Twin and triplet pregnancy - Progesterone for preventing preterm birth

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Birmingham City University - The Elizabeth Bryan Multiple Births Centre	Evidence Review C		**Cost effectiveness and resource use** Please could the committee recommend support for the consistent implementation of this amended recommendation as well as the *NICE Twin and Triplet Pregnancy* guideline in full, by considering the resource needed to support multidisciplinary team care and specialist multiple birth clinics. It is our concern that where multidisciplinary care teams and services for multiple pregnancy are not already established, the implementation of this guideline will be impeded.	Thank you for your comment. The guideline already makes recommendations in section 1.3 on the delivery of antenatal and intrapartum care which advise that care should be provided by a specialist and multidisciplinary team, and this recommendation has been in existence since 2011. The committee agreed that in the majority of settings this level of care was provided but that there may be some units or areas where appropriate specialist care was not being provided, and so this information has been passed to the NICE implementation team to consider when planning support activity.
Birmingham City University - The Elizabeth Bryan Multiple Births Centre	Evidence Review C		Page 19 Line 27: *"They therefore made research recommendation for women with twin and triplet pregnancies with a history of preterm birth to help inform future guidelines (see appendix K for full details of the research recommendation). The committee discussed that due to the low numbers of twin and triplet pregnancies compared to singleton pregnancies this research may not be possible using a randomised controlled trial but may*	Thank you for your comment. As you have noted, there are NICE research recommendations on the role and benefits of progesterone at preventing preterm labour and birth in both singleton and multiple pregnancies. The evidence for benefits and risks for these two populations may be very different, and hence evidence of benefit in singleton pregnancies is not just extrapolated to multiple pregnancies. As such it would not

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			need to consider cohort methods or the use of registry or NHS data." The evidence reviews that were undertaken to inform the *NICE Preterm Labour and Birth* guideline (NG25, 2019 - **singleton only**) highlighted uncertainties around the evidence of efficacy of progesterone to prevent preterm birth for women and pregnant people with a history of preterm birth with or without a short cervix, and the optimal time to start and stop progesterone. Research recommendations were made as a result (NG25, Evidence Review A, Appendix L). Please could the committee consider how research recommendations could include both populations within trials, cohort methods or registry data, given the acknowledged potential difficulties with conducting such a trial in multiple births only.	be usual to combine these two populations in the same research study.
Birmingham City University - The Elizabeth Bryan Multiple Births Centre	Table	1	*1.5.1. Offer a cervical length scan between 16 and 20 weeks to women or pregnant people with a twin or triplet pregnancy. [2024]* This recommendation would need to be included in with the schedule of appointments that are outlined in sections 1.3.7 – 1.3.10.	Thank you for your comment. The committee discussed the logistics and resource impact of the single cervical length scan recommended but agreed that as multiple births only account for 1 in every 65 pregnancies this additional cervical length scan (at 16 to 20 weeks)

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			Please consider combining this with the other recommended appointments to reduce additional hospital visits and to prevent interruption to care provision from the specialist multidisciplinary team outlined in 1.3.1. Also please consider including wording that promotes a discussion with women or pregnant people on the reason for the scan, the implications of a short cervix and that progesterone is the only treatment that is currently recommended.	would be achievable as part of the antenatal care provided to multiple pregnancies, and could be timed to coordinate with other antenatal appointments and scans. However, the committee agreed that units would schedule this in locally and so did not make detailed recommendations on this. The committee did amend a recommendation in section 1.4 of the guideline about providing information to women or pregnant people on the cervical scan, and added a new recommendation on discussing the reason for the cervical length scan and why treatment with progesterone may be offered.
Birmingham City University - The Elizabeth Bryan Multiple Births Centre	Table and Evidence Review C	1	*1.5.2 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, measured between 16 and 24 weeks of pregnancy. Continue treatment until 34 weeks (or birth if sooner). [2024]* AND *1.5.3 Consider progesterone 200 mg vaginal capsules once a day at bedtime for women or*	Thank you for your comment. The committee were aware of the ongoing PROSPECT study, which they had discussed and already noted in the evidence review and agreed that the results of this study may warrant a further review of these recommendations (as it includes serial scanning, different cervical length cut-offs and a pessary as an intervention as well). However, this study has been in progress for 9 years and it is not clear, despite reaching out to the main

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			pregnant people with a twin or triplet pregnancy who are found to have a cervical length of less than 25 mm later than 24 weeks of pregnancy. Continue treatment until 34 weeks (or birth if sooner). [2024] Please could the committee consider waiting until the PROSPECT Trial (NCT02518594) outcomes are known as this might impact the interpretation of the evidence and the implementation of the recommendations proposed.	study contact, if the planned end date will be achieved. The committee therefore agreed to make recommendations based on current evidence.
British Association of Perinatal Medicine	General		There does not appear to be any mention of fibronectin tests in this document, which are recommended for single pregnancies.	Thank you for your comment. The use of fibronectin to predict preterm birth in twin or triplet pregnancies was not within the scope of this update. The guideline already makes recommendations (recommendation 1.4.14) that fetal fibronectin testing should not be used alone to predict the risk of preterm birth in twin and triplet pregnancies.
British Association of Perinatal Medicine	General		A member of BAPM's Executive Committee was prescribed 200mg progesterone last year, however none was available (pharmacies only had the 50mg capsules). There was a lot of debate between her GP, the obstetric consultant and the pharmacist as to whether 4x the dose was appropriate or if this should	Thank you for your comment. The preparation recommended for prevention of preterm labour is the 200 mg vaginal capsule and we are not aware of any supply issues relating to this. The Serious Shortage Protocol in place from May to September 2023 related to the oral

