate) 1.5 mg, Nomegestrol acetate 2.5 mg	£0.24
Desogestrel 150 microgram, Ethinylestradiol 20 microgram	£0.09
Desogestrel 150 microgram, Ethinylestradiol 30 microgram	£0.08
Drospirenone 3 mg, Ethinylestradiol 20 microgram	£0.18
Drospirenone 3 mg, Ethinylestradiol 30 microgram	£0.23
Ethinylestradiol 20 microgram, Gestodene 75 microgram	£0.14
Ethinylestradiol 30 microgram, Gestodene 75 microgram	£0.11
Ethinylestradiol 35 microgram, Norethisterone 500 microgram	£0.03
Ethinylestradiol 35 microgram, Norethisterone 1 mg	£0.04

Source of costs; British National Formulary (BNF); date accessed 07/05/2025. Dosing is one tablet a day.

4.2.3 NICE recommendations

The relevant recommendations for this section are Rec 1.10.1 to 1.10.3 and 1.11.1 to 1.11.10.

4.2.4 The committee's discussion and interpretation of the evidence

Clinical

The committee discussed that all approaches to offering contraceptive medication options to people with PCOS should follow a personalised approach, including

highlighting the benefits and harms of medications such as the combined oral contraceptive pills. The committee also felt it might be useful to link to the UK Medical Eligibility Criteria for Contraceptive Use (UKMEC) guidance here. This was to provide a structured tool to aid decision-making for prescribing COCPs, taking into account various risk factors. As such a cross referral to this guidance was added to the recommendations as this described the criteria for prescribing COCP.

The committee agreed with the IG that COCP should be considered for people who had irregular menstrual cycles and hirsutism. IG recommendations 4.2.1 (on adults) and 4.2.2 (for adolescents) were contextualised in the NICE guideline into two separate sections, one for irregular or absent menstrual cycles and the other for hirsutism.

The committee discussed the dosage of ethinyl oestradiol, largely agreeing that 30 micrograms was not classed as a high dose in the UK, and was routinely used in current practice. The committee agreed that a recommended starting dose of 20-30 micrograms should be used to allow clinical judgement to be used. The committee discussed the increased risk of blood clots with increased doses of COCP, questioning whether 35 micrograms represented a higher risk than 30 micrograms. As such the committee agreed to contextualise IG recommendation 4.2.3 emphasising that the lowest effective dose of ethinylestradiol should be the starting point for this medication. The committee also raised that regular monitoring was important for people with PCOS taking COCP medication. They acknowledged that women on long term medication would already be receiving an annual review but wished to highlight the importance of the annual review to women with PCOS, and which aspects were important to be covered at the review, such as signs and symptoms, their concerns, medicine use and any long-term risks of other conditions associated with PCOS. For further information on this recommendation please see adaptation report 1, section 1.8. The committee noted that there are COCPs which contain estetrol rather than estradiol which committee members commented might be preferable for people with PCOS. Committee members were keen to ensure that

wording of the recommendation be inclusive of these options and not limited to those medicines containing estradiol. As such, NICE recommendation 1.10.2 states to offer the lowest effective dose of oestrogen, with ethinylestradiol given as an example. As such this cross referral was added to NICE recommendation 1.9.2.

The committee discussed IG recommendation 4.2.6 regarding the use of progestogen-only contraceptives. The committee felt that progestogen-only medications were an important option for people who cannot tolerate the COCP, or in whom COCP are contraindicated. As such this recommendation was contextualised to include the various types of progestogen-only medications and their value in people with prolonged amenorrhoea where endometrial protection is a concern.

The committee decided to contextualise IG recommendation 4.2.5, to allow the use of co-cyprindiol when COCP, self-management or both, were ineffective after 6 months of use. This treatment option was felt to only be relevant to hirsutism rather than irregular cycles, and as such has been included in the section around hirsutism only.

Health economic

No health economic evidence was identified in the IG, or as part of NICE's original health economic literature search on the oral contraception pill. Unit costs were presented to the committee to aid consideration of cost-effectiveness (**Table 1**).

The committee noted that all recommendations made in relation to the combined oral contraceptive pill are reflective of current practice and therefore no significant resource impact is anticipated.

4.3 Metformin

Review question 4.3: Is metformin effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?

4.3.1 Recommendations from the International evidence-based guideline for PCOS*

Evidence-based recommendation:

4.3.1 Metformin alone should be considered in adults with PCOS and a BMI ≥ 25 kg/m^2 for anthropometric, and metabolic outcomes including insulin resistance, glucose, and lipid profiles.

4.3.2 Metformin alone could be considered in adolescents at risk of or with PCOS for cycle regulation, acknowledging limited evidence.

Consensus recommendation:

4.3.3 Metformin alone may be considered in adults with PCOS and BMI < 25 kg/m^2, acknowledging limited evidence.

Practice point(s):

4.3.4 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 500 mg increments 1-2 weekly and extended-release preparations may minimise side-effects and improve adherence.
- Suggested maximum daily dose is 2.5 g in adults and 2 g 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.

IG clinical evidence

Critical Appraisal - ROBIS systematic review checklist

Section	Question	Answer
Study eligibility criteria	Did the review adhere to pre-defined objectives and eligibility criteria?	Probably yes *(No predefined objectives identified. PICOS is well defined)*
Study eligibility criteria	Were the eligibility criteria appropriate for the review question?	Probably yes *(Clearly defined PICOS)*
Study eligibility criteria	Were eligibility criteria unambiguous?	Probably no *(Appropriate inclusion and exclusion criteria according to the research question. However, inclusion criteria for comparator is 'placebo or any other listed intervention or their combination', which looks similar to the exclusion criteria for comparator 'Agent or combination used in the intervention')*
Study eligibility criteria	Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Yes *(This was a new systematic review. There was no time limit)*
Study eligibility criteria	Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Yes *(This is a new systematic review. Limits are applied based on English language which is appropriate)*
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low

Section	Question	Answer
		(Some areas would benefit from further explanation however no major issues noted)
Identification and selection of studies	Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Probably yes *(Sources are similar to the bibliographic databases used at NICE and additional references were obtained from other systematic reviews. However, trial registries could have also been included)*
Identification and selection of studies	Were methods additional to database searching used to identify relevant reports?	Yes *(Reference list checking only)*
Identification and selection of studies	Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	No *(RCT filter missing truncation on "random". No details on how searches were translated beyond Medline)*
Identification and selection of studies	Were restrictions based on date, publication format, or language appropriate?	Probably yes *(Limited to English language only but this is appropriate. Unable to tell if date restrictions have been applied correctly (by entry date rather than publication date) because the updated searches are not presented, only a reference to the 2017 versions)*
Identification and selection of studies	Were efforts made to minimise error in selection of studies?	Yes *(Study selection was carried out by two reviewers)*
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	High *(Search is the same as for Q4.2 with largely the same limitations. There is a typo in the RCT filter, plus a lack of transparency on search translations)*
Data collection and study appraisal	Were efforts made to minimise error in data collection?	Probably yes *(States that screening was carried out by two reviewers alongside the reviewing team. Does not clearly state who or how many reviewers carried out data extraction)*

Section	Question	Answer
Data collection and study appraisal	Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Probably yes *(The general study characteristics table is not given maybe because of the number of studies. However, the results section groups the studies based on the outcomes. And gives the outcome based statistical data for each study for a particular outcome)*
Data collection and study appraisal	Were all relevant study results collected for use in the synthesis?	Yes *(Study characteristics table sufficiently detailed)*
Data collection and study appraisal	Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Yes *(Risk of bias was included in summary tables for each study. Each study had a quality appraisal form completed)*
Data collection and study appraisal	Were efforts made to minimise error in risk of bias assessment?	Probably yes *(Does not clearly states how many reviewers assessed the quality)*
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low *(Methods are appropriate for review)*
Synthesis and findings	Did the synthesis include all studies that it should?	Yes *(All studies were included in the analysis)*
Synthesis and findings	Were all pre-defined analyses reported or departures explained?	Yes *(All analyses are mentioned and addressed in the results section. All necessary analyses (narrative analyses and meta-analyses) were carried out to include all of the studies)*
Synthesis and findings	Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Yes *(Study design and analyses are appropriate for review)*
Synthesis and findings	Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Yes *(No heterogeneity issues raised)*
Synthesis and findings	Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Probably yes *(Funnel plots are given for all of the meta-analysed comparisons)*

Section	Question	Answer
Synthesis and findings	Were biases in primary studies minimal or addressed in the synthesis?	Probably yes *(GRADE assessments were carried out)*
Synthesis and findings	Concerns regarding the synthesis and findings	Low *(Bias has been taken into account but further write up about this could have been useful)*
Judging risk of bias	Concerns regarding specification of study eligibility	Low *(some areas would benefit from further explanation however no major issues noted)*
Judging risk of bias	Concerns regarding methods used to identify and/or select studies	High *(Search is the same as for Q4.2 with largely the same limitations. There is a typo in the RCT filter, plus a lack of transparency on search translations)*
Judging risk of bias	Concerns regarding methods used to collect data and appraise studies	Low *(Methods are appropriate for review)*
Judging risk of bias	Concerns regarding the synthesis and findings	Low *(Bias has been taken into account but further write up about this would have been useful)*
Overall review ratings	Overall risk of bias	Low *(minor issues noted with lack of detailed explanations, however mostly well described)*
Overall review ratings	Applicability as a source of data	Fully applicable

IG evidence to recommendations justification: Section 4.3 has two EBRs, both of which are a conditional weak recommendation for the option. Evidence from 23 RCTs found that in adult women with PCOS, BMI reduction and improved metabolic outcomes were seen when 1-2g per day doses of metformin were taken. When used in combination with lifestyle improvements, metformin also saw improvements in

testosterone and menstrual cycles, however no significant improvement for hirsutism was seen. Metformin was also superior to placebo at decreasing FAI in women with a BMI <25 kg/m^2. Side effects were not well reported across the studies used, however women taking metformin reported more gastrointestinal side effects that those taking a placebo. This supports EBR 4.3.1 which states metformin should be considered for the specified outcomes. Two studies reported on adolescents, however only one of these studies was suitable for meta-analysis. The results of the meta-analysis found metformin to be superior at improving testosterone and HDL and cycle regulation, however certainty was low due to small sample size. As such a cautious recommendation (4.3.2) was made which highlights metformin can be used in adolescents but to be aware that the evidence was limited.

IG economic evidence

No health economic evidence was identified in the IG for review question 4.3 on metformin for effective management of hormonal and clinical PCOS features.

The IG noted that lifestyle intervention may be expensive to women and health systems, as in healthy food, and metformin is low in cost. Overall, the IG noted there was no clear evidence of cost-effectiveness of providing metformin.

4.3.2 NICE economic evidence

Included studies

A single health economic search was performed by NICE to identify published economic evaluations of relevance to all review questions in this guideline. See the literature search strategy in Appendix A.

No economic studies were identified which were applicable to this review question (see economic study selection flow chart in Appendix B).

Excluded studies

No economic studies were reviewed at full text and excluded from this review.

Economic model

No original health economic model was developed for review question 4.3 on metformin as the committee agreed that other areas of the guideline were of a higher priority for original health economic modelling.

Unit costs

Table 2: Unit costs for metformin

Resource	Unit costs per unit
Metformin 500mg	£0.03
Metformin 500mg modified release	£0.07
Metformin 1g	£0.22
Metformin 1g modified release	£0.03

Source of costs; British National Formulary, date accessed 29/04/2026. Dosing is typically up to a maximum dose of 2g a day.

4.3.3 NICE recommendations

The relevant recommendations for this section are Rec 1.12.1 and 1.12.2.

4.3.4 The committee's discussion and interpretation of the evidence

Clinical

Section 4.3 of the IG regarding the use of metformin, was discussed in detail. The committee acknowledged that metformin could improve various outcomes, such as anthropometric and metabolic features of PCOS. As such IG recommendation 4.3.1 was contextualised into the NICE guideline to advise on metformin use in women with PCOS with a BMI above 25 kg/m^2. Practice point 4.3.4 was also partially contextualised here to add information on starting at a low dose with 500mg increments 1-2 weekly but with a maximum dosage of 2g per day (rather than 2.5g in adults and 2g in adolescents in the IG) and to suggest considering starting with a modified-release (UK terminology rather than an extended-release) of metformin to aid adherence and tolerance to the medication.

Health economic

No health economic evidence was identified in the IG, or as part of NICE's original health economic literature search for this review question. Unit costs were presented to the committee to aid consideration of cost-effectiveness (**Table 2**).

The committee discussed that metformin is not commonly prescribed to people with PCOS. It was acknowledged that this is due to various factors such as, a lack of awareness that it can be prescribed to people with PCOS, concerns relating to the potential gastrointestinal side effects of metformin and the lack of information on which symptoms it may be effective at treating for those with PCOS. The committee acknowledged that, although the cost of metformin is relatively cheap £0.03 - £0.07 per day (see **Table 2** for further information), if all women with PCOS were prescribed metformin this would result in a significant resource impact for the NHS due to the size of the population with PCOS. The committee therefore considered the potential resource implications alongside the IG recommendations and clinical evidence when discussing the cost-effectiveness of metformin.

The committee decided to contextualise one of the two EBR for metformin, however they also made edits to this recommendation to reflect the limited benefits of prescribing metformin for weight loss and lipid benefits. Ultimately the committee recommended that metformin could be considered for those who are over 18 for metabolic health benefits (particularly if they have metabolic syndrome, impaired glucose tolerance or BMI of 25 kg/m^2 or more). The other EBR in the IG was for adolescents, but the committee concluded that there was not sufficient clinical evidence to demonstrate cost-effectiveness in this population.

The committee acknowledged that the recommendations made for this review question are reflective of best clinical practice. This recommendation may result in additional costs to the NHS, but the committee emphasised that because the recommendation is a consider recommendation and is only focused on a sub-population of those with PCOS, it is unlikely to result in a significant resource impact for the NHS.

