health
Department:
Health
REPUBLIC OF SOUTH AFRICA

2030 NDP

South African National Department of Health, National Essential Medicines List Committee

Progesterone, per vagina, for prevention of preterm labour In Twin Pregnancies[1]

DATE: 2 December 2025

Medicine Class	Progesterones (Progestins)	*If applicable* *Please consider therapeutic interchange policy*
Medicine/s name **-INN:** **- South African name (if differs from INN)**	Progesterone	*http://www.whocc.no/atc_ddd_index/*
Medicine/s (ATC5):	G03DA	*http://www.whocc.no/atc_ddd_index/*
Indication (ICD-10 code):	Z35.2	*https://www.health.gov.za/icd-10-master-industry-table/*
SAHPRA Approved	Yes	SAHPRA registered health products database *https://medapps.sahpra.org.za:6006/*
Dosage form/s	Pessary, vaginal tablet	
Route of administration/s	Vaginal	
Patient population	Pregnant woman with twin gestations, including both dichorionic and monochorionic twins, between16–26 weeks with a short cervix (≤ 25 mm) on ultrasound	

[1] The review template is a tool utilised to systematically synthesise evidence and aid decision-making by the National Essential Medicines Committee (NEMLC) on amendments to the Standard Treatment Guidelines and Essential Medicines List. The template was revised through collaboration between the South African Medical Research Council, University of Stellenbosch, NEMLC, the Essential Drugs Programme (EDP) and SA GRADE Network and approved for piloting by the NEMLC in February 2025. The template is to be reviewed annually, utilised along with the relevant NEMLC approved policies, guidelines, methodology and processes and naming of review documents must adhere to the naming conventions set by the EDP. Current version updated post tabling at NEMLC meeting held 16th October 2025.

Prevalence and/or incidence of condition	The rate of early preterm birth reported in twin pregnancies is approximately 10 %, compared to 1–2 % in singleton pregnancies.[1]	
Level of Care	Adult Hospital Level	
Prescriber level	Doctor prescribed	

EXECUTIVE SUMMARY

- We conducted a rapid review of available evidence that assessed the effect of vaginal progesterone compared to standard of care or placebo in pregnant woman with twin gestations, including both dichorionic and monochorionic twins, between16–26 weeks with a short cervix (≤ 25 mm) on ultrasound (restrictions: none).
- We searched the Guidelines International Network (GIN) library, the National Institute for Health and Care Excellence (NICE) website, the American College of Obstetrics and Gynaecology (ACOG), the Society for Maternal Fetal Medicine (SMFM), and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) for relevant guidelines [November 2025]. We identified five clinical practice guidelines and included two of these, and also included the evidence synthesis which informed the NICE NG137 guideline[2].
- Two clinical practice guidelines were included: (1) ACOG a practice bulletin for obstetrician-gynaecologists in the United States[3,4] published in 2021 as an update to 2012 guidance. The guideline addresses the prediction and prevention of spontaneous preterm birth in both single and multiple pregnancies. (2) The NICE guideline was published in 2024. The NICE guideline focuses on management guidance for twin and triplet pregnancies[5].
- A duplicate AGREE assessment rated the NICE guideline[5] as high quality, and the AMSTAR II of the underlying effectiveness review was moderate quality. The effectiveness results are summarised below.
- Summary of effectiveness results[5] for vaginal progesterone vs placebo. All comparisons were made to placebo only.
    - **Reduction in preterm birth < 34 weeks:** When vaginal progesterone (100 to 600mg per day) is compared to placebo in twin pregnancies in women with short cervixes, vaginal progesterone likely reduces preterm births < 34 weeks (moderate certainty)
        - Spontaneous preterm births < 34 weeks: RR 0.58 (95% Confidence interval (CI) 0.38 to 0.89), 273 fewer per 1000 (from 404 fewer to 72 fewer per 1000), NNT 4. (moderate certainty evidence)
        - Preterm birth <32 weeks: RR 0.56 (95% CI 0.33 to 0.93), 205 fewer per 1000 (from 312 fewer to 33 fewer), NNT 7. (moderate certainty evidence)
    - **NICU stay/prolonged hospital stay:**
        - Not reported
    - **Neonatal mortality:** When vaginal progesterone (100 to 600mg per day) is compared to placebo in twin pregnancies in women with short cervixes, there may be little to no difference in neonatal deaths or stillbirths (low certainty).
        - Neonatal deaths: RR 0.51 (95% CI 0.2 to 1.28), 51 fewer per 1000 (from 84 fewer to 29 more), NNT 16. (Low certainty evidence)
        - Stillbirths: RR 0.54 (95% CI 0.17 to 1.77), 21 fewer per 1000 (from 39 fewer to 36 more), NNT -90. (Low certainty evidence)
    - **Safety: serious adverse events and adverse events:**
        - Not reported
- Vaginal progesterone is currently an essential medicine at Adult Hospital Level in South Africa in singleton pregnancies in: (1) mid- trimester cervical shortening (defined as ≤25 mm before 24 weeks gestation) with no prior spontaneous singleton preterm birth, and/or (2) women with a history of spontaneous preterm birth or mid-trimester loss.[6]

KEY RECOMMENDATIONS

Type of ERC recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
	☐	☐	☐	X

High level summary of conclusions from Evidence to Decision Framework – See link	The review of the literature shows that when vaginal progesterone is compared to placebo in twin pregnancies in women with short cervixes, vaginal progesterone likely reduces preterm births < 34 weeks. There may be little to no difference in stillbirth or neonatal death.					
NEMLC Ratification	**Date**	**Comments**				
	26/02/26					
EML Status	EML[2]	Non-EML – contingent on stated reference price threshold in Rand Value classified as **NEML-PT (Non EML Price Threshold)**		Non-EML		
	X	☐		☐		
Therapeutic Interchange Considerations (if applicable)	If YES:	Alternative medicine/s name (INN)	Alternative/s SAHPRA registered?	Formulation/s	Equipotent dose/ Dose range and dosing interval	If NO, tick box
						X
Trigger for review	Alternative therapeutic agent at a lower price. Update based on new trial results.					