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			somehow be adjusted. If there are still supply issues, could some clear guidance be added in terms of smaller doses?	progesterone capsules used as HRT therapy. In the case of supply shortages, advice on alternative preparations is provided to clinicians by the Department of Health and may vary depending on the individual situation so this would not be included in NICE guidelines.
British Association of Perinatal Medicine	General		Subject to the above points, BAPM is very supportive of the document.	Thank you for your comment.
British Association of Perinatal Medicine	Table		1.51 and 1.52 appear to mention different gestations, which is confusing. Should we be repeating the cervical length after 20 weeks as point 1.5.2 states cervical length <25mm between 16 and 24 weeks? Please can this be clarified? We note that in the explanation NICE states: "Sometimes cervical length measurement would be carried out later in pregnancy, for example if a woman or pregnant person presented with threatened preterm labour, or if they were late booking. In this case, the committee agreed to make a strong 'offer' recommendation for progesterone up to 24 weeks (as there was evidence of benefit when started at this time) and a weaker 'consider' recommendation if a short cervix was identified	Thank you for your comment. The recommendations have been amended to clarify that a single cervical length scan should be conducted at 16 to 20 weeks, but that if a scan up to 24 weeks identifies, incidentally, a short cervix progesterone should be offered. This has simplified the recommendations and hopefully removed this confusion.

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			after 24 weeks, as there was less evidence of benefit at this gestation." Maybe point 1.53 should state that if cervical length is performed between 20 and 24 weeks (late booker or cervical length taken as part of assessment when presents in threatened preterm labour) and noted to be <25mm progesterone could also be considered.	
British Association of Perinatal Medicine	Table	1	The document suggests vaginal progesterone in specific circumstances in twin and triplet pregnancy can "reduce preterm births and the associated neonatal morbidity". On that basis, we have no issue. However, to be balanced, there should be some reference to any adverse effect of vaginal progesterone in the baby.	Thank you for your comment. The evidence review did not identify any adverse effects from progesterone used to prevent preterm labour with a short cervical length. However, a new recommendation has been added on discussing the reason for the cervical length scan and why treatment with progesterone may be offered.
British Association of Perinatal Medicine	Table	1	1.5.1 Offer a cervical length scan between 16 and 20 weeks to women or pregnant people with a twin or triplet pregnancy. A comment to NHS England rather than NICE, but this is not in the risk assessment in SBLv3 that all units are working hard to adopt and hence we will have one guideline on who needs cervical lengths and now another new addition.	Thank you for your comment. You are correct that the current version of Saving Babies Lives does not suggest a cervical length scan for all twin and triplet pregnancies, so this may require amending in a future version of SBL. As requested this comment will be passed to NHSE.

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			There needs to be an acknowledgement that this will have service implications.	
British Association of Perinatal Medicine	Table	1	1.5.2 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, measured between 16 and 24 weeks of pregnancy. Continue treatment until 34 weeks (or birth if sooner). Could NICE clarify whether this is a capsule or pessary as there are more than one preparation of vaginal progesterone – cyclogest is micronized progesterone and is described as a vaginal pessary and Utrogestan is a vaginal capsule? In preterm birth guideline NG25 it only states vaginal progesterone not vaginal progesterone capsule. Also, could a comment be added that the progesterone could be used vaginally or rectally? Some women describe increasing vaginal discharge with vaginal use which causes concern regarding ruptured membranes.	Thank you for your comment. The preparation approved for prevention of preterm labour in singleton pregnancies is vaginal capsules so this is the preparation recommended in the guideline. This is the Utrogestan preparation, but brand names are not usually included in NICE guidelines. Progesterone pessaries or vaginal tablets are not approved for the prevention of preterm birth (even for singleton pregnancies). You are correct that the preparation is not defined in the preterm labour and birth guideline but this will be corrected now this preparation is licensed for this indication. The evidence was for the effectiveness of vaginal progesterone and so the rectal route cannot be recommended in the guideline.
British Maternal & Fetal Medicine Society			We do not agree that cerclage should be offered routinely to twins with a short/very short cervix. This again should be limited to patients with other pre-existing risk factors that	Thank you for your comment. Cerclage has not been offered – recommendation 1.5.6 states that it should not be offered routinely to prevent spontaneous preterm