The committee also discussed the potential for gastrointestinal side-effects with metformin and noted that this medication is off label for PCOS. The committee therefore partially contextualised recommendation 4.3.4 to provide information on the dosing of metformin, also noting a preference for modified-release preparations. The cost-effectiveness of modified-release versus standard preparations was discussed and the committee were confident that modified-release preparations are the most cost-effective use of NHS resources. The committee acknowledged that the 1g modified-release preparation is cheaper than the standard preparation (£0.03 versus £0.22). It was also noted that although the 500mg modified-release tablets are slightly more expensive than the standard preparation (£0.07 versus £0.03), the gastrointestinal side-effects are likely be significantly less with the modified-release preparation. The committee acknowledged that one of the main reasons people stop treatment with metformin, even if they are seeing a clinical benefit, is due to the gastrointestinal side-effects. The committee concluded that the QALY gains associated with less gastrointestinal side-effects, in addition to being able to stay on treatment if a clinical benefit is being observed, will likely outweigh these differences in costs making the 500mg preparations of modified-release metformin cost-effective at NICE's £20,000 threshold.

4.4 Metformin and combined oral contraceptive pills in adolescents and adults

Review question 4.4: Is metformin versus the COCP with or without other agents effective for management of features of PCOS in adolescents and adults with PCOS?

4.4.1 Recommendations from the International evidence-based guideline for PCOS*

Evidence-based recommendations:

4.4.1 COCP could be used over metformin for management of hirsutism in irregular menstrual cycles in PCOS.

4.4.2 Metformin could be used over COCP for metabolic indications in PCOS.

4.4.3 The combination of COCP and metformin could be considered to offer little additional clinical benefit over COCP or metformin alone, in adults with PCOS with a BMI ≤30 kg/m2.

Practice point(s):

4.4.4 In combination with the COCP, metformin may be most beneficial in high metabolic risk groups including those with a BMI > 30 kg/m2, diabetes risk factors, impaired glucose tolerance or high-risk ethnic groups.

4.4.5 Where COCP is contraindicated, not accepted or not tolerated, metformin may be considered for irregular menstrual cycles. For hirsutism, other interventions may be needed.

IG clinical evidence

Evidence review 4.3 and 4.4 were combined and the ROBIS systematic review checklist is available in IG clinical evidence for 4.3.

IG evidence to recommendations justification: 111 RCTs met the inclusion criteria for this new systematic review. This review included 29 comparisons where metformin alone or in combination with other medications were compared to medications including saxagliptin, rosiglitazone and pioglitazone. Comparisons to placebo and lifestyle changes are covered in section 4.3. Eighteen comparisons had a GRADE outcome of very low, 7 were low, and 4 were moderate. Three EBRs were made, all of which are conditional weak recommendations for the option. Comparison 4 looked at metformin versus oral contraceptive pills (OCP) in 24 RCTs. Results found that Metformin had improved outcomes for fasting insulin, total cholesterol, triglycerides, CRP and HOMA-IR, all with low or very low certainty, compared with OCP. The evidence showed a dose of 1-2g/day led to improvements in metabolic outcomes. This supports recommendation 4.4.2 which states to use metformin over COCP for metabolic indications in PCOS. OCP had improved outcomes for improving hyperandrogenism (SHBG, FAI, testosterone, free testosterone, DHEAS and androstenedione) and improving regular menstrual cycle, with moderate to very low certainty evidence, when compared to metformin. This supports recommendation 4.4.1 which states COCP can be used over metformin for hirsutism and irregular menstrual cycles. Comparison 5 looked at metformin plus COCP versus metformin alone and found the combination of the two was more effective in lowering testosterone and DHEAS compared to metformin alone, low and very low certainty respectively. There were no studies comparing adolescents in this comparison. This comparison included 6 RCTs, 5 of which could be included in the meta-analysis, studies had high or moderate risk of bias, with studies having small numbers of participants. As such the recommendation made (4.4.3) is permissive of using a combination of COCP and metformin, highlighting that it may only offer a little clinical

benefit. This is a conditional (weak) recommendation for the option, with comparison 5 finding that metformin plus OCP is more effective at lowering testosterone and DHEAS, however this was low and very low certainty respectively. This recommendation appears to have been included to give clinicians the option to combine products if needed due to the reduction in testosterone and DHEAS which appears to be appropriate given the available evidence.

IG economic evidence

No health economic evidence was identified in the IG for review question 4.4 on metformin versus COCP for effective management of hormonal and clinical PCOS features.

The IG noted that although providing a combination of metformin with COCP might increase overall treatment costs versus COCP alone, the cost of metformin is low, and therefore omitting the combination treatment would not result in substantial cost savings for healthcare providers. Overall, the IG noted the cost-effectiveness of providing metformin instead of or in combination with COCP is unclear.

4.4.2 NICE economic evidence

Included studies

A single health economic search was performed by NICE to identify published economic evaluations of relevance to all review questions in this guideline. See the literature search strategy in Appendix A.

No economic studies were identified which were applicable to this review question (see economic study selection flow chart in Appendix B).

Excluded studies

No economic studies were reviewed at full text and excluded from this review.

Economic model

No original health economic model was developed for review question 4.4 as other areas were identified a higher priority for original health economic modelling.

Unit costs

Unit costs for both the combined oral contraceptive pill and metformin can be found respectively in **Table 1** (section 4.2) and **Table 2** (section 4.3).

4.4.3 NICE recommendations

No recommendations have been contextualised from this section of the IG.

4.4.4 The committee's discussion and interpretation of the evidence

Clinical

The committee discussed the IG recommendation that COCP could be used over metformin for hirsutism and irregular cycles, and the IG recommendation that metformin could be used over COCP for metabolic outcomes, however decided that this information had already been covered well by the areas on COCP alone and metformin alone and as such did not require further inclusion in this section. The committee also discussed the combined use of metformin and the COCP however felt there was not a sufficient evidence base to contextualise IG recommendation 4.4.3. As such no NICE recommendations were made for this section of the IG.

Health economic

No health economic evidence was identified in the IG, or as part of NICE's original health economic literature search for this review question. Unit costs were presented to the committee to aid consideration of cost-effectiveness.

As no recommendations were made for this review, there are no health economic implications associated with this review.

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4.5 Anti-obesity pharmacological agents

Review question 4.5: Are anti-obesity pharmacological agents alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?

4.5.1 Recommendations from the International evidence-based guideline for PCOS*

Consensus recommendation:

4.5.1 Anti-obesity medications including liraglutide, semaglutide, both glucagon-like peptide-1 (GLP-1) receptor agonists and orlistat, could be considered, in addition to active lifestyle intervention, for the management of higher weight in adults with PCOS as per general population guidelines.

Practice point(s):

4.5.2 Healthcare professionals should ensure concurrent effective contraception when pregnancy is possible, for women who take GLP-1 receptor agonists, as pregnancy safety data are lacking.

4.5.3 Gradual dose escalation for GLP-1 receptor agonists is recommended to reduce gastrointestinal adverse effects.

4.5.4 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.

IG clinical evidence

Critical Appraisal - ROBIS systematic review checklist

Section	Question	Answer
Study eligibility criteria	Did the review adhere to pre-defined objectives and eligibility criteria?	Probably yes *(No predefined objectives identified. PICOS is well defined)*
Study eligibility criteria	Were the eligibility criteria appropriate for the review question?	Probably yes *(Clearly defined PICOS)*
Study eligibility criteria	Were eligibility criteria unambiguous?	Yes *(Eligibility criteria clearly described in PICO)*
Study eligibility criteria	Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Probably yes *(Appropriate inclusion and exclusion criteria according to the research question; minimum 3 months duration of pharmacological agents is appropriate to show effect; cross-over studies are included but only the first phase is reported)*
Study eligibility criteria	Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Yes *(This is a new SR. Limits are applied based on English language which is appropriate and those limited to studies from the last 10 years, which they report was a decision from the 2018 Guideline)*
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low *(All areas are well covered with relevant information, and appropriate limits)*
Identification and selection of studies	Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Probably no *(Some suitable databases used, additional references included from other systematic reviews. However, lack of inclusion of trial registries)*
Identification and selection of studies	Were methods additional to database searching used to identify relevant reports?	Yes *(One additional study was added to the review from non-database sources but it is unclear where this was from)*
Identification and selection of studies	Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	No *(One search was used for Medline and Embase. Animal limit for both databases was not suitable. This may pose issues with potentially excluding some trials in humans)*

Section	Question	Answer
Identification and selection of studies	Were restrictions based on date, publication format, or language appropriate?	Probably no *(Date restriction set at 10 years with no explanation as to why. Lack of search terms included for systematic reviews and cross-over studies. English language limit applied)*
Identification and selection of studies	Were efforts made to minimise error in selection of studies?	Yes *(study selection was carried out by two reviewers)*
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	High *(Concern that studies in humans may have been accidentally omitted from the Embase search only)*
Data collection and study appraisal	Were efforts made to minimise error in data collection?	Yes *(The report suggests that 2 independent reviewers conducted data extraction)*
Data collection and study appraisal	Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Yes *(Study characteristics table sufficiently detailed)*
Data collection and study appraisal	Were all relevant study results collected for use in the synthesis?	Yes *(Results clearly listed for 11 included studies, the IG also lists 5 studies awaiting classification, however these were not included in the analyses)*
Data collection and study appraisal	Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Probably yes *(Risk of bias conducted using older version of Cochrane's ROB tool)*
Data collection and study appraisal	Were efforts made to minimise error in risk of bias assessment?	Yes *(Two independent reviewers appraised the studies alongside the reviewing team)*
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low *(Methods are appropriate for review)*
Synthesis and findings	Did the synthesis include all studies that it should?	Yes *(Study inclusion is appropriate. Meta analysis was done for 4 out of 11 studies,*

Section	Question	Answer
		reasons for not including rest of the studies is explained in the report due to one RCT in a comparison or non-parametric data, these studies were reported narratively)
Synthesis and findings	Were all pre-defined analyses reported or departures explained?	Yes *All analyses mentioned and addressed in the results section. All necessary analysis (narrative analyses and meta-analyses) was carried out to include all studies. Pre-defined analyses included BMI subgroup and adolescents, adults and post-menopausal subgrouping but no subgrouping possible due to lack of studies in analyses)*
Synthesis and findings	Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Yes *(Study design (RCTs) and analyses are appropriate for review. Synthesis conducted when 2 or more studies with same comparison and outcomes which could be meta-analysed)*
Synthesis and findings	Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Probably yes *(Consistency was assessed as part of GRADE and downgraded based on heterogeneity, limited overlap of confidence intervals and inconsistent direction of effect and random effects used. Narrative synthesis was carried out where possible which addressed heterogeneity where statistical combination was not possible)*
Synthesis and findings	Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Probably yes *(No funnel plots or sensitivity analysis, but these were not possible because too few studies in analyses)*
Synthesis and findings	Were biases in primary studies minimal or addressed in the synthesis?	Yes *(GRADE assessment is carried out and biases are addressed in the evidence summary section)*
Synthesis and findings	Concerns regarding the synthesis and findings	Low

Section	Question	Answer
		(Bias has been taken into account but further write up about this could have been useful)
Judging risk of bias	Concerns regarding specification of study eligibility criteria	Low *(All areas well covered with relevant information)*
Judging risk of bias	Concerns regarding methods used to identify and/or select studies	High *(Concern that a number of studies were accidentally omitted from the Embase search only, unable to determine impact of this on final number of included studies.)*
Judging risk of bias	Concerns regarding methods used to collect data and appraise studies	Low *(Methods appropriate for review)*
Judging risk of bias	Concerns regarding the synthesis and findings	Low *(Bias has been taken into account but further write up about this could have been useful)*
Overall review ratings	Overall risk of bias	High *(Search strategy likely excluded studies, may have affected outcomes)*
Overall review ratings	Applicability as a source of data	Fully applicable

IG evidence to recommendations justification: This new systematic review included 11 RCTs, however only 4 studies were suitable for inclusion in the meta-analysis and GRADE evidence tables. No EBRs were able to be made for this review question due to very small numbers of participants with PCOS being included. One CR and 3 practice points were created covering general advice on the use of weight loss medications for women with PCOS.

IG economic evidence

No health economic evidence was identified in the IG for review question 4.5 on anti-obesity pharmacological agents.

The IG noted that the cost of anti-obesity agents may make affordability difficult for some women both in the short and long-term. The IG also noted that the cost and regulation of these medications in different regions needs to be considered when implementing their recommendations.

The IG acknowledged that there is a need for high-quality well-designed studies with metabolic, reproductive and psychological outcomes of high certainty comparing anti-obesity medications to placebo for people with PCOS. The IG stated that the studies need to directly compare groups at the end of the intervention and also report adverse effects related to the medications, acknowledging that the adverse effects of long-term therapy requires more research.

4.5.2 NICE economic evidence

Included studies

A single health economic search was performed by NICE to identify published economic evaluations of relevance to all review questions in this guideline. See the literature search strategy in Appendix A.

No economic studies were identified which were applicable to this review question (see economic study selection flow chart in Appendix B).

Excluded studies

No economic studies were reviewed at full text and excluded from this review.

Economic model

No original health economic model was developed for review question 4.5 on anti-obesity pharmacological agents as the use indication of these drugs are covered by NICE's existing guideline on overweight and obesity management (NG246).

Unit costs

No unit costs were sourced for anti-obesity agents as existing evidence associated with this review question can be found in NICE's guideline NG246 (overweight and obesity management).

4.5.3 NICE recommendations

No recommendations were made. For guidance on the use of anti-obesity medications and bariatric surgery, see the section on medicines and surgery in NICE's guideline on managing overweight and obesity.