REVIEW TEAM

Review contributors as detailed below:

[2] An item designated as 'EML' indicates that item is not subject to price threshold set by NEMLC however may be subject to benchmark reference pricing during the contracting process as per the Framework for the Inclusion of Items in National Pharmaceutical Contracts: Therapeutic Classes, Reference Pricing, and Series-Based Specification

Name & Affiliation	Declaration of Interests	Defining the PICO	Protocol development	Literature search	Study selection	Data extraction & characteristics of included studies	Quality appraisal	Data analysis	GRADE assessment	Write up and referencing	Clinical Expertise & interpretation	Quality assurance
Dr Natasha Gloeck[1,2]	None to declare	X	X	X	X	X	X	X	X	X	X	X
Dr Millidhashni Reddy[3]	None to declare	X	X		X	X	X			X	X	X
Prof Stefan Gebhardt[4]	None to declare	X		X	X						X	X

1. Health Systems Research Unit, South African Medical Research Council,
2. South African GRADE Network
3. Pharmaceutical Consultant: Health Technology Assessment and Policy, National Department of Health
4. Stellenbosch University and Tygerberg Hospital

ACKNOWLEDGEMENTS

The members of the Expert Review Committee (ERC), and National Essential Medicines List Committee. This research was supported by the E2D Collaboration, which brings together the NDoH, the Health Systems Research Unit (HSRU) and Cochrane South Africa at the South African Medical Research Council (SAMRC), and the Centre for Evidence-based Health Care (CEBHC) at Stellenbosch University.

EVIDENCE TO DECISION FRAMEWORK

Question	
Should Progesterone(micronized vaginal progesterone) 200mg versus Standard of care or placebo be used in pregnant woman with twin gestations, including both dichorionic and monochorionic twins, between16–26 weeks with a short cervix (≤ 25 mm) on ultrasound?	
Population:	Pregnant woman with twin gestations, including both dichorionic and monochorionic twins, between16–26 weeks with a short cervix (≤ 25 mm) on ultrasound
Intervention:	Progesterone (micronized vaginal progesterone) 200mg, vaginally, at bedtime
Comparison:	Standard of care or placebo

Setting:	**PUBLIC SECTOR SOUTH AFRICA**
Perspective:	**PUBLIC HEALTH/ POPULATION**

ASSESSMENT

Problem Priority (optional)
Why is this medicine being evaluated?

The rate of early preterm birth reported in twin pregnancies is approximately 10%, compared to 1–2% in singleton pregnancies. In twin pregnancies an increase in risk for early preterm labour is observed in women with cervical length <25 mm[1]. Vaginal progesterone is currently an essential medicine at Adult Hospital Level in South Africa in singleton pregnancies in: (1) mid- trimester cervical shortening (defined as ≤25 mm before 24 weeks gestation) with no prior spontaneous singleton preterm birth, and/or (2) women with a history of spontaneous preterm birth or mid-trimester loss. In 2025, NEMLC requested a review of the literature to determine if the recommendation for singleton pregnancies as outlined above should be expanded to include twin pregnancies.[6]

Desirable Effects
How substantial are the desirable anticipated effects (i.e., benefits)?

Judgement	Research evidence	Additional considerations (by committee)
○ Trivial ○ Small ○ **Moderate** ○ Large ○ Varies (if so, why?) ○ Don't know	1. **Reduction in preterm birth < 34 weeks[5]:** Vaginal progesterone VS placebo in twin pregnancies in women with short cervixes, vaginal progesterone likely reduces preterm births < 34 weeks – Spontaneous preterm birth <34 weeks: One included study (IPD Review (Conde-Agudelo 2022[7]) RR 0.58 (0.38 to 0.89), 95 participants, moderate quality evidence. – 273 fewer per 1000 spontaneous preterm births <34 weeks, ranging from 72 fewer to 404 fewer per 1000. – Preterm birth < 32 weeks: One included study (IPD Review (Conde-Agudelo 2022[7]) RR 0.56 (0.33 to 0.93), 95 participants, moderate quality evidence. – 205 fewer per 1000 preterm births <32 weeks, ranging from 33 fewer to 312 fewer per 1000.	*The ERC judged that the reduction in preterm birth <34 weeks in the relevant population constituted a moderate desirable effect.*

	2. **NICU stay/prolonged hospital stay -** Not reported. 3. **Neonatal mortality[5]:** Vaginal progesterone VS placebo in twin pregnancies in women with short cervixes, there may be little to no difference in neonatal deaths or stillbirths. – Neonatal death: One included study (IPD Review (Conde-Agudelo 2022[7]) RR 0.51 (0.2 to 1.28), 190 participants, low quality evidence. – 51 fewer neonatal deaths per 1000, ranging from 84 fewer to 29 more per 1000. – Stillbirth: One included study (IPD Review (Conde-Agudelo 2022) RR 0.54 (0.17 to 1.77), 190 participants, low quality evidence. – 21 fewer stillbirths per 1000, ranging from 39 fewer to 36 more per 1000. 4. **Safety:** AEs, SAEs Not reported.	
Undesirable Effects **How substantial are the undesirable anticipated effects (i.e., harms and toxicity)?**		
Judgement	**Research evidence**	**Additional considerations (by committee)**
○ Large ○ Moderate ○ Small ○ **Trivial** ○ Varies (if so, why?) ○ Don't know	1. **Safety:** AEs, SAEs Not reported. The previous NEMLC approved review on the use of progesterone for prevention of preterm birth in a select "at risk" population reported that in women who choose to take progesterone for preterm birth prevention, it appears to be safe with no major adverse events. These results have been noted in follow-up studies up to two years.[6,8]	*The ERC noted/judged that, based on previous NEMLC review, the undesirable effects are likely trivial.*
Certainty of evidence[3] **What is the overall certainty of the evidence of effects (across all critical outcomes)?**		
Judgement	**Research evidence**	**Additional considerations (by committee)**

[3] **CERTAINTY OF EVIDENCE**
High certainty: confident in the evidence / We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: mostly confident, but further research may change the effect / We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: some confidence, further research likely to change the effect / Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

○ Very low ○ **Low** ○ **Moderate** ○ High ○ No included studies	Low (GRADE ratings ranged from low to moderate certainty evidence)	

Values
Is there important uncertainty in how people with conditions, caregivers, healthcare providers or decision-makers value the main outcomes?