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			triggered screening due a preexisting possibility of cervical weakness. RCTs have been done and cerclage has not significant impact on obvious outcomes in twin pregnancies. The meta analysis is hugely flawed. Many of the studies did not exclude women with known or suspected cervical weakness due to pre-existing PTB risk factors and is says itself were mostly observational.	birth in women or pregnant people with a twin or triplet pregnancy. Cerclage was not included in the evidence review conducted so it is not clear which meta-analysis you are referring too.
British Maternal & Fetal Medicine Society			Data on 95 women from 6 very small studies with statistically significant results driven largely by one trial with 16 women is not robust enough to recommend progesterone into routine practice, especially as there is potential evidence of harm from progesterone studies in an unselected population of twins. It is very possible that with the addition of new data from other studies the overall results may swing in the other direction. I feel strongly that we should wait for the results of the PROSPECT study. From a methodological point of view, findings from subgroup analyses should be used to generate hypothesis that should then be confirmed in new trials as there is a high risk of finding significant results by chance. If we recommend progesterone now based on weak evidence to make both patients and	Thank you for your comment. The committee acknowledge that the sample size was small but the population of interest – women or pregnant people with a twin or triplet pregnancy AND who have a short cervix – is a very small cohort and so a difficult group on whom to obtain large sets of data. However, the data was an individual patient data (IPD) meta-analysis. IPD meta-analysis is considered to be gold standard for meta-analysis, and this offers the most robust approach to answer the research question. The recommendations for women or pregnant people with short cervix are based on overall evidence from the Conde-Agudelo 2022 IPD meta-analysis which showed reduced preterm birth (<28 weeks and <32 weeks), spontaneous preterm birth (<34

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			clinicians feel better that 'something ' is being done to prevent PTB, we will be putting the cart before the horse. It may hinder recruitment to the PROSPECT study or feasibility of conducting other large, more robust trials in this very important subgroup. With regards to cervical length scans, I agree that the current evidence supports their use as a screening tool for PTB in twins, but in the absence of an effective preventative intervention, I think ROUTINE cervical length screening for ALL twin / triplet pregnancies is hard to justify because of the huge implications on resources and training. That is not to say it cannot be used in selected cases with additional risk factors for PTB, at the discretion of the clinician, after adequate counselling about the lack of evidence for effective preventative interventions.	weeks), and reduced the composite of serious neonatal complications. The committee were satisfied that this level of evidence warranted their recommendations, and this was further supported by the health economic modelling which confirmed that this was a cost-effective use of resources. The only evidence of harm identified by the meta-analysis was in women or pregnant people with a long cervix (no harms were identified with a short cervix), and this was exactly the reason for not recommending progesterone in a wider population of twin and triplet pregnancies. Furthermore, this study which identified harm used a high dosage of progesterone (600 mg per day) and early onset of therapy and the authors suggested this could have contributed to these effects. The committee were aware of the ongoing PROSPECT study and have followed up with the authors regarding any potential impact on the study of their recommendations. The committee discussed the study and noted in the evidence review that the results of the PROSEPCT study may warrant a further review of these recommendations

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				(as it includes serial scanning, different cervical length cut-offs, and pessary as an intervention as well). However, this study has been in progress for 9 years and it is not clear, despite reaching out to the main study contact, if the planned end date will be achieved. The committee therefore agreed to make recommendations based on current evidence. The committee discussed the resource impact of cervical length scans in all twin and triplet pregnancies but agreed that as multiple births only account for 1 in every 65 pregnancies this single additional cervical length scan (between 16 and 20 weeks) would be achievable as part of the antenatal care provided to multiple pregnancies and could be timed to coordinate with other antenatal appointments and scans. In addition, as mentioned above, the health economic modelling carried out demonstrated that the scan and use of progesterone in women or pregnant people with a short cervix was a cost-effective use of NHS resources due to the reduction in preterm births.

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British Maternal & Fetal Medicine Society			We also have concerns around the logistics of the delivery of care to these women • who and where will the 16 week TVUS take place. Especially in DCDA where this would not be normal schedule of scan. • Can the TVUS be added routinely for all twins at the end of the anomaly scan? • additional cost of transvaginal cervical length training and scanning time for ultrasonographers that will carry out the main bulk of these cervical lengths nationally • The additional potential pressures on the prematurity and wider Obstetric team thereafter.	Thank you for your comment. The committee discussed the logistics and resource impact of the single cervical length scan recommended, but agreed that as multiple births only account for 1 in every 65 pregnancies this single additional cervical length scan (between 16 and 20 weeks) would be achievable as part of the antenatal care provided to multiple pregnancies, and could be timed to coordinate with other antenatal appointments and scans. In addition, the health economic modelling carried out demonstrated that the additional cost of the scan, the additional time to discuss results and treat women and pregnant people, and the use of progesterone in women or pregnant people with a short cervix was a cost-effective use of NHS resources due to the reduction in preterm births.
British Maternal & Fetal Medicine Society			We are very concerned that regular screening, even for low risk women, and then serial screening for intermediate risk women (without the use of fibronectin), is only going to cause more anxiety in an already anxious high risk cohort of women with multiples. In addition, each unit will have a different criteria for	Thank you for your comment. The recommendations have been amended to make it clear that only a single cervical length scan (between 16 and 20 weeks) is recommended to determine if progesterone should be offered. These recommendations do not relate to the