4.5.4 The committee's discussion and interpretation of the evidence

Clinical

The committee discussed the use of anti-obesity pharmacological agents and agreed that there was not enough evidence in the IG to allow contextualisation of recommendations, as the IG were also unable to make any evidence based recommendations for this section. Committee members fed back that medications such as GLP-1 medications were leading to people having improved symptoms, however most people were having to fund this privately, as they do not meet the current criteria for access to treatment. Committee members raised that this felt like an inequity of care as those with fewer financial resources were unable to access the medication. The committee felt that this was an emerging area of research and an area where practice is developing rapidly. The committee discussed that Technology Appraisals were likely to be the preferred method for updating this area, particularly around the use of GLP-1 medication, see the summary of NICE guidance for GLP-1 receptor agonists and tirzepatide in adults. Therefore, a cross-reference to NICE guideline 246, overweight and obesity management was made.

Health economic

No health economic evidence was identified in the IG, or as part of NICE's original health economic literature search for review question 4.5 on anti-obesity pharmacological agents.

The committee acknowledged the lack of clinical evidence on anti-obesity pharmacological agents for a PCOS specific population. Anecdotally the committee discussed that pharmacological agents for people with PCOS have the potential to be a cost-effective treatment but ultimately were unable to make a recommendation for pharmacological agents for people with PCOS due to the lack of clinical and cost-effectiveness evidence. The committee did however cross-refer to NICE's existing guidance on overweight and obesity management (NG246) where information is provided on the criteria for those eligible for anti-obesity pharmacological agents.

As no new recommendations were made or contextualised for this review question no significant resource impact will be associated with this review question.

4.6 Anti-androgen pharmacological agents

Review question 4.6: Are anti-androgen pharmacological agents alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?

4.6.1 Recommendations from the International evidence-based guideline for PCOS*

Evidence-based recommendation:

4.6.1 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.

Consensus recommendation:

4.6.2 Given the negative psychological impact of female pattern hair loss, anti-androgens in combination with COCP could be trialled, acknowledging the lack of evidence in the PCOS population.

Practice point(s):

4.6.3 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).

4.6.4 Anti-androgens could be considered to treat hirsutism, in the presence of another effective form of contraception, for women with contraindications for COCP therapy or when COCPs are poorly tolerated.

4.6.5 When prescribing anti-androgens, based on general population recommendations, healthcare professionals should consider that:

- spironolactone at 25-100 mg/day appears to have lower risks of adverse effects
- cyproterone acetate at doses ≥ 10 mg is not advised due to an increased risk including for meningioma
- finesteride has an increased risk of liver toxicity
- 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.

IG clinical evidence

Critical Appraisal - ROBIS systematic review checklist

Section	Question	Answer
Study eligibility criteria	Did the review adhere to pre-defined objectives and eligibility criteria?	Probably yes *(No predefined objectives identified. PICOS is well defined)*
Study eligibility criteria	Were the eligibility criteria appropriate for the review question?	Yes *(Clearly defined PICOS. Appropriate to the review question)*
Study eligibility criteria	Were eligibility criteria unambiguous?	Yes *(Eligibility criteria clearly described in PICO)*
Study eligibility criteria	Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Probably yes *(Appropriate inclusion and exclusion criteria according to the research question. However, inclusion criteria for comparator is 'placebo or any other listed intervention or their combination', which looks similar to the exclusion criteria*

Section	Question	Answer
		for comparator 'Agent or combination used in the intervention')
Study eligibility criteria	Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Probably yes *(No limits applied)*
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low *(All areas are well covered with relevant information)*
Identification and selection of studies	Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Probably no *(Some suitable databases used, additional references harvested from other SRs. However, lack of inclusion of trial registries)*
Identification and selection of studies	Were methods additional to database searching used to identify relevant reports?	Yes *(Reference list checking)*
Identification and selection of studies	Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	*No* *(RCT filter missing truncation on "random". Translations beyond Medline not reported so accuracy of search cannot be checked)*
Identification and selection of studies	Were restrictions based on date, publication format, or language appropriate?	Probably yes *(English language limit applied which is appropriate for review. 2017 search strategies listed so unable to confirm if correct date ranges used)*
Identification and selection of studies	Were efforts made to minimise error in selection of studies?	Yes *(study selection was carried out by two reviewers)*
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	High *(Search is the same as for Q4.2 with largely the same limitations. Typo in RCT filter, lack of transparency on search translations)*
Data collection and study appraisal	Were efforts made to minimise error in data collection?	Yes

Section	Question	Answer
		(Data extraction and appraisal was carried out by two reviewers alongside the team)
Data collection and study appraisal	Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Unclear *(Study characteristics table is sufficiently detailed for 18 out of 26 of the included studies. We don't know the study characteristics of 8 studies which might be from previous guideline)*
Data collection and study appraisal	Were all relevant study results collected for use in the synthesis?	Yes *(results are present)*
Data collection and study appraisal	Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Yes *(Risk of bias conducted using older version of Cochrane's risk of bias tool)*
Data collection and study appraisal	Were efforts made to minimise error in risk of bias assessment?	Yes *(2 independent reviewers carried out quality assessment alongside the reviewing team)*
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low *(Methods are appropriate for review, however study characteristics are not present for all included studies)*
Synthesis and findings	Did the synthesis include all studies that it should?	Yes *(Studies have all been included)*
Synthesis and findings	Were all pre-defined analyses reported or departures explained?	Yes *(All analyses mentioned and addressed in the results section. All necessary analyses (narrative analyses and meta-analyses) were carried out to include all of the studies)*
Synthesis and findings	Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Yes *(Study design and analysis are appropriate for review)*

Section	Question	Answer
Synthesis and findings	Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Probably yes *(Subgroup analysis is not carried out. Forest plots have distorted pixels making it difficult to interpret. However, GRADE tables highlight random effects were used.*
Synthesis and findings	Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Yes *(Funnel plots are available)*
Synthesis and findings	Were biases in primary studies minimal or addressed in the synthesis?	Probably yes *(GRADE assessment is carried out and biases are addressed. They are also addressed in the discussions)*
Synthesis and findings	Concerns regarding the synthesis and findings	Low *(The syntheses are suitable for the review question)*
Judging risk of bias	Concerns regarding specification of study eligibility criteria	High *(Search is the same as for Q4.2 with largely the same limitations. Typo in RCT filter, lack of transparency on search translations)*
Judging risk of bias	Concerns regarding methods used to identify and/or select studies	Low *(All areas are well covered with relevant information)*
Judging risk of bias	Concerns regarding methods used to collect data and appraise studies	Low *(Methods are appropriate for review, however study characteristics are not present for all included studies)*
Judging risk of bias	Concerns regarding the synthesis and findings	Low *(The syntheses are suitable for review question)*
Overall review ratings	Overall risk of bias	Low *(Most areas are suitable for review question; however further explanation of search terms would have been helpful. Clarity needed on 8 studies where characteristics not listed)*

Section	Question	Answer
Overall review ratings	Applicability as a source of data	Fully applicable

IG evidence to recommendations justification: 26 studies were included in this updated systematic review, with 13 included in a pooled meta-analysis. 14 comparisons were made covering anti-androgen pharmacological agents compared to placebo, lifestyle interventions, metformin and COCP in various combinations. One EBR was made which was a conditional weak recommendation for the option. Comparison 2 looked at daily versus every 3 days anti-androgen medication and found there was little difference for outcomes including hirsutism when taking an anti-androgen medication daily or every 3 days. No difference for outcomes including hirsutism was seen in comparison 3 where anti-androgen medication plus a lifestyle intervention was compared to a placebo plus lifestyle intervention. Comparison 4 looked at anti-androgen plus lifestyle compared to anti-androgen plus metformin and lifestyle changes, however no significant difference was seen for most outcomes including hirsutism. However fasting glucose was significantly lower in the metformin group. Comparison 9 (anti-androgen and metformin versus COCP) found decreases in hirsutism were seen in the COCP group, however they state that no definitive recommendations could be made here due to the small number of subjects with moderate risk of bias. Comparisons 10 (Anti-androgen + metformin + COCP vs COCP - ADULTS + ADOLESCENTS) and 11 (Anti-androgen + COCP vs COCP +/- placebo – ADULTS) found no difference in outcomes including hirsutism. Comparison 14 (Anti-androgen + metformin + lifestyle vs metformin + lifestyle) also found no difference in weight, body mass index (BMI), waist-to-hip ratio (WHR), hirsutism, sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), fasting insulin, high-density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides and homeostatic model assessment for insulin resistance (HOMA-IR) score. Testosterone and fasting glucose were significantly lower in the anti-androgen group.

Comparison 13 (Anti-androgen + lifestyle vs metformin + lifestyle) found flutamide decreased BMI and hirsutism score in one study. Of the four studies used in this analysis, two studies were low and two studies had moderate risk of bias. From the meta-analysis, hirsutism was improved when the anti-androgen medication was used, fasting insulin was lower, SHBG was higher, and no difference was seen in testosterone, DHEAS, fasting glucose, quantitative insulin-sensitivity check index (QUICKI), androstenedione, HOMA-IR or BMI. The evidence from these 14 comparisons largely pointed at no difference between anti-androgen medications and comparators for a variety of PCOS outcomes such as hirsutism, with only one of the 14 comparisons showing a benefit for anti-androgen treatments. As such the evidence does not fully support an EBR, however it is a “consider” recommendation which might be suitable. Only one comparison (13) found any benefit of an anti-androgen (flutamide). The IG does describe a number of research priorities for this area, particularly the need for larger scale studies.

IG economic evidence

No health economic evidence was identified in the IG for review question 4.6 on anti-androgen pharmacological agents.

The IG noted that costs for the combined oral contraceptive pill (COCP), anti-androgens, and metformin vary according to specific preparations and health care arrangements. The IG acknowledged that using combinations of medications increases costs and noted that the clinical evidence regarding the benefits of multiple medications is limited.

In terms of cost-effectiveness the IG noted that no data are available to determine the most cost-effective treatment for pharmacological management of PCOS (e.g. the COCP, anti-androgens, and metformin). In IG discussion of the evidence for this review question, they also acknowledged that no data are available regarding lifestyle interventions but reiterated their point made in section three of the IG that weight loss and healthy lifestyle interventions will likely improve general health and therefore lower health care expenses.

4.6.2 NICE economic evidence

Included studies

A single health economic search was performed by NICE to identify published economic evaluations of relevance to all review questions in this guideline. See the literature search strategy in Appendix A.

No economic studies were identified which were applicable to this review question (see economic study selection flow chart in Appendix B).

Excluded studies

No economic studies were reviewed at full text and excluded from this review.

Economic model

No original health economic model was developed for review question 4.6 on anti-androgen pharmacological agents because other areas of the guideline were identified as a higher priority for original health economic modelling.

Unit costs

Table 3: Unit costs for anti-androgens

Resource	Unit costs per unit
Bicalutamide 50 mg	£0.04
Finasteride 1 mg (NHS indicative price)	£0.04
Finasteride 5 mg	£0.03
Flutamide 250mg	£2.00
Spironolactone 25mg	£0.03
Spironolactone 50mg	£0.06
Spironolactone 100mg	£0.06

Source of costs; British National Formulary, date accessed 07/05/2026. Dosing is one tablet a day.

4.6.3 NICE recommendations

The relevant recommendations for this section are Rec 1.11.5 to 1.11.16.

4.6.4 The committee's discussion and interpretation of the evidence

Clinical

The committee discussed the use of anti-androgens in combination with contraceptive medication for the purpose of treating hirsutism in women with PCOS. The suitable dose for this indication was also discussed, and whether this would be provided in primary or secondary care. As such recommendation 4.6.1 was contextualised into the NICE guideline into the section on hirsutism, under further treatment options with a separate new recommendation for suggested dosage of spironolactone. The committee also adapted IG recommendation 4.6.1 into a NICE recommendation as they felt it was important to include information on appropriate contraception due to the nature of the anti-androgen medications. The committee discussed the appropriate dosage for spironolactone, making a new recommendation to give further details on the starting dose and appropriate progression. The committee also felt a referral to the BNF would be helpful here so that more information on monitoring requirements could be given. The committee thought that under 18s should have the same options as adults and included similar recommendations except that further management should only be initiated in specialist care.

The committee decided to contextualise CR 4.6.2 into two recommendations in the NICE guideline, as it was felt the effect of hair loss on women with PCOS was significant. As such a recommendation was included which is permissive of the use of an anti-androgen with COCP for women with hair loss. The committee discussed the impact of acne in people with PCOS and decided to refer to existing NICE guidance in this area. This was a new recommendation and as such the committee felt it would sit well within this section of the guideline, as it would be helpful for users to have pharmacological management for PCOS related conditions in one area.

Health economic

No health economic evidence was identified in the IG, or as part of NICE's original health economic literature search for review question 4.6 on anti-androgens. Unit costs were presented to the committee to aid consideration of cost-effectiveness (**Table 3**).

The committee discussed the use of anti-androgens in the NHS noting that the use of these medications as a further treatment option for hirsutism and for the treatment of androgen-dependent hair loss is reflective of best clinical practice. Therefore, the subsequent recommendations the guideline committee made, and contextualised, are representative of best clinical practice in the NHS. The committee discussed that the prescription of anti-androgens is common for people who have been referred to secondary care to help manage their symptoms of PCOS. It was however, noted that the prescription of anti-androgens in primary care would likely represent a change in UK current practice.

The committee noted that the medication costs of anti-androgens are relatively cheap and are slightly cheaper than the combined oral contraceptive pill (see **Table 3** and **Table 1**), however, the committee noted that monitoring costs for anti-androgens are significantly more expensive. The committee discussed that monitoring for people receiving anti-androgens is required to prevent severe electrolyte imbalances. Monitoring requires baseline blood tests, followed by checks 1 week after starting treatment or changing doses – monitoring potassium and creatinine. Monthly monitoring is also required for the first 3 months of treatment and ongoing monitoring should then be conducted every 3 months. Conversely, for people receiving the combined oral contraceptive pill monitoring typically consists of annual blood pressure and weight checks, with medication being reviewed every 6 to 12 months.