Judgement	Research evidence	Additional considerations (by committee)
○ Important uncertainty ○ Possibly important uncertainty ○ **Probably no important uncertainty** ○ No important uncertainty	**Reduction in preterm birth < 34 weeks:** When vaginal progesterone is compared to placebo in twin pregnancies in women with short cervixes, vaginal progesterone likely reduces preterm births < 34 weeks **Neonatal mortality:** When vaginal progesterone is compared to placebo in twin pregnancies in women with short cervixes, there may be little to no difference in neonatal deaths or stillbirths.	*The ERC judged that there was no reason to suspect varying values among the affected population identified in the evidence.*

Balance of effects
Does the balance of effects favour the medicine being considered an essential medicine? Do the desirable effects outweigh the undesirable effects?

Judgement	Research evidence	Additional considerations (by committee)
○ **Yes (*Favours the intervention*)** ○ Probably Yes (*Probably favours the intervention*) ○ Probably No (*Probably favours the comparison*) ○ No (*Favours the comparison*) ○ Varies (if so, why?) ○ Don't know	1. **Reduction in preterm birth < 34 weeks[5]:** Vaginal progesterone VS placebo in twin pregnancies in women with short cervixes, vaginal progesterone likely reduces preterm births < 34 weeks – Spontaneous preterm birth <34 weeks: One included study (IPD Review (Conde-Agudelo 2022[7]) RR 0.58 (0.38 to 0.89), 95 participants, moderate quality evidence. – 273 fewer per 1000 spontaneous preterm births <34 weeks, ranging from 72 fewer to 404 fewer per 1000. – Preterm birth < 32 weeks: One included study (IPD Review (Conde-Agudelo 2022[7]) RR 0.56 (0.33 to 0.93), 95 participants, moderate quality evidence.	*The ERC determined that, on balance of health effects, progesterone was favoured over standard of care/placebo in pregnant women with twin pregnancies and a short cervix because due to the desirable effects outweighing the undesirable effects.*

Very low certainty: findings indicate uncertain effect / We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect

	– 205 fewer per 1000 preterm births <32 weeks, ranging from 33 fewer to 312 fewer per 1000. 2. **NICU stay/prolonged hospital stay -** Not reported. 3. **Neonatal mortality[5]:** For Vaginal progesterone vs placebo in twin pregnancies in women with short cervixes, there is little to no difference in neonatal deaths or stillbirths. – Neonatal death: One included study (IPD Review (Conde-Agudelo 2022) RR 0.51 (0.2 to 1.28), 190 participants, low quality evidence. – 51 fewer neonatal deaths per 1000, ranging from 84 fewer to 29 more per 1000. – Stillbirth: One included study (IPD Review (Conde-Agudelo 2022[7]) RR 0.54 (0.17 to 1.77), 190 participants, low quality evidence. – 21 fewer stillbirths per 1000, ranging from 39 fewer to 36 more per 1000. 4. **Safety:** AEs, SAEs Not reported.	

Resources required
How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations (by committee)
○ Large costs ○ Moderate costs ○ **Negligible costs or savings** ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Price of medicines/ treatment course Medicine | Tender price ZAR)* | SEP (ZAR)* December 2025 Cyclogest 200mg – 15 pessaries | | 407,84 Utrogestan, 200mg 15 pessaries | | 300,41	*The ERC judged that there was no reason to suspect different costs from that presented in the evidence.*

Equity*
What would be the impact on health equity?

Judgement	Research evidence	Additional considerations (by committee)
○ Reduced ○ Probably reduced ○ Probably no	Currently the product is only available for singleton pregnancies. Including the item on the EML for twin pregnancies would improve	

impact ○ **Probably increased** ○ Increased ○ Varies ○ Don't know	equity, given the evidence of efficacy in reducing preterm birth in twin pregnancies.	

Acceptability*
Is the option acceptable to recommend as an essential medicine to key stakeholders?

Judgement	Research evidence	Additional considerations (by committee)
○ No ○ Probably no ○ **Probably yes** ○ Yes ○ Varies (if so, why?) ○ Don't know	We examined a study on the acceptability of a trial of vaginal progesterone for the prevention of preterm birth among HIV-infected women in Lusaka, Zambia: a mixed methods study, participants reported a preference of a vaginal medication over injectable described their familiarity with the vaginal product, a fear of needles and resulting pain, and inconvenience of a weekly clinic visit. Those who preferred weekly injections cited fewer doses to remember.[9]	

Feasibility*
Is the option feasible to implement?

Judgement	Research evidence		Additional considerations (by committee)
○ No ○ Probably no ○ Probably yes ○ **Yes** ○ Varies (if so, why?) ○ Don't know	Alternative Medicine/s (INN)	Not applicable	•
	Is the alternative SAHPRA registered?		
	Formulation/s		
	Equipotent Dose/ Dose range		
	N/A		

SUMMARY OF JUDGEMENTS

Indicate the relevant judgements below per domain in **bold**

	Judgement						
Desirable effects	Trivial	Small	**Moderate**	Large		Varies	Don't know
Undesirable effects	Large	Moderate	Small	**Trivial**		Varies	Don't know
Certainty of evidence	Very low	**Low**	**Moderate**	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison		**Probably favors the intervention**	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
Equity	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION[4]

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	X

CONCLUSIONS

Recommendation

For pregnant woman with twin gestations, including both dichorionic and monochorionic twins, between 16–26 weeks with a short cervix (≤ 25 mm) on ultrasound, the NEMLC recommends the use of progesterone 200mg per vagina over standard of care/placebo (strong recommendation, [low to moderate the certainty of evidence]).