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			admission, intervention and low threshold for in- utero transfers.	serial cervical scanning of high risk singleton pregnancies as advised in Saving Babies Lives care bundle version 3, nor to the management of women or pregnant people presenting in threatened preterm labour where decisions about the likelihood of preterm labour, interventions or in-utero transfer will be necessary.
British Maternal & Fetal Medicine Society	General		We are very concerned about the about the impact in terms of workload, logistics of timing and patient expectation. Screening should be limited to women with PTB risk factors that are in addition to being pregnant with twins (or triplets) and that would have been implemented if the pregnancy had in fact been singleton.	Thank you for your comment. The committee agreed that women or pregnant people with a twin or triplet pregnancy are already at an increased risk of a preterm birth (compared to a singleton pregnancy) and the recommendations have been amended to make it clear that only a single cervical length scan (between 16 and 20 weeks) is recommended to determine if progesterone should be offered. The committee discussed the logistics and resource impact of the single cervical length scan recommended but agreed that as multiple births only account for 1 in every 65 pregnancies this additional cervical length scan (between 16 and 20 weeks) would be achievable as part of the antenatal care provided to multiple pregnancies, and could be timed to coordinate with other antenatal

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				appointments and scans. In addition, the health economic modelling carried out demonstrated that the scan and use of progesterone in women or pregnant people with a short cervix was a cost-effective use of NHS resources due to the reduction in preterm births.
British Maternal & Fetal Medicine Society	Guideline	16-24 Vaginal progesterone (100-600 mg per day) versus placebo in twin pregnancies (participants with a short cervix ≤25mm) (1IPD).	Page 15 The basis of this NG137 NICE update is to recommend a major change in the management of multiple pregnancies: the screening for and the use of a 'therapy' to reduce the incidence of spontaneous preterm birth in twins (extrapolated to triplets). The evidence base for this rests on one IPD (Conde-Agudelo A et al 2022) The use of vaginal progesterone in unselected twin pregnancies (i.e. not selected by cervical length) has been subject to two recent large publications (EPPPIC and EVENTS). These demonstrated that vaginal progesterone had no benefit in preventing preterm delivery and may have been associated with harm in some groups (higher tendency to PTB or premature rupture of membranes). Therefore, data to support the use of vaginal progesterone in a subgroup of twin pregnancies with a short cervical length requires to be of high quality to	Thank you for your comment. You are correct that the committee made their decisions based on the updated Conde-Agudelo 2022 IPD. This only found evidence of benefit in women with a short cervix, and this is in whom progesterone has been recommended. We will address your other points in turn. A. You are correct that a publication that was included in a previous analysis was retracted and was not included in the most recent Conde-Agudelo 2022 IPD. However, the committee had no reasons to doubt the validity of any of the data included in the Conde-Agudelo 2022 IPD. B1. The committee acknowledge that the sample size was small but the population of interest – women with a twin or triplet pregnancy AND who have a short cervix – is a very small cohort and so a difficult group on whom to obtain large sets of

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			inform safe practice. This is where our concerns lie: A. The NICE committee for NG137 Twin and Triplet Pregnancy (2019) recognized the efficacy of cervical length screening in twin pregnancies to predict spontaneous preterm birth. Still, it did not make a recommendation for the introduction of such a screening program due to the lack of proven intervention and therefore the lack of a cost-effectiveness model. The committee was particularly concerned about some of the data included in an IPD (comprising 303 pregnancies, Romero R, Conde-Agudelo A et al 2017) which suggested efficacy of progesterone to reduce the incidence of preterm birth in twins with a short cervical length. One RCT contributing the majority of data to this IPD had recruited 224 twin pregnancies (112 with a cervical length ≤ 25 in a concerningly small available national population) (El-Refaie W et al Arch Gynecol Obstet 2016;293:61-67). The committee and the wider obstetric academic population were concerned as to: 1. The validity of the El-Refaie data.	data. However, the data was an individual patient data (IPD) meta-analysis. IPD meta-analysis is considered to be gold standard for meta-analysis, and this offers the most robust approach to answer the research question. The recommendations for women with short cervix are based on overall evidence from the Conde-Agudelo 2022 IPD meta-analysis which showed reduced preterm birth (<28 weeks and <32 weeks), spontaneous preterm birth (<34 weeks), and reduced the composite of serious neonatal complications. The committee were satisfied that this level of evidence warranted their recommendations, and this was further supported by the health economic modelling which confirmed that this was a cost-effective use of NHS resources due to a reduction in preterm births. The committee were aware of the ongoing PROSPECT study, which they had discussed and already noted in the evidence review and agreed that the results of this study may warrant a further review of these recommendations (as it includes serial screening, different cervical length cut-offs and a pessary as an