The committee noted that the use of anti-androgens as a further treatment option for hirsutism and androgen-dependent hair loss is the only treatment option available to people if the combined oral contraceptive pill cannot be taken or has not been successful at managing symptoms. The committee made a recommendation noting

that treatment with anti-androgens should not be continued if no benefit is seen after six months of treatment. Therefore in terms of cost-effectiveness the committee agreed that the overall additional costs associated with the treatment of anti-androgens (compared to the combined oral contraceptive pill) would likely be a cost-effective use of NHS resources as any meaningful reduction in hirsutism or improvement in androgen-dependent pattern hair loss for people with PCOS will result in an improvement in quality of life, particularly in relation to anxiety and depression.

The committee also acknowledged that there may be an increase in costs to the NHS resulting from the recommendations made on providing anti-androgens as a further treatment option for hirsutism and androgen-dependent hair loss – primarily driven by an increase in awareness of this treatment option and a subsequent uptake of treatment. However, as the recommendations made as part of this guideline potentially omit the need for referral to secondary care for the prescription of anti-androgens, part of this cost increase could be offset by this. The committee also noted that anti-androgens are commonly prescribed in primary care for other indications so very minimal additional training would be required for GPs to prescribe anti-androgens for people with PCOS. In general, the overall costs of these recommendations are likely to be low as treatment with anti-androgens should not be continued if no benefit is seen after six months. The committee also discussed that these recommendations, alongside the other recommendations in the guideline, should help people with PCOS access better treatment and deepen peoples understanding of the condition, which could have the potential to reduce overall health care contacts due to the increased efficiencies of the overall management of PCOS.

For the treatment of acne, the guideline committee cross-referred to NICE existing guideline on acne (NG198), specifically the section on treatment option for people with PCOS.

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4.7 Inositol

Review question 4.7: In adolescents and adults with PCOS, is inositol alone or in combination with other therapies, effective for management of hormonal and clinical PCOS features, weight and reproductive outcomes?

4.7.1 Recommendations from the International evidence-based guideline for PCOS*

Evidence-based recommendations:

4.7.1 Inositol (in any form) could be considered in women with PCOS based on individual preferences and values, noting limited harm, potential for improvement in metabolic measures, yet with limited clinical benefits including in ovulation, hirsutism or weight.

4.7.2 Metformin should be considered over inositol for hirsutism and central adiposity, noting that metformin has more gastrointestinal side-effects than inositol.

Practice points:

4.7.3 Women taking inositol and other complementary therapies are encouraged to advise their health professional.

4.7.4 Specific types, doses or combinations of inositol cannot currently be recommended in adults and adolescents with PCOS, due to a lack of quality evidence.

4.7.5 Shared decision making should include discussion that regulatory status and quality control of inositol in any form (like other nutrient supplements) can differ from those for pharmacological products and doses and qualities may vary.

4.7.6 Policy makers and healthcare professionals have a responsibility to ensure women have access to unconflicted, evidence-based information to inform shared-

decision making, whilst also acknowledging and respecting individual values and preferences, including for complementary therapies.

IG clinical evidence

Critical Appraisal - ROBIS systematic review checklist

Section	Question	Answer
Study eligibility criteria	Did the review adhere to pre-defined objectives and eligibility criteria?	Probably yes *(No predefined criteria identified. PICOS is well defined)*
Study eligibility criteria	Were the eligibility criteria appropriate for the review question?	Yes *(Clearly defined PICOS. Appropriate to the review question)*
Study eligibility criteria	Were eligibility criteria unambiguous?	Yes *(Eligibility criteria clearly described in PICO)*
Study eligibility criteria	Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Probably yes *(Restrictions on date are present but not well described)*
Study eligibility criteria	Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Yes *(Study inclusion limited to English language. No publication date or format limits applied)*
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low (*All areas are well covered with relevant information)*
Identification and selection of studies	Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Probably no *(Some suitable databases used, additional references harvested from other SRs. However, lack of inclusion of trial registries)*

Section	Question	Answer
Identification and selection of studies	Were methods additional to database searching used to identify relevant reports?	No information *(Complete PRISMA flow chart not available as it appears to have not had space on the page to be fully inserted. No information in the text)*
Identification and selection of studies	Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Yes *(MeSH terms used in non-MeSH indexed databases, however search runs as a full translation would)*
Identification and selection of studies	Were restrictions based on date, publication format, or language appropriate?	Probably yes *(No study-type restrictions in search. English language limit applied appropriately for review)*
Identification and selection of studies	Were efforts made to minimise error in selection of studies?	Yes *(Study selection was carried out by 9 reviewers)*
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	High *(No searching beyond databases, lack of PRISMA diagram)*
Data collection and study appraisal	Were efforts made to minimise error in data collection?	Probably yes *(Does not clearly state how many reviewers conducted data extraction)*
Data collection and study appraisal	Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Yes *(Study characteristics table sufficiently detailed)*
Data collection and study appraisal	Were all relevant study results collected for use in the synthesis?	Probably yes *(Outcomes from all included studies have been used across the 11 comparisons)*
Data collection and study appraisal	Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Probably yes *(ROB conducted using older version of Cochrane's ROB tool)*
Data collection and study appraisal	Were efforts made to minimise error in risk of bias assessment?	Probably yes

Section	Question	Answer
		(Does not clearly state how many reviewers conducted quality appraisal)
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low *(Methods are appropriate for review)*
Synthesis and findings	Did the synthesis include all studies that it should?	Yes *(29 studies were included in the review and 19 in the meta-analyses)*
Synthesis and findings	Were all pre-defined analyses reported or departures explained?	Yes *(All analyses are mentioned and addressed in the results section)*
Synthesis and findings	Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Yes *(Study design and analysis are appropriate for review)*
Synthesis and findings	Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Probably yes *(Heterogeneity has been taken into account and downgraded appropriately for imprecision and moderate risk of bias)*
Synthesis and findings	Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Probably yes *(No funnel plots or sensitivity analysis)*
Synthesis and findings	Were biases in primary studies minimal or addressed in the synthesis?	Probably yes *(GRADE assessment is carried out and biases are addressed, however, they are addressed in the discussions)*
Synthesis and findings	Concerns regarding the synthesis and findings	Low *(Appears to have taken bias into account but further write up about this could have been useful)*
Judging risk of bias	Concerns regarding specification of study eligibility criteria	Low (*All areas appear to be well covered with relevant information)*
Judging risk of bias	Concerns regarding methods used to identify and/or select studies	High

Section	Question	Answer
		(No searching beyond databases, lack of PRISMA diagram)
Judging risk of bias	Concerns regarding methods used to collect data and appraise studies	Low *(Methods are appropriate for review)*
Judging risk of bias	Concerns regarding the synthesis and findings	Low *(Appears to have taken bias into account but further write up about this could have been useful)*
Overall review ratings	Overall risk of bias	Low *(All sections scored low except for minor issues with search, no other concerns noted)*
Overall review ratings	Applicability as a source of data	Fully applicable

IG evidence to recommendations justification: this new systematic review consisted of 29 RCTs with 11 comparisons. Two EBRs were made, both of which were strong recommendations for the option. Ten studies had high risk of bias, 16 had low or moderate and 3 were an unclear risk of bias. When myoinositol was compared to placebo in a meta-analysis, myoinositol was found to be more effective for weight, BMI, testosterone, androstenedione fasting insulin and HOMA-IR compared to placebo. However, this evidence is from one trial with only 26 adult women included, the trial had a serious risk of bias. When myoinositol plus folic acid was compared to folic acid alone, the combination was found to be superior for insulin, HOMA-IR, total testosterone and androstenedione. Folic acid alone was better for BMI. The IG notes that the population for the studies included here was heterogeneous, with some people having impaired glucose tolerance, infertility, and insulin sensitivity issues. Myoinositol was compared to metformin, with pooled evidence finding myoinositol had less adverse effects than metformin. The metformin group saw improved outcomes for fasting insulin (FINS), weight-to-height ratio (WHR), waist circumference (WC) and Ferriman-Gallwey (FG) scores. Improvements in BMI and HOMA-IR were also seen with metformin however they were not

significant. Myoinositol was superior for resuming regular cycles. D-chiro inositol (DCI) improves free testosterone, total testosterone, androstenedione, DHEAS and lipids compared to placebo, low certainty evidence. Placebo was superior to DCI for BMI. Myoinositol plus DCI was compared to myoinositol alone however no differences were seen for primary outcomes such as HOMA-IR, BMI, or FG score. Some improvements in metabolic outcomes were seen at 3 months however this was not sustained at 6 months. The two recommendations made for this section were worded in a way to ensure that choice was available, and to highlight areas where evidence was limited or side effects were likely. As such the evidence provided is appropriate for these recommendations.

IG economic evidence

No health economic evidence was identified in the IG for review question 4.7 on inositol.

4.7.2 NICE economic evidence

Included studies

A single health economic search was performed by NICE to identify published economic evaluations of relevance to all review questions in this guideline. See the literature search strategy in Appendix A.

No economic studies were identified which were applicable to this review question (see economic study selection flow chart in Appendix B).

Excluded studies

No economic studies were reviewed at full text and excluded from this review.

Economic model

No original health economic model was developed for review question 4.7 on inositol as inositol is an over-the-counter supplement and therefore the cost of providing inositol is not incurred by the NHS.

Unit costs

Unit costs were not sourced for inositol as this is an over-the-counter supplement.

4.7.3 NICE recommendations

The relevant recommendation for this section is Rec 1.12.3.

4.7.4 The committee's discussion and interpretation of the evidence

Clinical

The IG made two evidenced-based recommendations (4.7.1 and 4.7.2) and four practice point recommendations (4.7.3 to 4.7.6). The committee discussed the use of inositol for women with PCOS and acknowledged the limited evidence in this area and noted that the majority of clinical studies in this area were funded by producers of inositol.

The committee decided to contextualise recommendation 4.7.1 from the IG which highlights that there may be benefits in metabolic outcomes, but not in ovulation, hirsutism or weight outcomes. However, because the evidence was limited for all outcomes, including metabolic (lack of studies and number of participants) the committee removed metabolic benefits and noted that there remains significant uncertainty in the effectiveness of inositol.

In general, the committee wanted to emphasise the uncertainty of the clinical evidence-base due the prevalent discussions on social media advocating for the use of inositol. The committee noted that they were not against people trying inositol but wanted to make sure people's expectations are managed as people may benefit to varying degrees.

The other EBR was not contextualised as the committee concluded that the structure and wording of the guideline implied that metformin should be considered over inositol.

Health economic

No health economic evidence was identified in the IG, or as part of NICE's original health economic literature search for review question 4.7 on inositol.

The committee acknowledged the uncertainty of any clinical benefit for inositol. The committee contextualised but also adapted one of the IG's EBRs to further reflect this uncertainty of clinical benefit. As inositol is an over-the-counter supplement the committee acknowledged that no costs would be incurred to the NHS as result of this recommendation.

4.8 Mechanical laser and light therapies for hair reduction

Review question 4.8: Is mechanical laser and light therapy for hair reduction alone, or in combination with other therapies, effective for management of hirsutism in adolescents and adults with PCOS?

4.8.1 Recommendations from the International evidence-based guideline for PCOS*

Evidence-based recommendation:

4.8.1 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.

4.8.2 A greater number of laser treatment sessions may be required in women with PCOS, compared to women with idiopathic hirsutism, to achieve hair reduction.

Consensus recommendation:

4.8.3 Adverse effects appear limited in the hands of experienced and suitably qualified providers, and women should be encouraged to seek hair reduction therapies from such providers.

Practice points:

4.8.4 Where laser hair removal is prescribed, the following need to be considered:

- Wavelength and delivery of laser treatment varies by skin and hair colour.
- Laser is relatively ineffective in women with blond, grey or white hair.
- The addition of COCP, with or without anti-androgens, to laser treatment may provide greater hair reduction and maintenance compared to laser alone.

Low and high fluence laser appear to have similar efficacy in reducing facial hair, while low fluence laser has reduced associated pain.

4.8.5 Mechanical hair removal with Intense Pulse Light (IPL) could be considered, albeit benefits may be less pronounced compared to laser treatment. There is no evidence to support the efficacy of home-based IPL kits.

4.8.6 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.