Justification

N/A

Monitoring and evaluation

N/A

Research priorities

- Review results when new trials are published

[4] **STRENGTH OF THE RECOMMENDATION:**
Strong recommendation
Strong recommendations are those recommendations for which the guideline development group is confident that the desirable consequences of implementing the recommendation outweigh the undesirable consequences. Strong recommendations can be adopted as practice (most patients should receive the recommended medicine) or policy (adapted as policy) in most situations. For patients, most people would want the recommended medicine and only a small proportion would not.
Conditional recommendation
The guideline development group is less certain that the desirable consequences of implementing the recommendation outweigh the undesirable consequences or when the anticipated net benefits are very small. Therefore, discussion (or substantial debate) may be required before a conditional recommendation can be adopted as practice or policy. For patients, the majority if people would want the recommended medicine, but many would not.

Restrictions

N/A

Implementation considerations

N/A – this is already standard practice in singleton pregnancies in women with a cervix ≤25mm.

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REPORT

BACKGROUND

In December 2019 the National Essential Medicine List Committee (NEMLC), based on an evidence review conducted by the Adult Hospital Level Committee[6], aligned with NICE Guidelines[10], recommended daily vaginal progesterone treatment up to 34 weeks of gestation for singleton pregnancies in:

- mid- trimester cervical shortening (defined as ≤25 mm before 24 weeks gestation) with no prior spontaneous singleton preterm birth, and/or
- women with a history of spontaneous preterm birth or mid-trimester loss.

This recommendation for singleton pregnancies was based on recommendations that were informed by a systematic review and meta-analysis that included the OPPTIMUM study[11]. Although the OPPTIMUM study showed conflicting results of no benefit of vaginal progesterone in preventing preterm labour, a subgroup analysis and individual participant data meta-analysis of low to moderate quality evidence showed that for women with a history of spontaneous preterm birth, or women with a short cervix (≤25mm), vaginal progesterone decreases the number of preterm births (at < 34 weeks' gestation) compared to placebo. It was also noted that from a feasibility and acceptability point of view pharmacological management with vaginal progesterone is non-invasive and less costly compared to cerclage (intervention that used a strong suture to reinforce the cervix during pregnancy).

The rate of early preterm birth reported in twin pregnancies is approximately 10%, compared to 1–2% in singleton pregnancies. In South Africa, the Saving Babies report (2020–2023) identified spontaneous preterm labour as the leading obstetric cause of death, accounting for 21% of deaths. The perinatal mortality rate was reported as 30.2 per 1,000 for singleton deliveries and 80.5 per 1,000 for multiple gestations. It is important to highlight that most clinical trials investigating the use of progesterone for the prevention of preterm birth were conducted in high-income countries, where access to advanced neonatal intensive and high-care facilities is substantially greater. Consequently, any reduction in the risk of preterm labour is likely to have a more profound impact on neonatal morbidity in low- and middle-income countries (LMICs). Supporting this, the Saving Babies report further noted that prematurity was the primary cause of neonatal mortality in South Africa, contributing to 46% of all neonatal deaths.[12]

In twin pregnancies the increase in risk for preterm labour is observed in women with cervical length <25 mm.[13] In 2025, NEMLC requested a review of the literature to determine if the recommendation for singleton pregnancies as outlined above should be expanded to include twin pregnancies.[6]

Table 1: PURPOSE/OBJECTIVE i.e., PICO question:

Population Subgroups	Pregnant woman with twin gestations, including both dichorionic and monochorionic twins, between 16–26 weeks with a short cervix (≤ 25 mm) on ultrasound
Intervention(s)	Progesterone (micronized vaginal progesterone) 200mg, vaginally, at bedtime

Comparator(s)	Standard of care or placebo
Outcome(s)	• Reduction in preterm births < 34 weeks • Neonatal morbidity: NICU stay/prolonged hospital stay • Neonatal mortality • Safety: AEs, SAEs
Study types	Clinical practice guidelines (CPGs), Systematic Reviews of Randomised Controlled Trials (RCTs) or other, RCTs

METHODS

1. **Data Sources**
   Clinical practice guidelines: We searched the Guidelines International Network (GIN) library, the National Institute for Health and Care Excellence (NICE) website, the American College of Obstetrics and Gynaecology (ACOG), the Society for Maternal Fetal Medicine (SMFM), and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) for relevant guidelines.

2. **Search Strategy**
   We searched the relevant guideline repositories using keywords “twin”, “multiple”, and “multiple gestation”.

3. **Study selection and eligibility criteria, data extraction and analysis, and evidence synthesis**
   Relevant clinical practice guidelines were identified by one reviewer and checked by a second reviewer. Guidelines were screened using a tool that matched the guideline PICO with our PICO and guidelines included or excluded accordingly (see Figure 1 Search flow Chart). Relevant recommendations were extracted from the included guidelines by one reviewer (NG) and checked by a second reviewer (MR). Data were extracted from the included systematic review (NICE) by one reviewer (NG) and checked by a second reviewer (MR). Any disagreements were resolved through discussion.

4. **Assessment of methodological quality**
   We used the AGREE II tool[14] to assess clinical practice guidelines, and the AMSTAR II[15] tool to assess the evidence review within the included NICE and ACOG guideline.

5. **GRADE assessment**
   We adopted the GRADE assessment in the evidence review by NICE[2,5].

RESULTS

1. **Result of the search**
   We identified seven guidelines through searching guideline databases (see figure 1). We excluded five of these guidelines. The German guideline[16,] was excluded as their

recommendation was based on older NICE guidance than the included NICE guidance. The RANZCOG[17,18,19] guidance was excluded due to a PICO mismatch and one of the ACOG guidelines[3] was excluded due to the wrong intervention being included. The two included guidelines are described and discussed below.