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			2. Why the volume of the El-Refaie data was not questioned by the authors of the (2017) IPD. B. The current NICE committee is suggesting that the updated IPD data from the same group (Conde Agudelo A, et al al 2022) is now robust enough to support the efficacy of progesterone. The IPD has added patient data from one further study and has removed the El-Refaie data (this has been retracted from the published literature allegedly on the basis that 'the authors did not obtain approval from a research ethics committee'' before conducting the RCT). This IPD data (2022) continues to have some limitations: 1. The number of pregnancies included. (95 women with a short cervix ≤ 25mm: comprising the remaining 79 women from the original 2017 IPD and 16 women identified in the EVENTS trial by Rehal et al. 2021). 52 women were treated with progesterone, 24 with placebo. Due to the limited study size the authors of the IPD themselves state that although progesterone showed promise (i.e. pooled RR of preterm birth < 28 weeks = 0.41(0.19-0.91)	intervention as well). However, this study has been in progress for 9 years and it is not clear, despite reaching out to the main study contact, if the planned end date will be achieved. The committee therefore agreed to make recommendations based on current evidence. B2. This evidence was not just taken from the EVENTS trial, which as you state contributed only 16 of the 95 women, but the majority of the studies in the evidence review initiated treatment with vaginal progesterone after 18 weeks of gestation, and cervical length was measured pre-randomisation in these studies. This was consistent with the committee's view of when it would be measured in practice which is between 16 and 20 weeks of gestation. B3. The evidence was from the IPD meta-analysis and not just from the EVENTS trial. B4. We specified in our protocol to only consider a 25 mm cut-off for cervical length as this cut-off is used in clinical practice. We did not specify a cervical length cut-off of 30mm in our protocol, hence outcomes reported in relation to 30

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			the data should not be used to recommend that women in a twin pregnancy with a short cervix should commence progesterone. The authors recommend 'awaiting evidence from an ongoing randomized control trial (PROSPECT study)' to establish more certainty of outcomes. 2. The 16 new cases included within the IPD from the EVENTS trial had cervical length measured at 11-14 weeks gestation NOT at mid-gestation. Patients were commenced progesterone or placebo from 11-14 weeks gestation. This data is therefore not able to support the NICE suggested strategy of cervical length screening between 16-20 weeks and progesterone thereafter. 3. The IPD suggests from its included Forrest plot that the EVENTS data (n=16) gave a relative risk of preterm birth < 33 weeks of 0.13 (0.02-0.84). This is a substantially different RR to that given for the other studies contributing women. Indeed the EVENTS data are the only data where the confidence intervals for RR do not cross 1. 4. The EVENTS data seems to give particular strength to the benefit of progesterone in pregnancies with a short cervix ≤ 25mm in the IPD publication in contrast to 'weak' potential	mm have not been reviewed in this update and no recommendations have been made relating to a cervical length less than 30 mm. B5. The recommendations on vaginal progesterone in women or pregnant people with twin pregnancies with short cervix were based on overall results from Conde-Agudelo 2022 IPD meta-analysis) not on results from EVENTS trial alone, and the time of progesterone initiation started at 11 weeks, but the exact time of cervical screening was not stated. No other interventions were reported as women or pregnant people were randomised to progesterone or placebo. The scope of this review was not to look at the benefits of cervical length scans as an intervention and so while the other benefits you cite sound plausible there is no evidence from this review to confirm or deny these benefits. However, the committee concluded, based on the evidence currently available that offering progesterone to women or pregnant people with twin and triplet pregnancies and a short cervix was likely to lead to

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			benefit of progesterone published within the EVENTS publication itself. Rehal et al 2021 performed their own sub-analysis of their data for women with a short Cx < 30mm. Progesterone therapy was associated with a non-significant reduction in preterm birth. 5. Given that the EVENTS data drives the outcome of the 2022 IPD it may be of concern this data comprises only 16 women within a larger trial of 1194 women. Were these the only women who had a cervical length measured ≤25 mm? all < 14 weeks gestation? It would be worth confirming that the 8/9 that had a short cervix and delivered beyond 33 weeks did not have any other intervention than progesterone (particularly cervical cerclage). The potential benefits of screening for the risk of preterm birth in multiple pregnancies extend far beyond the ability to prevent preterm birth. There is value in preparing women for the potential outcome of their pregnancy. There may also be a potential value for neonatal outcomes with preterm birth optimization strategies (place of birth, antenatal steroids, neuroprotection). However, the role of NICE is evidence-based practice and there remains uncertainty as to the efficacy of progesterone	benefits, without any identifiable harms, and was a cost-effective use of NHS resources.

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			therapy to prevent preterm birth in multiple pregnancies. The cost-effective model requires effective therapy, furthermore, cost-effectiveness requires effective therapy to progress pregnancies from potential loss to beyond severe preterm birth.	
GPs championing perinatal care (GPCPC)	General		We are pleased to support this change in recommendation that will help reduce the risk of pre-term birth in twin and triplet pregnancy	Thank you for your comment.
Guy's & St Thomas' NHS Foundation Trust - multiple pregnancy and preterm teams			Adjust tests like QUIPP in addition to cervical length enable more robust risk stratification, rather than serial cervical length alone. We are very concerned that regular unselected screening, and then serial screening for intermediate risk women (without the use of fibronectin), is only going to increase admissions, intervention and low threshold for in- utero transfers, and increased uptake of steroids.	Thank you for your comment. The QUIPP tool is designed for use when women or pregnant people are in threatened preterm labour. These recommendations relate to the assessment of cervical length in earlier pregnancy and the use of progesterone to reduce the risk of preterm labour. The recommendations have been amended to make it clear that only a single cervical length scan (between 16 and 20 weeks) is recommended to determine if progesterone should be offered. These recommendations do not relate to the serial cervical scanning of high risk singleton pregnancies as advised in Saving Babies Lives care bundle version 3, nor to the management of women or pregnant people presenting in threatened preterm labour where decisions about the