IG clinical evidence

Critical Appraisal - ROBIS systematic review checklist

Section	Question	Answer
Study eligibility criteria	Did the review adhere to pre-defined objectives and eligibility criteria?	Probably yes *(No predefined objectives identified. PICOS is well defined)*
Study eligibility criteria	Were the eligibility criteria appropriate for the review question?	Probably yes *(Clearly defined PICOS. Appropriate to the review question)*
Study eligibility criteria	Were eligibility criteria unambiguous?	Yes *(Eligibility criteria clearly described in PICO)*
Study eligibility criteria	Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Probably no *(No information for the exclusion criteria for intervention, comparator, outcomes or study type. Included cohort studies as well as RCTs, accepting cross-sectional and case-control studies)*
Study eligibility criteria	Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Yes *(Studies limited by language)*

Section	Question	Answer
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low *(All areas appear to be well covered with relevant information)*
Identification and selection of studies	Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Probably no *(No unpublished sources used)*
Identification and selection of studies	Were methods additional to database searching used to identify relevant reports?	No *(No additional search methods reported)*
Identification and selection of studies	Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Probably no *("Hirsutism" missing from free-text terms - adding this retrieves about 1/3rd more than just using the MeSH term and hypertrichosis.ti,ab, which is what they have included. Embase/PsycInfo translations were either not carried out or not reported)*
Identification and selection of studies	Were restrictions based on date, publication format, or language appropriate?	*Yes* *(English language limit used but not detailed in search strategy. No other limits applied)*
Identification and selection of studies	Were efforts made to minimise error in selection of studies?	Yes *(Two independent reviewers carried out the selection process)*
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	High *(No searching beyond databases and questionable search strategy)*
Data collection and study appraisal	Were efforts made to minimise error in data collection?	Yes *(Studies selected and appraised by 2 reviewers)*
Data collection and study appraisal	Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Yes *(Study characteristics table is sufficiently detailed)*
Data collection and study appraisal	Were all relevant study results collected for use in the synthesis?	Yes *(All appear to be included)*

Section	Question	Answer
Data collection and study appraisal	Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Yes *(Risk of bias conducted using older version of Cochrane's risk of bias tool)*
Data collection and study appraisal	Were efforts made to minimise error in risk of bias assessment?	Yes *(Two reviewers plus evidence team)*
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low *(Methods seem appropriate for review)*
Synthesis and findings	Did the synthesis include all studies that it should?	Yes *(Four RCTs and four cohort studies were included. They were unable to be meta-analysed)*
Synthesis and findings	Were all pre-defined analyses reported or departures explained?	Probably yes *(All analyses mentioned and addressed in the results section)*
Synthesis and findings	Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Yes *(Descriptive analysis was done due to significant differences in intervention and outcomes so meta-analysis could not be conducted)*
Synthesis and findings	Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Yes *(Variation is not minimal, but addressed in the analysis)*
Synthesis and findings	Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Probably yes *(Funnel plot not included)*
Synthesis and findings	Were biases in primary studies minimal or addressed in the synthesis?	Probably yes *(Biases are addressed, however, they are not addressed in the discussions)*
Synthesis and findings	Concerns regarding the synthesis and findings	Low *(Appears to have taken bias into account but further write up about this could have been useful)*

Section	Question	Answer
Judging risk of bias	Concerns regarding specification of study eligibility criteria	Low *(All areas appear to be well covered with relevant information)*
Judging risk of bias	Concerns regarding methods used to identify and/or select studies	High *(No searching beyond databases and issues with the search strategy)*
Judging risk of bias	Concerns regarding methods used to collect data and appraise studies	Low *(Methods seem appropriate for review)*
Judging risk of bias	Concerns regarding the synthesis and findings	Low *(Appears to have taken bias into account but further write up about this could have been useful)*
Overall review ratings	Overall risk of bias	Low *(All areas bar one scored low though more detail as to how conclusions were reached would be helpful)*
Overall review ratings	Applicability as a source of data	Fully applicable

IG evidence to recommendations justification: this new systematic review included 8 studies, 4 RCTs and 4 cohort studies. Meta-analysis was not possible due to significant heterogeneity of types of hair removal techniques used and the variety of outcomes recorded. Five studies had high risk of bias, 3 had moderate risk of bias. Two EBRs, one CR and 3 practice points were included in this section. Recommendation 4.8.1 was a strong recommendation and 4.8.2 was a conditional weak recommendation for the option. Laser treatment was concluded to be an effective method of permanent hair removal for facial hirsutism, four studies also reported that this improved psychological outcomes such as patient satisfaction, quality of life and depression and anxiety scores. When the additions of other treatments to laser was considered, such as metformin or COCP, hirsutism appeared to be better controlled compared to laser treatment alone. However, these results focus on the additional medication, not the benefit of laser treatment itself. Similar

results were found when comparing IPL and metformin to IPL alone. No studies compared IPL + medication to laser therapy + medication. One study found laser therapy alone to be superior to IPL alone.

The IG highlights both laser and IPL were recommended due to potential implementation considerations, despite laser being more effective, it might not be universally available due to the high cost and equipment requirements. As such IPL was included as it was thought to be more accessible and affordable. Research priorities for this were highlighted to include comparisons with COCP alone, COCP with anti-androgens versus laser, feasibility studies and efficacy studies for laser treatment of hirsutism in various groups such as age groups and breastfeeding women. More information on adverse events and cost effectiveness would also be beneficial.

The evidence found for recommendation 4.8.1 came from four RCTs, all of which had very small sample sizes. The authors describe that meta-analysis was not possible due to the high heterogeneity and difference in types of treatments used. Some of the RCTs compare laser alone to laser plus medication whilst some of the cohort studies compare groups with and without PCOS. There is a lack of studies in women with PCOS comparing laser therapy to no treatment or current practice. As such it is difficult to conclude that the evidence presented supports this strongly worded recommendation. Additionally, the IG states the inclusion of IPL was due to implementation concerns as there was little evidence available. Recommendation 4.8.2 was a weak conditional recommendation, however very little evidence was discussed for this, either in the descriptive summary or GRADE justifications. As such the evidence found for this section does not conclusively support the EBRs made.

IG economic evidence

No health economic evidence was identified in the IG for review question 4.8 on mechanical laser and light therapies for hair reduction.

The IG acknowledged that women currently pay for their own permanent hair reduction treatment and therefore if their recommendations are implemented, this will the shift some of those costs to healthcare providers. The IG noted that if laser therapy use is implemented within a healthcare setting, costs may be moderate to large including training and expanding the workforce for provision of this treatment.

4.8.2 NICE economic evidence

Included studies

A single health economic search was performed by NICE to identify published economic evaluations of relevance to all review questions in this guideline. See the literature search strategy in Appendix A.

No economic studies were identified which were applicable to this review question (see economic study selection flow chart in Appendix B).

Excluded studies

No economic studies were reviewed at full text and excluded from this review.

Economic model

A simple cost–utility analysis was developed to assess the cost effectiveness of high-fluence alexandrite laser hair reduction compared with no treatment for women, trans men and non-binary people aged 18 and over who have not had, or are not having, gender affirming hormone therapy or surgery, with PCOS and facial hirsutism. The analysis was undertaken from an NHS and Personal Social Services (PSS) perspective, following the NICE reference case.

The model used comparative quality-of-life data from Clayton 2005, the only identified study providing outcomes suitable for QALY estimation. WHOQOL-BREF physical domain scores were mapped to EQ-5D-5L using the Kangwanrattanakul 2023 mapping function and WHOQOL-BREF scoring instructions (date accessed

23/03/26). The time horizon was 6 months in the base case, reflecting the follow-up duration in Clayton 2005, with a sensitivity analysis extending this to 1 year.

Resource use reflected typical delivery observed in the trial: 1 patch test plus a mean of 4.8 treatments over 6 months. Laser treatment costs were sourced from the Salisbury Laser Clinic (accessed 23 March 2026) and NHS England National Cost Collection Data 2024/25 (accessed 23 March 2026).

Probabilistic analysis was used as the base case. Deterministic and scenario analyses explored uncertainty in utility mapping, area of treatment (upper lip vs full face), time horizon, and assumptions around psychological wellbeing (not captured by the WHOQOL-BREF physical domain).

The base-case analysis over 6 months showed that laser hair reduction produced only very small QALY gains (<0.01), resulting in ICERs well above standard NICE thresholds. Extending the time horizon to 1 year produced slightly larger QALY gains but ICERs remained high.

Scenario analyses exploring hypothetical improvement in anxiety/depression suggested that, were psychological benefits substantial, laser hair reduction might become cost effective. However, such improvements were not shown within the clinical evidence and therefore were treated as exploratory only.

Overall, the model results indicate that laser hair reduction for PCOS-related hirsutism is unlikely to be cost-effective at current costs and with currently available evidence. Limitations of this analysis include reliance on a single small RCT, absence of UK-specific mapping algorithms, lack of long-term outcome data, and uncertainty around true NHS delivery costs. The uncertainties and mapping limitations mean that true HRQoL benefits may be underestimated, but available evidence does not demonstrate cost-effectiveness at this time.

A summary of the guideline model characteristics is provided in **Table 4**. The economic model evidence summary is shown in **Table 5**. The full model write up is provided in the supplementary document B.

Table 4: Summary of characteristics of the guideline economic model

Study design and type of analysis	Population	Interventions and comparators	Perspective	Primary outcome	Time horizon
Study design: Decision analytic model. Type of analysis: cost utility analysis	Adults with PCOS and facial hirsutism. Mean age 33 years.	**Intervention:** High-fluence alexandrite laser (1 patch test + mean 4.8 sessions over 6 months). **Comparator:** No treatment (low-fluence laser arm used as sham).	NHS/PSS	QALYs (WHOQOL-BREF physical mapped to EQ-5D-5L).	6 months (base case). 1 year (sensitivity analysis).

Abbreviations: PSS: personal social services; QALY: quality-adjusted life year; RCT: randomised controlled trial

Table 5: Guideline economic model evidence summary table

Applicability and limitations	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty	Economic evidence statement
Partially applicable[1] Potentially serious limitations[2]	**6-month horizon**: Upper lip: £503 vs no treatment. Full face: £767 vs no treatment. **1-year horizon**: Upper lip: £679 vs no treatment. Full face: £1,119 vs no treatment. Cost year: 2024 / 2025	**6-month horizon:** 0.006 QALYs (upper lip and full face). **1-year horizon:** 0.019 QALYs (upper lip and full face).	**6-month ICERs:** Upper lip: £79,243 per QALY gained. Full face: £120,834 per QALY gained. **1-year ICERs:** Upper lip: £35,828 per QALY gained. Full face: £59,046 per QALY gained.	Probability of high fluence alexandrite laser (upper lip or full face) being cost-effective at £20K threshold: 0%. Sensitivity analyses showed ICERs remained above threshold unless applying hypothetical psychological benefit scenarios (not evidence-based).	Laser hair reduction was not cost-effective compared with no treatment at £20,000 per QALY gained.

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: Quality-adjusted life-year; RCT: randomised controlled trial

1. QALYs based on mapping of WHOQOL-BREF to EQ-5D-5L Thai value set.
2. Reliance on a single small RCT, lack of long-term outcome data, and uncertainty around true NHS delivery costs

Unit costs

Table 6: Unit costs used in economic model

Intervention	Resource use details and unit costs	Total intervention cost per person
Laser treatment	Dermatology appointment, £184 Patch test, £55 Upper lip, £55 per session Full face, £110 per session Number of sessions over 6 months: 4.8 Number of sessions over 1 year: 8	Upper lip, 6 months: £503 Full face, 6 months: £767 Upper lip, 1 year: £679 Full face, 1 year: £1,119

Sources: NHS National cost collection data 2024/2025 (Non-Admitted Face-to-Face Attendance, First, Consultant-led, Currency code: WF01B, Service code: 330), Salisbury Laser Clinic 2026, Clayton 2005, committee expert opinion.

4.8.3 Resource impact assessment

In addition to the de novo model, NICE performed a resource impact assessment to gauge the potential cost and resource implications to the NHS of adopting laser hair reduction for adults with PCOS as per the IG.

To do this work, an eligible population in England was estimated as per **Table 7**.

Table 7: Estimate of the number of women in England with PCOS and hirsutism

Population	Rate	Number	Source
Women aged 18 years and above	-	24,148,298	ONS*
Prevalence of PCOS	3.48%	840,361	Berni et al.

Population	Rate	Number	Source
Hirsutism in PCOS	70%	588,253	Spritzer el al.
Eligible population		**588,253**	

*The total number of women aged 18 years and above using mid-2022 ONS data was 23,554,205, but this was inflated by an assumed growth rate of 2.52% and calculated to be 24,148,298. Source: ONS, dare accessed 23/03/26.

The eligible population of 588,253 was then used to calculate the potential cost and resource use to the NHS of adopting laser hair reduction.

Table 8 below shows the cost of laser treatment on the upper lip and full face for 5%, 10% and 25% of the population when the total intervention costs outlined in **Table 6** for a six-month treatment period are applied.

Table 8: Estimate of the overall costs of laser treatment for the populations outlined

Uptake	5%	10%	25%
Number treated	29,413	58,825	147,063
Cost of treating upper lip @ £503	£14.79 m	£29.59 m	£73.97 m
Cost of treating full face @ £767	£22.56 m	£45.12 m	£112.80 m

It was noted to the committee that the above costings may be conservative estimates as some people would likely need treatment beyond a six-month period or top-up treatments over time.

The de novo model assumes that each person treated will require a dermatology appointment. The number of whole-time dermatologists required to fulfil demand is shown in **Table 9** when it is assumed that each appointment is 20 minutes.

Table 9: Dermatologist appointments needed for laser treatment in the populations outlined

Uptake	5%	10%	25%
Number treated	29,413	58,825	147,063
Cost of treating upper lip @ £503	29,413	58,825	147,063
Cost of treating full face @ £767	9,804 hrs	19,608 hrs	49,021 hrs
Number treated	7.13	14.25	35.63

*It is assumed that the annual hours available for work total 1,376. This is based on 8 sessions (out of 10) of 4 hours per week worked over 43 weeks of the year. The remainder is taken up with annual leave and CPD/training.

The resource impact workings show that if laser hair reduction were recommended as per the IG, this would result in a significant resource impact to the NHS.

4.8.4 NICE recommendations

NICE has not made a recommendation about mechanical laser and light therapies for hair reduction. A research recommendation was made, see Appendix E.