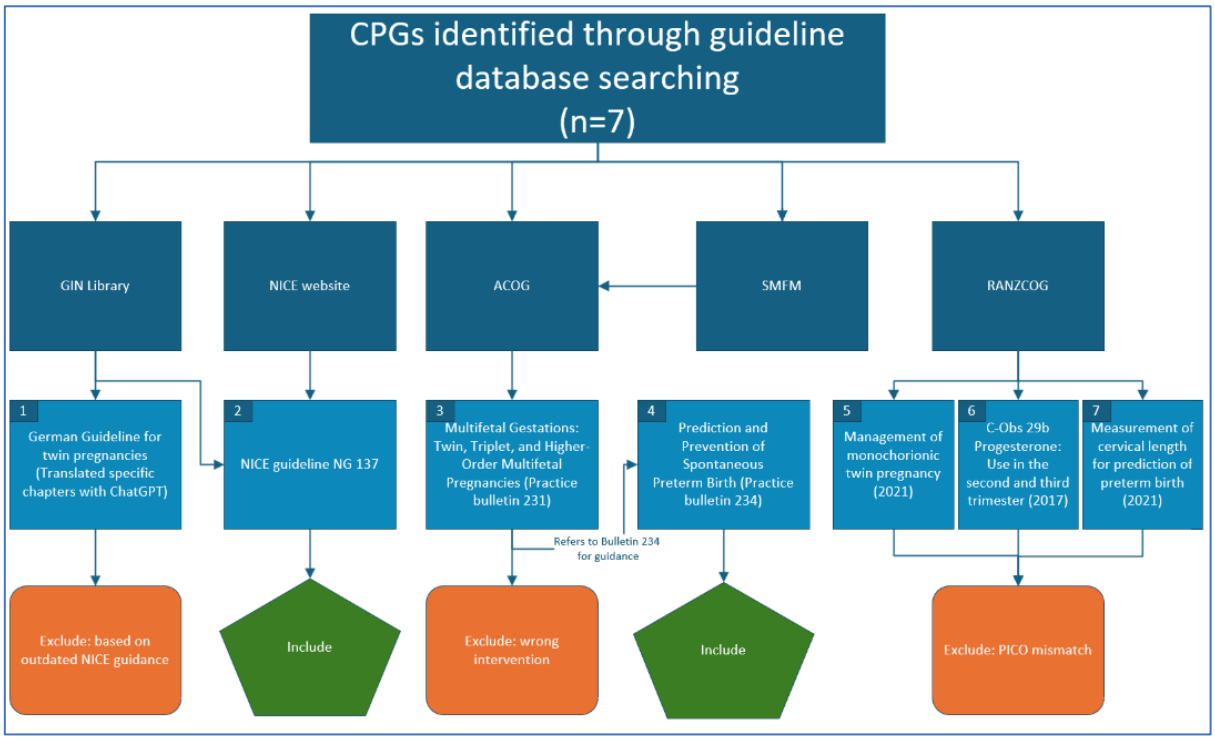

Figure 1 Search flow chart

2. Description of included studies (clinical practice guidelines, systematic reviews and RCTs) and critical appraisal

Table 2 reports a summary of the guideline recommendations, Table 3: PICO table from NICE review and Table 4 reports the main characteristics and outcomes of the studies included in the systematic review. Appendix 1 provides the full AGREE II scoring for the guidelines and Appendix 2 provides the AMSTAR 2 Appraisal of the systematic review, in duplicate.

2.1. Clinical Practice Guidelines

We included two clinical practice guidelines.

The first guideline by ACOG is a practice bulletin for obstetrician-gynaecologists in the United States[4]. It was published in 2021 as an update to previous guidance from 2012. The guideline addresses the prediction and prevention of spontaneous preterm birth in both single and multiple pregnancies. The evidence rating system used was according to methods outlined by the US Preventative Service Task Force. The recommendations relevant to our PICO are summarised below in Table 1. Two reviewers (NG, MR) assessed the quality of this guideline using the AGREE II tool and it was rated as moderate quality (Appendix 1)

The second included guideline by NICE was published in 2024[5]. This guideline focuses on management guidance for twin and triplet pregnancies. The GRADE evidence rating system was used to assess the quality of evidence and the relevant recommendations are summarised in Table 1. Two reviewers (NG, MR) assessed the quality of this guideline using the AGREE II tool and it was rated as high quality (See Appendix 1 for both reviewer assessments and scoring per domain). A secondary appraisal of the guidelines for overall timeousness and credibility was also conducted. The top-scoring guidance in this assessment was the NICE guidance[5].

Table 2 Recommendations from included clinical practice guidelines

Citation	Recommendation	AGREE II (combined)
American College of Obstetricians and Gynaecologists: Committee on Practice Bulletins. Prediction and prevention of spontaneous preterm birth: number 234. ACOG Practice Bulletin. 2021.	"Cervical pessary is not recommended for prevention of preterm birth in twin pregnancies with a short Cervix." Level A[5] evidence	– Scope and purpose (D1) 72% – Stakeholder involvement (D2) 33% – Rigour of development (D3) 43% – Clarity of presentation (D4) 89% – Applicability (D5) 4% – Editorial independence (D6) 29% **Overall 45%**
National Institute for Health and Care Excellence (NICE). NG 137 Twin and triplet pregnancy. 2024.	Under section 1.5 Preventing Preterm Birth "Offer a single cervical length scan between 16 and 20 weeks to women or pregnant people with a twin or triplet pregnancy. [2024]" "Offer progesterone 200 mg vaginal capsules once a day at bedtime to women or pregnant people with a twin or triplet pregnancy and a cervical length of 25 mm or less. Continue treatment until 34 weeks (or birth if sooner). [2024]" "If a cervical length of 25 mm or less is found incidentally on a scan conducted between 20 and 24 weeks, offer progesterone 200 mg vaginal capsules once a day at bedtime. Continue treatment until 34 weeks (or birth if sooner). [2024] In April 2024, this was an off-label use of progesterone 200 mg vaginal capsules. See NICE's information on prescribing medicines."	– Scope and purpose (D1) 97% – Stakeholder involvement (D2) 86% – Rigour of development (D3) 93% – Clarity of presentation (D4) 94% – Applicability (D5) 79% – Editorial independence (D6) 83% **Overall 89%**

2.2. *Systematic reviews*

We included the systematic review which informed relevant recommendations within the NICE guideline[2]. This systematic review examined effectiveness of progesterone use (vaginal, oral or intramuscular) from 16 to 37 weeks gestational age compared to standard of care, placebo or progesterone given through different routes in women at risk of preterm birth in twin and triplet pregnancies – this population was further stratified by cervical length (short ≤25mm and long>25mm) and whether there had been a previous preterm birth or not.