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				likelihood of preterm labour, interventions or in-utero transfer will be necessary.
Guy's & St Thomas' NHS Foundation Trust – multiple pregnancy and preterm teams			The basis of this NG137 NICE update is to recommend a major change in the screening for and the use of a 'therapy' to reduce the incidence of spontaneous preterm birth in twins (extrapolated to triplets). The evidence base for this rests on one IPD (Conde-Agudelo A et al 2022). The number of pregnancies included (95 women with a short cervix ≤ 25mm: comprising the remaining 79 women from the original 2017 IPD and 16 women identified in the EVENTS trial by Rehal et al. 2021). The 16 new cases included within the IPD from the EVENTS trial had cervical length measured at 11-14 weeks gestation NOT at mid-gestation. Patients were commenced progesterone or placebo from 11-14 weeks gestation. This data is therefore not able to support the NICE suggested strategy of cervical length screening between 16-20 weeks and progesterone thereafter. 52 women were treated with progesterone, 24 with placebo. Due to the limited study size the authors of the IPD themselves state that although progesterone showed promise (i.e. pooled RR of preterm birth < 28 weeks = 0.41(0.19-0.91) the data should not be used to recommend that women	Thank you for your comment. The recommendations for women with short cervix are based on overall evidence from the Conde-Agudelo 2022 IPD meta-analysis which showed reduced preterm birth (<28 weeks and <32 weeks), spontaneous preterm birth (<34 weeks), and reduced the composite of serious neonatal complications. This effect was not just from the EVENTS trial, which as you state contributed only 16 of the 95 womenThis formed part of the data but the majority of the studies in the evidence review initiated treatment with vaginal progesterone after 18 weeks of gestation, and cervical length was measured pre-randomisation in these studies. This was consistent with the committee's view of when it would be measured in practice which is between 16 and 20 weeks of gestation. The committee acknowledge that the sample size was small but the population of interest – women or pregnant people with a twin or triplet pregnancy AND who have a short cervix – is a very small cohort and so a difficult

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			in a twin pregnancy with a short cervix should commence progesterone. The authors recommend 'awaiting evidence from an ongoing randomized control trial (PROSPECT study)' to establish more certainty of outcomes. We feel that NICE should wait for the results of the PROSPECT study. From a methodological point of view, findings from subgroup analyses as in EVENTS and the IPD should be used to generate hypothesis that should then be confirmed in new trials as there is a high risk of finding significant results by chance.	group on whom to obtain large sets of data. However, the data was an individual patient data (IPD) meta-analysis. IPD meta-analysis is considered to be gold standard for meta-analysis, and this offers the most robust approach to answer the research question. The committee were satisfied that this level of evidence warranted their recommendations, and this was further supported by the health economic modelling which confirmed that this was a cost-effective use of resources. The committee were aware of the ongoing PROSPECT study, which they had discussed and already noted in the evidence review and agreed that the results of this study may warrant a further review of these recommendations (as it includes serial scanning, different cervical length cut-offs and pessary as an intervention as well). However, this study has been in progress for 9 years and it is not clear, despite reaching out to the main study contact, if the planned end date will be achieved. the committee therefore agreed to make recommendations based on current evidence.

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HealthSense UK	Table	1	Under the heading "Who is it for" on p1 the document refers to "pregnant women and pregnant people". In the context of pregnancy and childbirth the term "women" is all that is required. Similarly, the correct term for the parent who is a woman is "mother", not anything else. As if this were not bad enough, the document see-saws between different terms, for example, on p3 there is reference to "pregnant people with a twin or triplet pregnancy" in the same table as a reference to "vaginal progesterone in women with a triplet pregnancy". The issue here is female biology, a lifelong and immutable characteristic associated with the possession of ovaries and female reproductive organs. Gender preference and lifestyle choice are not relevant. The term "pregnant people" is one of many examples in NICE documents of the confused and confusing choice of language where female reproductive health is concerned. This is especially disappointing for an organisation that has clarity, consistency and evidence at its heart. We believe that these attempts to de-	Thank you for your comment. It is NICE style to use additive language including both women and people who are pregnant but who do not identify as women. We have, however, made changes to ensure consistency of terminology across all the documents. We have addressed your other points in turn: 1. The term woman or women is used throughout and has not been replaced. 2. The policy retains the use of the word woman and uses other terms in addition to this so is not discriminatory. 3. Legal advice was not required to add additional terms for people who do not identify as women. 4. There is an equality impact assessment which accompanies the guideline. 5. The changes are kept as simple as possible (for example the NICE policy is not to list all possible alternative genders). 6. The changes are being introduced sequentially as NICE products are revised and updated, but we recognise that during this process there will be a