4.8.5 The committee's discussion and interpretation of the evidence

Clinical

The committee had a detailed discussion around the evidence base for laser and mechanical hair reduction. This is an area the committee thought would be highly beneficial for people with PCOS and hirsutism, particularly in relation to the psychological impact of hirsutism, however due to the very small evidence base presented in the IG, they were not able to make any recommendations in this section. The committee agreed that in order to contextualise a recommendation, the intervention must still meet the NICE cost per QALY threshold. This could not be met due to the high costs of the procedures and the limited evidence. The IG presented only one study that compared laser to no laser, which had a small number of participants and was over 20 years old. None of the other studies had quality of life outcomes necessary for the health economic assessment. A health economic model

was undertaken based on this single study (see economic section below). This trial and the resulting cost-effectiveness analysis did not provide enough evidence on which to base a recommendation. Equity was a key concern for the committee. They noted that because laser treatment is largely accessed privately, people with fewer financial resources or from marginalised backgrounds currently face restricted access. Introducing laser into the NHS could reduce inequity but only if delivered in a way that ensured fair access across regions and socio-economic groups. The committee also discussed equity considerations related to skin tone. Some laser types are less effective or less safe for individuals with darker skin tones, requiring alternative technologies and additional training. Without such provision, NHS rollout could inadvertently widen disparities. The committee discussed the lack of evidence for alternative comparators such as electrolysis, IPL, or laser in combination with COCP or metformin. They agreed that this limits understanding of where laser therapy might sit within a treatment pathway. As such the committee decided to make a research recommendation to highlight the gap in the evidence for laser and mechanical hair reduction for adults with PCOS.

Health economic

No health economic evidence was included in the IG nor identified through the literature review. A de novo cost-utility analysis was conducted comparing high fluence alexandrite laser to no treatment and found that laser resulted in higher costs and very small QALY gains across all base case scenarios compared to no treatment. The resulting ICERs at 6 months (£79,243 per QALY gained for upper lip and £120,834 per QALY gained for full face) and at 1 year (£35,828 per QALY gained for upper lip and £59,046 per QALY gained for full face) were substantially above NICE's £20,000 per QALY gained cost-effectiveness threshold.

Committee members agreed that the model was appropriately designed given the evidence constraints, but highlighted several limitations: mapping limitations, cost uncertainty uncaptured costs and limited time horizon.

Mapping limitations relate to the fact that the WHOQOL-BREF to EQ-5D-5L algorithm uses only the physical health domain, omitting psychological health which the committee considered a major component of disease burden. They agreed this likely leads to an underestimation of QALYs. With regards to cost uncertainty, the costs were based on an NHS-hosted clinic offering self-funded treatment, which may underestimate the real cost of NHS delivery, especially where specialised equipment or clinician training would be required. The committee highlighted concerns with regards to uncaptured costs as the model did not include resource consequences associated with untreated hirsutism, such as mental health service utilisation. Finally, the analysis had a limited time horizon with data allowing only a 6-month analysis, with cautious extrapolation to 1 year. Long-term sustainability of benefit and top-up treatments were not modelled.

The committee noted that scenario analyses showed that if laser therapy generated substantial improvements in psychological wellbeing, the ICER could fall meaningfully. For example, in an exploratory scenario assuming a large improvement in anxiety/depression from level 3 to 1 of the EQ5D-5L, the ICER was £16,651/QALY. However, these scenarios lacked an evidence base and relied on external value sets. Therefore, they were viewed as illustrative rather than decision-informing.

Overall, the committee concluded that cost-effectiveness could not be demonstrated with the available evidence, and the results were associated with substantial uncertainty. Additional resource impact work was conducted alongside this de novo model which found that if laser hair reduction were recommended as per the IG, this would have resulted in a significant resource impact to the NHS.

4.9 Bariatric/metabolic surgery

Review question 4.9: In adults and adolescents with PCOS, is bariatric surgery effective for management of hormonal and clinical PCOS features and weight?

4.9.1 Recommendations from the International evidence-based guideline for PCOS*

Consensus recommendations:

4.9.1 Bariatric/metabolic surgery could be considered to improve weight loss, hypertension, diabetes (prevention and treatment), hirsutism, irregular menstrual cycles, ovulation and pregnancy rates in women with PCOS.

4.9.2 Bariatric/metabolic surgery in women with PCOS should be informed by general population guidelines.

4.9.3 PCOS is a metabolic condition and could be considered an indication at a lower BMI threshold for bariatric/metabolic surgery similarly to other metabolic conditions including diabetes.

4.9.4 Women should be strongly counselled on the likelihood of rapid return of fertility and the need to commit to effective contraception, ideally prior to surgery. Even when pregnancy is desired, contraception should be continued until a stable weight is achieved, usually after one year, to avoid significantly increased risk of growth restriction, prematurity, small for gestational age, pregnancy complications and prolonged hospitalisation of the infant.

IG clinical evidence

Critical Appraisal - ROBIS systematic review checklist

Section	Question	Answer
Study eligibility criteria	Did the review adhere to pre-defined objectives and eligibility criteria?	Probably yes *(No predefined objectives identified. PICOS is well defined)*
Study eligibility criteria	Were the eligibility criteria appropriate for the review question?	Yes *(Clearly defined PICOS. Appropriate to the review question)*
Study eligibility criteria	Were eligibility criteria unambiguous?	Probably yes *(Eligibility criteria clearly described in PICO)*
Study eligibility criteria	Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Yes *(Eligibility criteria are sufficiently detailed, restrictions around study characteristics are applied)*
Study eligibility criteria	Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Yes *(Restrictions on date are present but not well described. Limited to English language)*
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low *(All areas appear to be well covered with relevant information)*
Identification and selection of studies	Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	No *(No consideration of unpublished material)*
Identification and selection of studies	Were methods additional to database searching used to identify relevant reports?	No *(None reported in PRISMA chart)*
Identification and selection of studies	Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	No *(No index terms used. Field codes appear incorrectly translated for CINAHL)*
Identification and selection of studies	Were restrictions based on date, publication format, or language appropriate?	Yes *(English language limit included in protocol)*
Identification and selection of studies	Were efforts made to minimise error in selection of studies?	Yes *(Two independent reviewers carried out the selection process)*

Section	Question	Answer
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	High (*Flaws in search strategy)*
Data collection and study appraisal	Were efforts made to minimise error in data collection?	Probably yes *(Report suggests that 2 independent reviewers appraised data. Does not clearly state how many reviewers conducted data extraction)*
Data collection and study appraisal	Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Yes *(Study characteristics table is sufficiently detailed)*
Data collection and study appraisal	Were all relevant study results collected for use in the synthesis?	Yes *(Appears suitable)*
Data collection and study appraisal	Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Probably yes *(Risk of bias conducted using older version of Cochrane's Risk of bias tool)*
Data collection and study appraisal	Were efforts made to minimise error in risk of bias assessment?	Yes *(Two independent reviewers appraised the studies alongside the reviewing team)*
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low *(Methods are appropriate for review)*
Synthesis and findings	Did the synthesis include all studies that it should?	Yes *(10 studies were included in the review - 1 non-randomised controlled trial, 1 cross-sectional study and 8 cohort studies. Analysis is conducted based on the outcomes reported. Meta-analysis is conducted where possible)*
Synthesis and findings	Were all pre-defined analyses reported or departures explained?	Yes *(All analyses mentioned and addressed in the results section. All necessary analysis (narrative analyses and meta-analyses) was carried out to include all of the studies)*
Synthesis and findings	Was the synthesis appropriate given the nature and similarity in the	Yes

Section	Question	Answer
	research questions, study designs and outcomes across included studies?	*(Study design and analysis are appropriate for review)*
Synthesis and findings	Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Probably yes *(Narrative synthesis was carried out where possible which addressed heterogeneity as statistical combination was not possible. Secondly, forest plot indicates that random effects model was used, however, report does not address the heterogeneity when I^2 is high)*
Synthesis and findings	Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Yes *(Funnel plots are available)*
Synthesis and findings	Were biases in primary studies minimal or addressed in the synthesis?	Yes *(GRADE assessment is carried out and biases are addressed, however, they are addressed in the discussions*.)
Synthesis and findings	Concerns regarding the synthesis and findings	Low (*Appears to have taken bias into account but further write up about this could have been useful)*
Judging risk of bias	Concerns regarding specification of study eligibility criteria	Low *(All areas appear to be well covered with relevant information)*
Judging risk of bias	Concerns regarding methods used to identify and/or select studies	High (*Flaws in search strategy)*
Judging risk of bias	Concerns regarding methods used to collect data and appraise studies	Low *(Methods seem appropriate for review)*
Judging risk of bias	Concerns regarding the synthesis and findings	Low (*Has taken bias into account but further write up about this could have been useful)*
Overall review ratings	Overall risk of bias	Low *(Some issues with detailed explanations missing but otherwise all areas scored low)*

Section	Question	Answer
Overall review ratings	Applicability as a source of data	Fully applicable

IG evidence to recommendations justification: 10 studies were included in this new systematic review, with 8 of these being suitable for inclusion in the meta-analysis. These were mostly cohort in design, with one cross-sectional and one non-randomised trial. Bariatric surgery was compared to medical therapy, conservative management and in people with and without PCOS in 3 comparisons. One study compared bariatric surgery to medical therapy in women with PCOS, as such meta-analysis was not possible. Metabolic outcomes such as fasting glucose, fasting insulin, triglycerides, LDL, HbA1C, body weight, BMI, total testosterone and sex hormone binding globulin improved in the bariatric surgery group compared to the medical therapy group. The study had high risk of bias and had serious imprecision.

When bariatric surgery was compared to conservative management, improvements in ovulation, percentage total weight loss and intermenstrual length were seen in women with PCOS in the bariatric surgery group. As this was a single study, meta-analysis was not possible, the IG notes the study had a high risk of bias and serious imprecision

For comparison 3, the effect of bariatric surgery in women with PCOS was compared to those without PCOS. Across the 9 studies, 6 reported on reproductive outcomes and 8 reported on non-reproductive outcomes. Meta-analysis was not possible for reproductive outcomes as the studies all reported on different outcomes to each other. The impact of bariatric surgery on regular menstrual cycles, ovulation, pregnancy rates and intermenstrual length favoured the PCOS group. Birth weight favoured the non-PCOS group. All other outcomes had no difference. For non-reproductive outcomes, fasting glucose was the only outcome that favoured the PCOS group. Fasting insulin and free testosterone favoured the non-PCOS group. All other outcomes had no difference between groups. The results for all studies had

low certainty due to a high risk of bias. Due to this, no EBRs were made, only CRs which is appropriate given the lack of certainty and lack of evidence.

IG clinical evidence

No health economic evidence was identified in the IG for review question 4.9 on bariatric/metabolic surgery.

4.9.2 NICE economic evidence

Included studies

A single health economic search was performed by NICE to identify published economic evaluations of relevance to all review questions in this guideline. See the literature search strategy in Appendix A

No economic studies were identified which were applicable to this review question (see economic study selection flow chart in Appendix B

Excluded studies

No economic studies were reviewed at full text and excluded from this review.

Economic model

No original health economic model was developed for review question 4.9 on bariatric / metabolic surgery as this is covered in NICE's existing guideline on managing overweight and obesity.

4.9.3 NICE recommendations

For guidance on the use of anti-obesity medications and bariatric surgery, see the section on medicines and surgery in NICE's guideline on managing overweight and obesity.

4.9.4 The committee's discussion and interpretation of the evidence

Clinical

The committee decided to refer to the NICE guideline on obesity and overweight management as the IG had only CR for this area with no EBRs. As such a cross referral was made to NG246.

Health economic

No health economic evidence was identified in the IG, or as part of NICE's original health economic literature search for review question 4.9 on bariatric/metabolic surgery.

As the committee cross-referred to NICE's existing guidance on obesity and overweight management (NG246), no health economic implications are associated with this review question.

4.10 Pregnancy outcomes

Review question 4.10: Are women with PCOS at increased risk of adverse pregnancy outcomes?

4.10.1 Recommendations from the International evidence-based guideline for PCOS*

Evidence-based recommendation:

4.10.1 Women with PCOS have higher risk pregnancies, and healthcare professionals should ensure that PCOS status is identified during antenatal care, and appropriate monitoring and support is provided.

4.10.2 Healthcare professionals should recognise that pregnant women with PCOS have an increased risk of:

- higher gestational weight gain
- miscarriage
- gestational diabetes
- hypertension in pregnancy and preeclampsia
- intrauterine growth restriction, small for gestational age babies and low birth weight
- preterm delivery
- caesarean section

4.10.3 Assisted reproductive technology in women with PCOS should be considered as not conferring additional risk of miscarriage, preterm birth, impaired fetal growth and caesarean section, over that observed in women without PCOS.

4.10.4 Women with PCOS should be considered as not having an increased risk of large for gestational age babies, macrosomia and instrumental delivery.

Practice points:

4.10.5 Early lifestyle intervention should be offered to pregnant women with PCOS, given the risk of higher baseline weight, excess gestational weight gain and pregnancy complications.

4.10.6 Blood pressure measurement should be performed when planning pregnancy or seeking fertility treatment, given the high risk of hypertensive disorders in pregnancy and the associated comorbidities in women with PCOS.

4.10.7 An OGTT should be offered to all women with PCOS when planning pregnancy or seeking fertility treatment, given the high risk of hyperglycaemia and the associated comorbidities in pregnancy. If not performed in the preconception phase, an OGTT should be offered at the first antenatal visit and repeated at 24-28 weeks gestation.