Critical outcomes included stillbirth or neonatal death, preterm birth at 22+0 to 27+6 weeks, 28+0 to 31+6 weeks, and 32+0 to 36+6 weeks, and spontaneous preterm birth < 34 weeks of gestation.

[5] Level A: Recommendations are based on good and consistent scientific evidence.

Important outcomes included a composite outcome of serious neonatal complications[6], and a composite of adverse maternal outcomes[7]. The PICO is summarised in the table below. This review included two randomised controlled trials, and two individual patient data (IPD) reviews – all studies compared vaginal progesterone to placebo or control (no intervention) in women with twin pregnancies. We judged it as having a moderate AMSTAR II rating (see Appendix 2 for judgements). GRADE evidence ratings as judged by the team at NICE are included below the effectiveness of the intervention section.

Table 3: PICO table from NICE review[2]

Population	Women at risk of preterm birth in twin and triplet pregnancy Strata Cervical length - Women with a short cervix (≤25mm) - Women with a longer cervix (>25mm) Previous preterm birth - Women with previous preterm birth - Women with no previous preterm birth
Intervention	• Vaginal progesterone • Oral progesterone • Intramuscular 17-hydroxyprogesterone caproate (17-OHPC) *Progesterone use in first, second and third trimester (part) will be included as all are relevant
Comparison	Placebo or control or standard of care or With each other
Outcomes	**Critical** • Stillbirth or neonatal death* (to report neonatal death outcome separately if reported) • Preterm birth** at 22+0 - 27+6 weeks • Preterm birth** at 28+0 - 31+6 weeks • Preterm birth** at 32+0 - 36+6 weeks • Spontaneous preterm birth <34 weeks of gestation (this will include spontaneous preterm birth <33 weeks) *Stillbirth defined as "a baby that dies after 24 weeks of pregnancy but before they are born", and a neonatal death defined as "death within 28 days after birth" **This includes spontaneous preterm birth and indicated preterm birth (in which a baby is delivered by early induction of labour or caesarean birth due to maternal or fetal illness). **Important** • Composite of serious neonatal complications (for example, severe necrotising enterocolitis stages 2–3, intraventricular haemorrhage grades 3–4, retinopathy of prematurity stage 3 or worse, bronchopulmonary dysplasia, confirmed sepsis, patent ductus arteriosus, and neonatal infection) • Composite of adverse maternal outcomes (for example, gestational hypertension, pre-eclampsia, gestational diabetes, and maternal infection including chorioamnionitis)

[6] This could include severe necrotising enterocolitis stages 2–3, intraventricular haemorrhage grades 3–4, retinopathy of prematurity stage 3 or worse, bronchopulmonary dysplasia, confirmed sepsis, patent ductus arteriosus, and neonatal infection
[7] This could include gestational hypertension, pre-eclampsia, gestational diabetes, and maternal infection such as chorioamnionitis

Table 4: Characteristics of the study included in the NICE Systematic Review that informed our PICO (Extracted from NICE Evidence Review)[2]:

Study	Population	Intervention	Comparison	Outcomes
Conde-Agudelo 2022[7] International	N=95, Vaginal progesterone: N=52, Placebo: N=43 N=6 RCTs investigating vaginal progesterone for the prevention of preterm birth in women with a twin pregnancy and short cervix (≤25 mm) or women with an unselected twin pregnancy and short cervix. Participants characteristics not reported	Vaginal progesterone (100-600 mg per day)	Placebo	• Stillbirth (fetal death) • Neonatal death • Preterm birth <28 weeks Preterm birth <32 weeks • Preterm birth <37 weeks • Spontaneous preterm birth <34 weeks • Composite of serious neonatal complications

2.3. *Randomised controlled trials (RCTs)*

During review of the above systematic review, we identified the PROSPECT trial (NCT02518594).[20] This is a randomised controlled trial of 630 women evaluating the use of vaginal progesterone compared to placebo to prevent early preterm birth in women pregnant with twins and with a cervical length less than 30mm. The primary outcome was delivery or foetal loss of either twin prior to 35 weeks gestation. Secondary outcomes included interval from randomisation to delivery or foetal demise, gestational age at delivery, preterm delivery or foetal demise prior to 28 weeks, 32 weeks, and 37 weeks gestation, spontaneous preterm delivery (following preterm labour or preterm rupture of membranes) < 32 weeks and 35 weeks gestation, indicated preterm delivery < 35 weeks gestation, caesarean delivery, foetal or neonatal death, small for gestational age, composite neonatal outcome, and length of hospital stay, need for NICU or immediate care admission and length of stay if admitted. The trial started in November 2015 and concluded in February 2025. There are no published results available – we have reached out to study investigators to request access to results.

EFFECTIVENESS OF THE INTERVENTION

Comparison	Number of included studies
Vaginal progesterone compared to SoC or placebo	one

Comparison 1

1. **Reduction in preterm birth < 34 weeks:** When vaginal progesterone is compared to placebo in twin pregnancies in women with short cervixes, vaginal progesterone likely reduces preterm births < 34 weeks (moderate certainty evidence)
   - Spontaneous preterm birth <34 weeks: One included study (IPD Review (Conde-Agudelo 2022[7])) RR 0.58 (95% Confidence interval (CI) 0.38 to 0.89), 95 participants, moderate certainty evidence rated down for serious imprecision due to the confidence interval crossing one minimally important difference. In absolute terms, there were 273 fewer per 1000 spontaneous preterm births <34 weeks, ranging from 72 fewer to 404 fewer per 1000.
   - Preterm birth < 32 weeks: One included study (IPD Review (Conde-Agudelo 2022[7])) RR 0.56 (95% CI 0.33 to 0.93), 95 participants, moderate certainty evidence rated down for serious imprecision due to the confidence interval crossing one minimally important difference. In absolute terms, there were 205 fewer per 1000 preterm births <32 weeks, ranging from 33 fewer to 312 fewer per 1000.