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			sex language are misguided and potentially harmful, for the following reasons: 1. There are many services users without English as a first language or who have learning difficulties. For such people, referring to the mother of a child or to a pregnant woman by using terms such as "birthing person" or "pregnant person" will be very confusing. 2. Your new editorial policy on the use of supposedly inclusive language is mistaken and maybe even discriminate against anyone who is pregnant or on maternity leave (protected characteristics under the Equality Act 2010). 3. It is not clear whether legal advice was taken before making the change. 4. It is not clear whether there was an Equality Impact Assessment. 5. The changes are clunky and introduce confusion into the meanings of sentences. 6. The changes in terminology are inconsistent across NICE products. It is disappointing for	period where there will be some inconsistencies across NICE products. We agree that language changes alone cannot improve care or inclusivity, but by making language as inclusive as possible the guidelines are more relatable to a wider population.

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			NICE to diminish its reputation for quality on a gamble rather than checking the necessity. We are unaware of any evidence that de-sexing language in favour of 'inclusivity' does indeed 'work' in terms of improving inclusion and achieving better outcomes (especially if other vulnerable groups are excluded), in ways that cannot be better dealt with in specified, targeted training and communications. Given the wealth of evidence that it is from relationships that benefit arises, this 'top-down' imposition looks superficial by comparison with actual skilled and compassionate clinical care. If NICE wishes to make crystal clear what it means by 'women' in its pregnancy guidelines it could add an explanatory note to the effect that the word means those people whose sex is female but who may have a non-binary, trans or other gender identity. References. 1. Gribble KD, Bewley S, Bartick MC et al. Effective Communication About Pregnancy, Birth, Lactation, Breastfeeding and Newborn Care: The Importance of Sexed Language. Frontiers in Global Womens' Health, 07	

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			February 2022. Volume 3 - 2022 | https://doi.org/10.3389/fgwh.2022.818856 2. Council of Deans of Health. Midwifery Network position paper: use of sexed language. Published online February 2024: https://www.councilofdeans.org.uk/2024/02/midwifery-network-position-paper-use-of-sexed-language/	
NHS England	Table	General	The role of primary care will be a supportive one and this draft describes with clarity the recommendation and rationale.	Thank you for your comment.
NHS England	Table	1	Autistic birthing parents are more likely to have a preterm birth, most likely due to increased likelihood of having an elective C-section delivery. Therefore, the guideline may wish to consider the effect of changes on pregnant autistic people further.	Thank you for your comment. Women or pregnant people with autism would be offered cervical length screening and progesterone, and making reasonable adjustments to services for people with autism is required by the Equality Act is a statutory requirement and so this would not be repeated in each individual NICE guideline.
NHS England	Table	2	Autistic people can experience heightened sensory and physical symptoms during pregnancy compared to non-autistic people. Reasonable adjustments, including sensory adjustments and time to process verbal information, are important in delivering pregnancy care for autistic people. The	Thank you for your comment. Making reasonable adjustments to services for people with autism is required by the Equality Act and is a statutory requirement and so this would not be repeated in each individual NICE guideline.

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			Sensory Friendly Resource Pack is a helpful resource to support the delivery of high quality care for autistic people.	
NHS England	Draft Consultation		We are not as sanguine as the Committee in believing that offering an additional tranche of cervical scans is likely to be as deliverable as it seems – especially when individual Trusts are already finding it difficult to offer women with singleton pregnancies at risk of preterm birth the same service (together with the required pre-test information and post-test interpretation/reflection/advice). Obstetricians serving the twins community may be more confident, however, and we would defer to their knowledge re capacity in their clinics.	Thank you for your comment. The committee discussed the resource impact of cervical length scans in all twin and triplet pregnancies but agreed that as multiple births only account for 1 in every 65 pregnancies this 1 additional cervical length scan (at 16 to 20 weeks) would be achievable as part of the antenatal care provided to multiple pregnancies, and could be timed to coordinate with other antenatal appointments and scans. In addition, the health economic modelling carried out demonstrated that the scan and use of progesterone in women or pregnant people with a short cervix was a cost-effective use of NHS resources due to the reduction in preterm births.
NHS England	Evidence Review and Draft Consultation		Is the evidence so compelling and consistent to the Committee to justify such a change? The IPD MA quoted throughout the Evidence Review as 'Conde-Agudelo 2022' is actually a letter credited to Romero by both the journal and Pubmed (https://pubmed.ncbi.nlm.nih.gov/34941003/);	Thank you for your comment. The recommendations on vaginal progesterone in women or pregnant people with short cervix is based on an individual patient data (IPD) meta-analysis (Conde-Agudelo 2022). It is not a letter to the editor. This IPD was published in Ultrasound in Obstetrics & Gynecology (UOG), the