IG clinical evidence

Critical Appraisal - ROBIS systematic review checklist

Section	Question	Answer
Study eligibility criteria	Did the review adhere to pre-defined objectives and eligibility criteria?	Probably yes *(No predefined objectives identified. PICOS is well defined)*
Study eligibility criteria	Were the eligibility criteria appropriate for the review question?	Yes *(Clearly defined PICOS. Appropriate to the review question, however, systematic review question is about risk/prognosis.* *The clinical practice point is an intervention/management decision based on that risk)*
Study eligibility criteria	Were eligibility criteria unambiguous?	Probably yes *(Eligibility criteria clearly described in PICO)*
Study eligibility criteria	Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g.	Yes *(Review is an update on their previous systematic review.*

Section	Question	Answer
	date, sample size, study quality, outcomes measured)?	*Eligibility criteria are sufficiently detailed, restrictions around study characteristics are applied)*
Study eligibility criteria	Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Yes *(Study inclusion limited to English language. No publication date or format limits applied)*
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low *(All areas appear to be well covered with relevant information)*
Identification and selection of studies	Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Probably yes *(No use of sources for unpublished reports, otherwise acceptable)*
Identification and selection of studies	Were methods additional to database searching used to identify relevant reports?	No *(None reported in PRISMA chart)*
Identification and selection of studies	Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Probably no (*Some search terms not in accordance with protocol.* *No obvious effort to translate search for databases other than Medline.)*
Identification and selection of studies	Were restrictions based on date, publication format, or language appropriate?	Probably no *(Date limit applied using publication date, not database entry date – small date range may have therefore not been included.* *English language limit applied)*
Identification and selection of studies	Were efforts made to minimise error in selection of studies?	Yes *(Two independent reviewers carried out the selection process)*
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	High *(No searching beyond databases, doesn't look like searches were translated for databases beyond Medline)*
Data collection and study appraisal	Were efforts made to minimise error in data collection?	Probably yes *(The report suggests that 2 independent reviewers appraised data. Does not clearly state how many reviewers conducted data extraction)*

Section	Question	Answer
Data collection and study appraisal	Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Yes *(Study characteristics table is sufficiently detailed)*
Data collection and study appraisal	Were all relevant study results collected for use in the synthesis?	Yes *(All included)*
Data collection and study appraisal	Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Probably yes *(ROB conducted using older version of Cochrane's ROB tool)*
Data collection and study appraisal	Were efforts made to minimise error in risk of bias assessment?	Yes *(Two independent reviewers appraised the studies alongside the reviewing team)*
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low *(Methods are appropriate for review)*
Synthesis and findings	Did the synthesis include all studies that it should?	Yes *(All 109 studies were included)*
Synthesis and findings	Were all pre-defined analyses reported or departures explained?	Yes *(All analyses mentioned and addressed in the results section. All necessary analysis (narrative analyses and meta-analyses) was carried out to include all of the studies)*
Synthesis and findings	Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Yes (*Study design and analysis are appropriate for review)*
Synthesis and findings	Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Probably yes *(Subgroup analyses were present however they were written up narratively rather than presenting statistical outcomes. Heterogeneity was appropriately downgraded in GRADE)*
Synthesis and findings	Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Probably yes *(Funnel plots are reported where possible)*

Section	Question	Answer
Synthesis and findings	Were biases in primary studies minimal or addressed in the synthesis?	Yes *(GRADE assessment is carried out, and biases are addressed in the evidence summary section)*
Synthesis and findings	Concerns regarding the synthesis and findings	Low *(Authors have taken bias into account but further written explanation about this could have been useful)*
Judging risk of bias	Concerns regarding specification of study eligibility criteria	Low *(All areas are well covered with relevant information)*
Judging risk of bias	Concerns regarding methods used to identify and/or select studies	High *(No searching beyond databases, searches were not correctly translated for databases beyond Medline)*
Judging risk of bias	Concerns regarding methods used to collect data and appraise studies	Low *(Methods are appropriate for review)*
Judging risk of bias	Concerns regarding the synthesis and findings	Low *(Authors have taken bias into account but further written explanation about this could have been useful)*
Overall review ratings	Overall risk of bias	Low *(Some issues with search terms and subject headings, this question was part of the search for section 4.7)*
Overall review ratings	Applicability as a source of data	Fully applicable

IG evidence to recommendations justification: This updated systematic review consisted of 109 studies. One comparison with 17 outcomes was explored. Meta-analysis found that women with PCOS had significantly higher odds of miscarriage, gestational diabetes, gestational hypertension, pre-eclampsia, preterm birth, low birth weight, intrauterine growth restriction and caesarean section compared to women without PCOS. When BMI was matched in subgroup analyses, significantly higher odds of miscarriage, gestational diabetes, gestational hypertension, pre-eclampsia, low birth weight and caesarean section were still seen in women with PCOS

compared to controls. When studies were age matched in subgroup analyses, gestational diabetes, gestational hypertension, pre-eclampsia, pre-term birth and caesarean section was significantly higher in women with PCOS compared to controls. In post ART pregnancies, significantly higher odds of miscarriage, gestational diabetes, gestational hypertension, pre-eclampsia, pre-term birth, low birth rate and higher BMI were seen in women with PCOS compared to controls. In a subgroup analysis of high-quality studies, miscarriage, gestational diabetes, gestational hypertension, pre-eclampsia, pre-term birth, low birth weight and caesarean section were significantly higher in women with PCOS compared to those without. Babies being small for their gestational age changed to be significantly higher in women with PCOS in this subgroup only. All 4 EBRs were strong recommendations for the option; this is well supported by the evidence provided. A large number of studies were included for this section, with sufficient subgroup analyses to determine whether the outcomes were still affected for women with PCOS.

IG economic evidence

No health economic evidence was identified in the IG for review question 4.10 on pregnancy outcomes.

The IG acknowledged the higher cost to screen for adverse outcomes in pregnancies of women with PCOS and noted, that in terms of cost-effectiveness, no judgement could be made on screening women with PCOS. The IG did, however, note that increased screening for pregnancy complications for people with PCOS will increase equity.

4.10.2 NICE economic evidence

Included studies

A single health economic search was performed by NICE to identify published economic evaluations of relevance to all review questions in this guideline. See the literature search strategy in Appendix A.

No economic studies were identified which were applicable to this review question (see economic study selection flow chart in Appendix B).

Excluded studies

No economic studies were reviewed at full text and excluded from this review.

Economic model

No original health economic model was developed for review question 4.10 on pregnancy outcomes as this review question was not concerned with comparing two or more alternative courses of action.

4.10.3 NICE recommendations

The relevant recommendations for this section are Rec 1.22.1 to 1.22.3.

4.10.4 The committee's discussion and interpretation of the evidence

Clinical

The IG made four EBRs (4.10.1 to 4.10.4) and three practice point recommendations (4.10.5 to 4.10.7) for this review question. The committee discussed the risk factors associated with PCOS in terms of pregnancy outcomes and felt it was important to contextualise IG recommendation 4.10.2, to prompt discussion around these risk factors and how this might affect women with PCOS. The committee added an additional recommendation to state that the increased risk factors from IG rec 4.10.2 should be monitored during pregnancy. A new recommendation was also made for this section as the committee felt it would be a good opportunity to direct users to other NICE guidelines relating to pregnancy and post-natal care.

Health economic

No health economic evidence was identified in the IG, or as part of NICE's original health economic literature search for review question 4.10 on pregnancy outcomes.

The committee cross-referred to several of NICE's existing guidelines as part this section of this guideline. The committee also contextualised the IG's recommendations that they concluded were specifically important for a PCOS population that were not covered in NICE's existing guidelines. As this contextualised recommendation was only concerned with informing people of the associated higher risk areas of pregnancy for people with PCOS, very little resource implications are anticipated with this recommendation. In addition, no resource implications are associated with cross-referring to existing NICE guidance.

4.11 Metformin in pregnancy

Review question 4.11: In women with PCOS in pregnancy, is metformin compared to placebo/standard care effective in reducing pregnancy complications and adverse neonatal outcomes?

4.11.1 Recommendations from the International evidence-based guideline for PCOS*

Evidence-based recommendations:

4.11.1 Healthcare professionals should be aware that metformin in pregnant women with PCOS 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

4.11.2 Metformin could be considered in some circumstances (e.g. risk for preterm birth), to reduce preterm delivery and limit excess gestational weight gain, in pregnant women with PCOS.

Practice point(s):

4.11.3 Women should be counselled that the consequences of metformin exposure on long-term offspring health remain unclear and there is a suggestion of increased childhood weight, although causality is not certain.

4.11.4 Side-effects of metformin are mostly mild, transient gastrointestinal symptoms and are not worse in pregnancy.

1 **IG clinical evidence**

2 **Critical Appraisal - ROBIS systematic review checklist**

Section	Question	Answer
Study eligibility criteria	Did the review adhere to pre-defined objectives and eligibility criteria?	Probably yes *(No predefined objectives identified. PICOS is well defined)*
Study eligibility criteria	Were the eligibility criteria appropriate for the review question?	Yes *(Clearly defined PICOS. Appropriate to the review question)*
Study eligibility criteria	Were eligibility criteria unambiguous?	Probably yes *(Eligibility criteria clearly described in PICO)*
Study eligibility criteria	Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Yes *(Eligibility criteria are sufficiently detailed, restrictions around study characteristics are applied)*
Study eligibility criteria	Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Yes *(Study inclusion limited to English language. No publication date or format limits applied)*
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low (*All areas are well covered with relevant information)*
Identification and selection of studies	Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Probably yes *(Searches were carried out for 5 databases - Medline, PsycINFO, EMBASE, All EMB and CINAHL)*
Identification and selection of studies	Were methods additional to database searching used to identify relevant reports?	Yes *(Reasonable selection of databases + PRISMA chart reports additional articles and grey literature identified via manual searches,*

Section	Question	Answer
		registries and reference lists)
Identification and selection of studies	Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Probably no *(Search terms likely to over-retrieve results. Not clear that searches were translated for databases beyond Medline - could invalidate search filters if not properly adapted. Further clarity in this area would have been helpful to determine impact)*
Identification and selection of studies	Were restrictions based on date, publication format, or language appropriate?	Probably yes *(Search is updating prior work from 2020, however update date is also unclear. English language limit used)*
Identification and selection of studies	Were efforts made to minimise error in selection of studies?	Yes *(2 independent reviewers carried out the selection process)*
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Unclear *(Further information on search translations and prior searches would have been helpful, however what is present is acceptable)*
Data collection and study appraisal	Were efforts made to minimise error in data collection?	Probably yes *(Report suggests that 2 independent reviewers appraised data. Does not clearly state how many reviewers conducted data extraction)*
Data collection and study appraisal	Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Yes *(Study characteristics table is sufficiently detailed)*

Section	Question	Answer
Data collection and study appraisal	Were all relevant study results collected for use in the synthesis?	Yes *(All were included)*
Data collection and study appraisal	Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Probably yes *(Risk of bias conducted using older version of Cochrane's risk of bias tool)*
Data collection and study appraisal	Were efforts made to minimise error in risk of bias assessment?	Yes *(Two independent reviewers appraised the studies alongside the reviewing team)*
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low *(Methods seem appropriate for review)*
Synthesis and findings	Did the synthesis include all studies that it should?	Yes *(Seven studies were included in the review - all RCTs, comparing metformin vs. placebo/control reporting 20 outcomes of interest. Only 2 out of 7 RCTs were not placebo controlled - where applicable, sensitivity analyses were performed to exclude these two studies from the overall analysis to examine their impact on results. Meta-analysis is conducted where possible)*
Synthesis and findings	Were all pre-defined analyses reported or departures explained?	Yes *(All analyses mentioned and addressed in the results section. All necessary analysis (narrative analyses and meta-analyses) was carried out to include all of the studies)*
Synthesis and findings	Was the synthesis appropriate given the nature and similarity in the research	Yes

Section	Question	Answer
	questions, study designs and outcomes across included studies?	*(Study design and analysis are appropriate for review)*
Synthesis and findings	Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Probably yes *(Subgroups were considered in narrative synthesis, however authors state that women at high risk of preterm delivery were not the focus of the review. Forest plot indicates that random effects model was used. Two out of 7 RCTs were not placebo controlled - where applicable, sensitivity analyses were performed to exclude these two studies from the overall analysis to examine their impact on results)*
Synthesis and findings	Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Yes *(Funnel plots are available)*
Synthesis and findings	Were biases in primary studies minimal or addressed in the synthesis?	Yes *(GRADE assessment is carried out and biases are addressed, however, they are not addressed in the discussions)*
Synthesis and findings	Concerns regarding the synthesis and findings	Low *(Appears to have taken bias into account but further write up about this could have been useful)*
Judging risk of bias	Concerns regarding specification of study eligibility criteria	Low (*All areas well covered with relevant information)*
Judging risk of bias	Concerns regarding methods used to identify and/or select studies	Unclear *(Further information on search translations and*

Section	Question	Answer
		prior searches would have been helpful, however what is present is acceptable)
Judging risk of bias	Concerns regarding methods used to collect data and appraise studies	Low *(Methods are appropriate for review)*
Judging risk of bias	Concerns regarding the synthesis and findings	Low *(Authors have taken bias into account but further write up about this could have been useful)*
Overall review ratings	Overall risk of bias	Low *(Further detailed discussion and information on search strategies could be useful in some places, otherwise the study eligibility, identification of studies, methods and synthesis are appropriate)*
Overall review ratings	Applicability as a source of data	Fully applicable

IG evidence to recommendations justification: Seven studies were included in this new systematic review, comparing metformin use to placebo/control across 20 outcomes. Outcome 6 – preterm birth, included 6 studies and favoured the use of metformin compared to placebo with low heterogeneity. For outcome 9 – gestational age at delivery, 5 studies were included, favouring metformin with low heterogeneity. No differences were seen in glycaemic measures such as gestational diabetes, or in preeclampsia, neonatal anthropometry or measures of foetal wellbeing. People treated with metformin also had less gestational weight gain. Evidence certainty was high for both preterm birth and gestational age at delivery. The subgroup of women at high risk from preterm delivery was not well represented by the studies used, as such the IG states that this group would theoretically benefit more from metformin therapy, but there is a lack of evidence at present. An EBR was made which was a

conditional weak recommendation for either option, highlighting that there is no evidence that metformin in women with PCOS prevents gestational diabetes, late miscarriage, hypertension in pregnancy, preeclampsia or macrosomia. This is an appropriate strength of recommendation given that although there was no evidence of a difference between the metformin and placebo groups for these outcomes, the studies for these outcomes were downgraded due to issues with bias. A second EBR was made for the use of metformin in specific circumstances (e.g. risk of pre-term birth), this is well supported by the evidence presented.

IG economic evidence

No health economic evidence was identified in the IG for review question 4.11 on metformin in pregnancy.