2. **NICU stay/prolonged hospital stay**
   Not reported.

   A composite outcome of serious neonatal complications was reported in the review which included neonatal morbidity/mortality, including respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis proven neonatal sepsis, or neonatal death. As this

composite outcome combined both neonatal morbidity and mortality we did not report this outcome.

3. **Neonatal mortality:** When vaginal progesterone is compared to placebo in twin pregnancies in women with short cervixes, there may be little to no difference in neonatal deaths or stillbirths (low certainty evidence).
   - Neonatal death: One included study (IPD Review (Conde-Agudelo 2022[7]) RR 0.51 (95% CI 0.2 to 1.28), 190 participants, low certainty evidence rated down for very serious imprecision due to the low event rate. In absolute terms, there were 51 fewer neonatal deaths per 1000, ranging from 84 fewer to 29 more per 1000.
   - Stillbirth: One included study (IPD Review (Conde-Agudelo 2022[7]) RR 0.54 (95% CI 0.17 to 1.77), 190 participants, low certainty evidence rated down for very serious imprecision due to the low event rate. In absolute terms, there were 21 fewer stillbirths per 1000, ranging from 39 fewer to 36 more per 1000.

4. **Safety:** AEs, SAEs
   Not reported.

GRADE EVIDENCE TABLE (Table 11 copied from NG 137 evidence review)[2]

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaginal progesterone	Placebo	Relative (95% CI)	Absolute		
Stillbirth (fetal death, adjusted analysis) (baby or fetus)												
1 (Conde-Agudelo 2022)	IPD review	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	None	6/104 (5.8%)	4/86 (4.7%)	RR 0.54 (0.17 to 1.77)	21 fewer per 1000 (from 39 fewer to 36 more)	LOW	CRITICAL
Neonatal death (adjusted analysis) (baby or fetus)												
1 (Conde-Agudelo 2022)	IPD review	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	None	4/104 (3.8%)	9/86 (10.5%)	RR 0.51 (0.2 to 1.28)	51 fewer per 1000 (from 84 fewer to 29 more)	LOW	CRITICAL
Preterm birth <32 weeks (pregnant women)												
1 (Conde-Agudelo 2022)	IPD review	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	None	16/52 (30.8%)	20/43 (46.5%)	RR 0.56 (0.33 to 0.93)	205 fewer per 1000 (from 33 fewer to 312 fewer)	MODERATE	CRITICAL
Spontaneous preterm birth <34 weeks (pregnant women)												
1 (Conde-Agudelo 2022)	IPD review	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	None	20/52 (38.5%)	28/43 (65.1%)	RR 0.58 (0.38 to 0.89)	273 fewer per 1000 (from 72 fewer to 404 fewer)	MODERATE	CRITICAL

CI: confidence interval; IPD: individual participant data; OIS: optimal information size; RR: risk ratio
[1] <150 events
[2] 95% CI crosses 1 MID

DISCUSSION

Summary of results
The review of the literature shows that when vaginal progesterone is compared to placebo in twin pregnancies in women with short cervixes, vaginal progesterone likely reduces preterm births < 34 weeks. There may be little to no difference in stillbirth or neonatal death.

Limitations in the review process
ICU stay and adverse events was not reported in the NICE guideline. However, a previous NEMLC approved review on the use of progesterone for prevention of preterm birth in a select “at risk” population reported that in women who choose to take progesterone for preterm birth prevention, it appears to be safe with no major adverse events. These results have been noted in follow-up studies up to two years. [6,8]

CONCLUSION

International guidelines including the NICE guidelines[5] reviewed here have accepted the levels of evidence to recommend vaginal progesterone in twin pregnancies in women with short cervixes as vaginal progesterone likely reduces preterm births < 34 weeks. In South Africa vaginal progesterone is recommended for prevention of preterm labour in singleton pregnancies. The evidence shows that that when vaginal progesterone is compared to placebo in twin pregnancies in women with short cervixes, vaginal progesterone likely reduces preterm births < 34 weeks for twin pregnancies too.

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Appendix 1: AGREE II Individual reviewer ratings

AGREE II assessment scores																							
ACOG Guidance																							
72																							
	Scope and purpose			**Stakeholder involvement**			**Rigour of development**								**Clarity of presentation**			**Applicability**				**Editorial independence**		**Overall assessment**
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1 (NG)	7	7	3	1	1	6	5	1	5	4	5	6	1	4	7	6	7	1	1	1	1	1	4	4
Appraiser 2 (MR)	7	7	1	3	2	5	5	3	4	2	4	5	1	2	5	6	7	2	1	2	1	1	5	3
Item Total	14	14	4	4	3	11	10	4	9	6	9	11	2	6	12	12	14	3	2	3	2	2	9	7
Domain Total	32			18			57								38			10				11		166
Minimum possible score	6			6			16								6			8				4		46
Maximum possible score	42			42			112								42			56				28		322
Domain score	**72%**			**33%**			**43%**								**89%**			**4%**				**29%**		**45%**

Twin and triplet pregnancy - NICE																								
Scoring the guidelines																								
	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	7	7	7	7	5	7	7	5	7	6	7	7	6	7	7	6	6	3	6	7	6	6	6	6
Appraiser 2	7	6	7	6	5	7	7	7	6	7	6	6	7	7	7	7	7	4	6	7	7	5	7	6
Item Total	14	13	14	13	10	14	14	12	13	13	13	13	13	14	14	13	13	7	12	14	13	11	13	12
Domain Total	41			37			105								40			46				24		293
Minimum possible score	6			6			16								6			8				4		46
Maximum possible score	42			42			112								42			56				28		322
Domain score	**97%**			**86%**			**93%**								**94%**			**79%**				**83%**		**89%**

Using an approach used in Mc Allister *et al*. Advancing guideline quality through country-wide and regional appraisal of CPGs: a scoping review, 22 September 2022, PREPRINT (Version 1) available at Research Square [https://doi.org/10.21203/rs.3.rs-1850020/v1][20]