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			not that this disqualifies its evidence, but will have been less scrutinised by peer review. It is interesting to note that the principal authors (Romero and Conde-Agudelo), usually keen advocates for evidence-based intervention, have in peer-reviewed publications on two occasions since stepped back from promoting the use of progesterone in women carrying twins with a cervix measuring <25mm in the midtrimester (see: https://pubmed.ncbi.nlm.nih.gov/36475431/ and https://pubmed.ncbi.nlm.nih.gov/37196896/) saying 'more evidence is needed before recommending this intervention to this subset of patients', so we should be cautious in the UK to recommend to our women what is a step change in the care of women carrying twins and triplets in this way (largely based on a non-UK population). An additional concern is that intervention may not necessarily stop at this point. A further cervical length scan will probably be offered to determine efficacy, and this may lead to placement of a cerclage or other treatment intended to reduce the chance of a preterm	official journal of the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG). UOG is an international peer-reviewed journal. IPD meta-analysis is considered to be gold standard for meta-analysis, and this offers the most robust approach to answer the research question. In IPD meta-analysis, data from individual patients are sought from the primary researchers/trial investigators to conduct meta-analysis. The evidence from Conde-Agudelo 2022 showed that vaginal progesterone reduced preterm birth (<28 weeks and <32 weeks), spontaneous preterm birth (<34 weeks), and reduced the composite of serious neonatal complications. The evidence did not show any harm associated with vaginal progesterone in women or pregnant people with twin pregnancies and a short cervix. The committee considered the benefit of vaginal progesterone in short cervix in reducing preterm birth with no evidence of negative effects when compared to placebo group was sufficient to justify their recommendations. In addition, the health economic modelling

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			birth. This may create unforeseen consequences, not least the possibility of sepsis which remains a key cause of maternal and fetal morbidity and mortality in midpregnancy. If the Committee felt able to recommend that risk assessment would be limited to a single cervical length scan and this intervention this risk would be obviated.	carried out demonstrated that the scan and use of progesterone in women or pregnant people with a short cervix was a cost-effective use of NHS resources due to the reduction in preterm births. The recommendations advise a single cervical length scan and have been amended to emphasise this.
Twins Trust	General		Lack of robust evidence around the efficacy of progesterone in management of women with twins at risk of preterm birth	Thank you for your comment. The recommendations for women or pregnant people with short cervix are based on overall evidence from the Conde-Agudelo 2022 IPD meta-analysis which showed reduced preterm birth (<28 weeks and <32 weeks), spontaneous preterm birth (<34 weeks), and reduced the composite of serious neonatal complications. The committee acknowledge that the sample size was small but the population of interest – women or pregnant people with a twin or triplet pregnancy AND who have a short cervix – is a very small cohort and so a difficult group on whom to obtain large sets of data. However, the data was an individual patient data (IPD) meta-analysis. IPD meta-analysis is considered to be gold standard for meta-analysis, and

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				this offers the most robust approach to answer the research question. The committee were satisfied that this level of evidence warranted their recommendations, and this was further supported by the health economic modelling which confirmed that this was a cost-effective use of NHS resources due to the reduction in preterm births.
Twins Trust	General		In our experience in care for multiple pregnancy across the units that engaged with Healthcare Engagement Programme, not all women with multiple pregnancy have routine screening for preterm labour, and there is no institutional provision for the increased workload in many units.	Thank you for your comment. The recommendations advise a single cervical length scan in all women or pregnant people with a twin or triplet pregnancy. The committee recognised that not all women currently have this scan and discussed the resource impact of cervical length scans in all twin and triplet pregnancies but agreed that as multiple births only account for 1 in every 65 pregnancies this single additional cervical length scan (between 16 and 20 weeks) would be achievable as part of the antenatal care provided to multiple pregnancies, and could be timed to coordinate with other antenatal appointments and scans. In addition, the health economic modelling carried out demonstrated that the additional cost of

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				the scan, the additional time to discuss results and treat women and pregnant people, and the use of progesterone in women or pregnant people with a short cervix was a cost-effective use of NHS resources due to the reduction in preterm births.
Twins Trust	General		The preterm birth surveillance team will look at the women according to the risk stratification for preterm birth rather than multiples and their complex needs. This would need education of the preterm teams and multiples core team together to support the women we advocate for.	Thank you for your comment. The guideline already makes recommendations in section 1.3 on the delivery of antenatal and intrapartum care which advise that care should be provided a specialist and multidisciplinary team who have expertise in the care of women or pregnant people with twin or triplet pregnancies. It would not therefore be expected that these pregnancies would be cared for solely by a preterm birth team in the same way as a singleton pregnancy.
Twins Trust	General		Women with multiple pregnancies already have anxiety around the pregnancy outcomes and the complexity of the pregnancy. Regular screening, even for low risk women, and then for intermediate risk women (without the use of fibronectin), is only going to cause more anxiety, low threshold for admissions and in utero transfers. What is the support that NICE	Thank you for your comment. The recommendations have been amended to make it clear that only a single cervical length scan (between 16 and 20 weeks) is recommended to determine if progesterone should be offered. These recommendations do not relate to the serial cervical scanning of high risk singleton pregnancies as advised in

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			recommends should be in place for these women?	Saving Babies Lives care bundle version 3, nor to the management of women or pregnant people presenting in threatened preterm labour where decisions about the likelihood of preterm labour, interventions or in-utero transfer will be necessary.

**None of the stakeholders who comments on this clinical guideline have declared any links to the tobacco industry.*