The IG noted that they made a recommendation to not routinely use metformin in pregnancy, even though metformin is cheap.

4.11.2 NICE economic evidence

Included studies

A single health economic search was performed by NICE to identify published economic evaluations of relevance to all review questions in this guideline. See the literature search strategy in Appendix A.

No economic studies were identified which were applicable to this review question (see economic study selection flow chart in Appendix B).

Excluded studies

No economic studies were reviewed at full text and excluded from this review.

Economic model

No original health economic model was developed for review question 4.11 on metformin in pregnancy as other areas of the guideline were of a higher priority for original health economic modelling.

Unit costs

Unit costs for metformin can be found in **Table 2** which can be found in section 4.3 of this report.

4.11.3 NICE recommendations

The relevant recommendations for this section are Rec 1.22.4 and 1.22.5.

4.11.4 The committee's discussion and interpretation of the evidence

Clinical

The IG made two EBR and two practice point recommendations for review question 4.11. The committee contextualised the two EBRs (4.11.1 and 4.11.2). The committee discussed the IG's recommendations regarding the use of metformin in pregnancy and concluded that it was important to highlight that using metformin in women with PCOS does not prevent gestational diabetes, late miscarriage, hypertension, pre-eclampsia or macrosomia (IG rec 4.11.1).

The committee also discussed the potential benefits of metformin and highlighted that metformin could be considered to reduce the risk of preterm delivery and limit excess gestational weight gain. The committee noted that metformin often causes gastrointestinal side effects, which many women may find difficult to tolerate during pregnancy. They also emphasised that metformin for this indication is unlikely to be available in primary care, meaning women would need referral to, or management within, secondary care.

Health economic

No health economic evidence was identified in the IG, or as part of NICE's original health economic literature search for review question 4.11 on metformin in pregnancy. Unit costs were also presented to the committee to aid their consideration of cost-effectiveness.

The committee acknowledged that the daily costs associated with taking metformin are small – typically £0.03 - £0.07 per day (see **Table 2** for further information). However, because the clinical evidence indicated that prescribing metformin in pregnancy does not prevent, gestational diabetes, late miscarriage, hypertension, pre-eclampsia and birthweight ≥4000g, the committee agreed that it was appropriate to contextualise the IG's recommendation (4.11.1) that details this information.

In terms of instances where metformin in pregnancy could be of clinical benefit, the committee acknowledged that in some circumstances (for example, those at risk of pre-term birth) metformin could be considered to reduce pre-term delivery and limit excess weight gain. The committee noted that in clinical practice the prescription of metformin for this indication is varied. The gastrointestinal side-effects of metformin were also discussed, and the committee acknowledged that a large proportion of people being prescribed metformin in pregnancy may find these side effects difficult to tolerate. The committee therefore noted a preference for modified release preparations but still emphasised the importance of discussing the potential for gastrointestinal side-effects prior to prescribing metformin so people can make an informed decision as to whether they wish to commence treatment. The relative discussion concerning the cost-effectiveness of modified-release metformin compared to standard release metformin can be found section 4.3.4 of this report.

The committee noted that the prescription of metformin in pregnancy would typically be conducted in secondary care. The committee discussed that the costs associated with prescribing metformin are the medication costs and the staff time to provide the associated information and support for those receiving metformin. For the sub-group of people where metformin could be considered, the committee were confident in the cost-effectiveness of metformin due to the small costs associated with treatment and the higher costs associated with pre-term birth and potential complications associated with excess weight gain in pregnancy. The committee reasoned that the costs of metformin would be more than offset by savings from averted pre-term birth.

Therefore, they were confident that metformin was likely to be cost-effective in this group.

Overall, the potential increase in uptake of metformin is uncertain, but not expected to be substantial, for the reasons outlined above and because this is only a consider recommendation. The committee therefore concluded that no significant resource impact is anticipated as a result of this recommendation.

Appendix A Health economic literature review search strategy

The searches for the cost effectiveness evidence were run on 5 December 2024 and re-run on 25 March 2026. The following databases were searched: Medline (Ovid), Embase (Ovid; Econlit (Ovid) and the International HTA Database. Limits were applied to remove study types. The validated NICE cost utility filter was used on MEDLINE and Embase. English language limits were applied, and the search was run for evidence published since 2009.

A NICE Senior Information Specialist (SIS) conducted the searches. The MEDLINE strategy was quality assured by another NICE SIS. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2015 PRESS Guideline Statement.

The Medline strategy is presented below

1 Polycystic Ovary Syndrome/

2 ((polycystic or poly cystic) adj4 ovar*).tw.

3 pco*.tw.

4 ((degenerat* or sclerocystic) adj4 ovar*).tw.

5 stein leventhal.tw.

6 Anovulation/

7 anovulat*.tw.

8 (oligo ovulat* or oligoovulat*).tw.

9 ((hyperandrogen* or hyper androgen*) adj4 ovar*).tw.

10 or/1-9 55812

11 Economics/

12 Value of life/

13 exp "Costs and Cost Analysis"/

14 exp Economics, Hospital/

15 exp Economics, Medical/

16 Economics, Nursing/

17 Economics, Pharmaceutical/

18 exp "Fees and Charges"/

19 exp Budgets/

20 budget*.ti,ab.

21 cost*.ti.

22 (economic* or pharmaco?economic*).ti.

23 (price* or pricing*).ti,ab.

24 (cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.

25 (financ* or fee or fees).ti,ab.

26 (value adj2 (money or monetary)).ti,ab.

27 or/11-26

28 10 and 27

29 letter.pt. or letter/

1 30 note.pt.

2 31 editorial.pt.

3 32 case report/ or case study/

4 33 (letter or comment*).ti.

5 34 or/29-33

6 35 randomized controlled trial/ or random*.ti,ab.

7 36 34 not 35

8 37 animals/

9 38 exp Animals, Laboratory/

10 39 exp Animal Experimentation/

11 40 exp Models, Animal/

12 41 exp Rodentia/

13 42 (rat or rats or mouse or mice or rodent*).ti.

14 43 or/37-42

15 44 43 not humans/

16 45 36 or 44

17 46 28 not 45

18 47 limit 46 to english language/

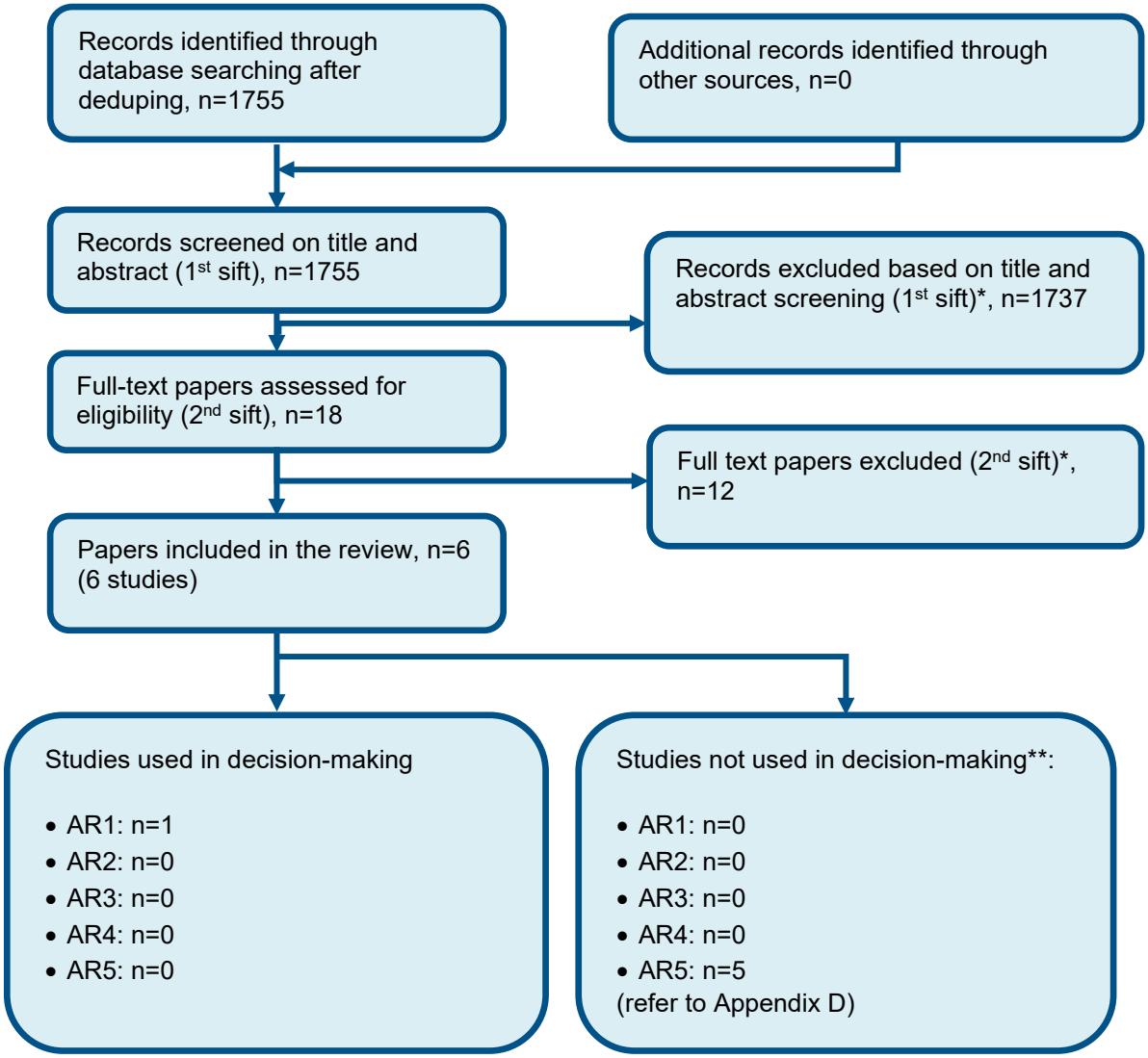
19 48 limit 47 to ed=20090101-20241

1 49 limit 47 to dt=20090101-20241205

2 50 48 or 49

3

Appendix B Health economic PRISMA diagram



* Not an economic evaluation, non-relevant population, intervention, comparison, design, setting or perspective; non-English language, not a full paper

**please refer to Review strategy described in the Economic review protocol in Methods document (Appendix B)

Appendix C Economic evidence tables

None

Appendix D Excluded health economic studies

None

1

Appendix E Research recommendation

Recommendation for research

Are long-term hair reduction methods - alone or in combination with other therapies – clinically and cost effective for management of hirsutism in adolescents and adults with PCOS?

Why this is important

There is a lack of evidence for long-term hair reduction methods in those with PCOS and hirsutism comparing long-term hair reduction to other methods of hair reduction. The cost of long-term hair reduction needs to be established with sufficient high-quality evidence reporting appropriate long-term outcomes that can be modelled for cost-effectiveness.

Rationale for the recommendation for research

Importance to 'patients' or the population	Hirsutism is common for those with PCOS and can be particularly detrimental to their emotional wellbeing and quality of life.
Relevance to NICE guidance	The NICE PCOS guideline, which was based on the International Guideline on PCOS, was unable to recommend laser hair reduction due to a lack of evidence and the resultant lack of evidence for cost-effectiveness. A research recommendation was proposed.
Relevance to the NHS	The impact on the NHS if new guidance is recommended is unclear as there is no evidence with measurable quality of life outcomes for cost-effectiveness at present.
National priorities	The question 'What is the most effective treatment for hirsutism (i.e. unwanted excess hair growth) for women and people living with PCOS?' was ranked 3rd in the prioritisation survey in the James Lind Alliance Priority Setting Partnership in PCOS and 11th after the workshop. National (Verity-PCOS) and international surveys consistently rank hirsutism among the top 3 most important patient priorities.

Current evidence base	Only four randomised controlled trials were found in the International Guideline, of which only one small randomised controlled trial compared laser hair reduction (high-fluence laser) to low-fluence laser (sham). There were no long-term outcomes and no outcomes of relevant cost-effectiveness measures (e.g. EQ-5D). There were no adolescent studies or studies of other types of long-term hair reduction.
Equality considerations	The effectiveness of laser treatment can differ depending on hair and skin colour, therefore there can be variability in results by ethnicity or skin type.

Modified PICO table

Population	Hirsute females with PCOS (diagnosed by Rotterdam criteria) of any age, ethnicity or weight. Subgroups: • adolescents, adults post-menopausal • different skin colour • BMI
Intervention	Long-term hair reduction methods • Lasers • Pulsed light devices • Electrolysis Alone or in combination with other treatments.
Comparator	• Each long-term hair reduction compared to another • Placebo/no-hair removal (e.g. low-fluence [sham] laser) • Other hair removal/reduction methods e.g. shaving, waxing, bleaching, plucking, epilation Alone or in combination with other pharmacological or non-pharmacological treatments
Outcome	• Self-reported data on hirsutism QoL • PCOS QoL scale (PCOSQ, EQ5D)

	• Participant-reported time spent on hair removal • Participant-reported cost of hair removal • Self-esteem • Anxiety and depression score • Safety (skin scars, skin spots) • Objective/clinician-rated measures of hirsutism e.g. modified Ferriman-Gallwey score, trichoscopic methods (hair shaft thickness, hair shaft colour, terminal vs. vellus hair ratio and hair density per cm^2) • Cost
Study design	Randomised controlled trials
Timeframe	Long-term outcomes (1 and 2 years)
Additional information	This protocol is based on the International Guideline protocol for Q4.8 Is permanent hair reduction alone or in combination with other therapies, effective for the management of hirsutism in adolescents and adults with PCOS?

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Appendix F References

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Kangwanrattanakul K (2022) Mapping of the World Health Organization Quality of Life Brief (WHOQOL-BREF) to the EQ-5D-5L in the general Thai population. PharmacoEconomics 7: 139–148.

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