	Scope and purpose	Stakeholder involvement	Rigour of development	Clarity of presentation	Applicability	Editorial independence	Overall Assessment Score
Guideline	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	
NICE	97%	86%	93%	94%	79%	83%	89%
ACOG	72%	33%	43%	89%	4%	29%	45%

Low: < 40%	Moderate: 40% - 59%	High: ≥ 60%

Assessment of Timeliness and Credibility of Guidelines				
Guideline	Timeliness	Credibility	Use of GRADE	Overall Assessment Score
NICE	3	5	5	13
ACOG	3	3	2	8

Key to Scoring:

Timeliness (CPG level)

- Guideline is out-of-date and likely to miss important recent evidence 1
- Guideline is recent and unlikely to miss recent important evidence 3

Credibility (CPG level)

- Guideline is not credible (e.g., < 60% overall for Domain 1, 3 and 6) 1
- Guideline is credible but has significant limitations (e.g., > 60% in either D1, D3 or D6) 3
- Guideline is credible (e.g., high overall scores across domains) 5

Use of GRADE (CPG Level)

- Does not use/report GRADE or GRADE EtD 1
- Guidelines uses GRADE 2
- Guidelines reported GRADE EtD tables 3

Appendix 2: AMSTAR 2 Judgements

AMSTAR 2 assessment of [Progesterone for preventing spontaneous preterm birth in twin and triplet pregnancy: Twin and triplet pregnancy: Evidence review K. London: National Institute for Health and Care Excellence (NICE); 2024 Apr. PMID: 38829974.]

		Reviewer 1 (NG)		Reviewer 2 (MR)	
No.	**Criteria**	**Comments**	**Y/ PY/ N#**	**Comments**	**Y/ PY/ N#**
1	Research questions and inclusion criteria for the review included the components of PICO	Table included with PICO	Y	Eligibility criteria are outlined in Table 1 as Population, Intervention, Comparison and Outcome (PICO) characteristics of the review.	Y
2*	Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol	Protocol is available for review (Appendix A) – no significant deviations reported	Y	Appendix A outlines a protocol. Unclear if there were no deviations in the review as no explicit explanations of deviations or non-deviations. are provided. Deviations in the individual study appraisals included in the review were considered.	PY
3	Review authors explained selection of the study designs for inclusion in the review	Review done as per NICE manual guidelines	PY	The literature search was systematic and conducted in terms of the Developing NICE guidelines: the manual, searches were restricted b systematic reviews or randomised control trials (RCTs) and RCTs.	Y
4*	Review authors used a comprehensive literature search strategy	Yes (Appendix B)	Y	Outlined in Appendix B Literature search strategies	Y
5	Review authors perform study selection in duplicate	"potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary"	PY	Not explicitly stated, however methods conducted according to the Developing NICE guidelines: the manual which implies duplicate search	PY
6	Review authors perform data extraction in duplicate	"One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer"	PY	Not explicitly stated, however methods were conducted according to the Developing NICE guidelines: the manual which implies duplicate search and dual sifting was performed on at least 10% of records; requiring 90% agreement.	PY
7*	Review authors provided a list of excluded studies and justify the exclusions	Appendix J	Y	Excluded studies for review question: What is the clinical and cost-effectiveness of progesterone in preventing spontaneous preterm birth in twin and triplet pregnancy? And reasons for exclusion were provided.	Y
8	Review authors described the included studies in adequate detail	"Table 2: Summary of included studies" page 9	Y	Summary of included studies are provided in tables and narrative.	Y

9*	Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review	"Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs and quasi-RCTs • Wang et al checklist for assessing the methodological quality of IPD meta-analysis https://www.bmj.com/content/bmj/373/bmj.n736.full.pdf"	Y	Quality assessment of individual studies will be performed using the following checklists: ROBIS tool for systematic reviews , Cochrane RoB tool v.2 for RCTs and quasi-RCTs and Wang et al checklist for assessing the methodological quality of IPD meta-analysis https://www.bmj.com/content/bmj/373/bmj.n736.full.pdf	Y
10	Review authors reported on the sources of funding for the studies included in the review.	Included in the evidence tables	Y	Relevant outcome data and source of funding was included in the protocol for data extraction and considered in the critical appraisals.	Y
11*	For meta-analyses, review authors used appropriate methods for statistical combination of results	Plan for MA is available in the protocol Appendix A	Y	Where possible, meta-analyses was conducted using Cochrane Review Manager software.	Y
12	For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis	"The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/"	Y	Risk of Bias reviewed at all steps through the assessment and presented in GRADE	Y
13*	Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review	Authors used GRADE to assess review quality and reflected on this when interpreting results	Y	Risk of Bias reviewed at all steps through the assessment and presented in GRADE	Y
14	Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review	Authors had a plan for managing heterogeneity but there was no specific need to explain or discuss further	PY	In the protocol it is explicitly stated that heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Not reported.	Y
15*	For quantitative synthesis, review authors carried out adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review	Authors considered publication bias when assessing included studies	PY	Considered in review of studies	Y
16	Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review	"Declarations of interest were recorded according to NICE's conflicts of interest policy. " – although it is not so easy to find this document. It is stated that the review was funded by NICE	PY	Declarations of interest were recorded according to NICE's conflicts of interest policy.	Y
OVERALL QUALITY ASSESSMENT:		**Moderate quality**			
Rationale and conclusion:				See below for respective rating	

[#] Y= Yes, PY = Partial yes, N = No

** Critical domains = 2, 4, 7, 9, 11, 13, 15*

*** Berild JD, et al. A Systematic Review of Studies Published between 2016 and 2019 on the Effectiveness and Efficacy of Pneumococcal Vaccination on Pneumonia and Invasive Pneumococcal Disease in an Elderly Population. Pathogens. 2020 Apr 3;9(4):259. doi: 10.3390/pathogens9040259.*

Rating overall confidence in the results of the review

- *High:* No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest
- *Moderate:* More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that *were* included in the review
- *Low:* One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the *question* of interest
- *Critically low*: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

(*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence).