NICE National Institute for Health and Care Excellence

Appendix B: Stakeholder consultation comments table

2020 surveillance of Preterm labour and birth (2015)

Consultation dates: Thursday 13 February to Wednesday 26 February 2020

1. Do you agree with the proposal to not update the guideline?			
Stakeholder	**Overall response**	**Comments**	**NICE response**
Besins Healthcare	No	Whilst there is emerging evidence, we acknowledge that these are insufficient presently to warrant a detailed and comprehensive update to the NICE guideline NG25 Preterm labour and birth. However, there has been new evidence in 2019 (see comment 2) that has shown the benefits of sequential approach to management of pre-term labour and therefore, we would recommend updating this section of the current NG25 guideline.	Thank you for your comment and for referencing the Daskalakis et al 2019 paper. This study was not considered in our surveillance review as it was a prospective study and NICE were only considering randomised controlled trials and Cochrane reviews due to the large volume of evidence found. There were also no confidence intervals provided for the results in the abstract which lessens the usefulness of the study for decision making in surveillance. We have now considered this study through an assessment of the abstract. Women in the study were treated with elective cervical cerclage, vaginal progesterone or progesterone plus cervical cerclage. There were no significant differences between the three groups in terms of perinatal outcomes and gestational latency periods, however there was a significant difference in terms of the frequency of P-PROM in the cerclage group. No further

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			evidence was found regarding the safety and efficacy of cerclage and there were only 25 women in this cerclage group in this study. This small sample size is considered insufficient to trigger an update and we also did not find any evidence regarding sequential approach to management of preterm labour during our surveillance review. Section 1.2 of the guideline will therefore remain and will not be updated.
Neonatal Critical Care Clinical Reference Group	No	1. The current guideline does not consider place of birth and in-utero transfer for threatened preterm labour <27 weeks gestation. We understand that this is because it was considered to be outside of the scope of the guideline. We strongly disagree with this and urge reconsideration of place of birth as part of the guideline as this has a significant influence on mortality and other outcomes for babies born <27 weeks. 2. Without considering place of birth and in-utero transfer as an intervention, the cost-effectiveness study of a 'treat all' policy for threatened preterm labour <30 weeks gestation is invalid. We recommend that this is therefore reconsidered. 3. We are aware that there are a significant number of maternity services not currently using this guideline as they recognise its deficiencies and applicability.	1) Thank you for your comment. Place of birth and in-utero transfer was considered during the development and the surveillance of NG25. It was noted that in utero transfer to hospitals with appropriate care is important for the safety and wellbeing of mother and child. The British Association of Perinatal Medicine (BAPM) guideline on Perinatal Management of Extreme Preterm Birth before 27 weeks of gestation gives specific advice in this area. It is also stated in the UK Preterm Clinical Network guideline for Commissioners and Providers on Reducing Preterm Birth that it is now a priority NHS England recommendation for local maternity systems (LMS) to take action to ensure that all women <27 weeks are delivered in centres with a neonatal intensive care unit and that LMS and corresponding Operational Delivery Networks have clear guidelines for antenatal transfer in the event of impending delivery <27 weeks. NG25 already mentions that clinicians should make an assessment on the need to transfer to another unit in recommendation 1.8.1. However it is agreed that this recommendation could be refreshed to ensure that in utero transfer and place of birth are considered. Therefore NICE will add in an editorial

			amendment to ensure that clinicians consider the relevant NHS England guidance. 2) Thank you for your comment. The full guideline states: "There is also a concern that the implications of a 'treat all' strategy might require some units to transfer women out of their hospital and therefore a sensitivity analysis was undertaken where the treatment cost was increased by £300 per woman to allow for the costs of such transfers. As expected this change lowers the threshold for diagnostic accuracy to be considered cost effective relative to 'treat all' and increases the threshold for diagnostic accuracy to be considered cost effective relative to 'no diagnosis and no treat'. At the lowest gestational ages the higher treatment cost has a relatively small impact on the diagnostic threshold but this increases with increasing gestational age. The overall impact of this sensitivity analysis would be to tend to push down the gestational age at which the cost-effective strategy would change from 'treat all' to treatment based on a diagnostic test. However, given the uncertainty with respect to the diagnostic accuracy of the tests reviewed, the committee, on balance, did not consider that this sensitivity analysis had a sufficiently large impact on the diagnostic accuracy threshold to justify using a diagnostic test at gestational age lower than 30 weeks". No further evidence was identified through the surveillance review to change this view. Therefore, we will not be updating this area of the guideline at this time. 3) Thank you for your comment. We are not aware of any issues around implementation of the guideline. We will

			inform our implementation team so they can investigate in more detail and if there are any issues we will feed this into the next surveillance.
Royal College of Pathologists	Yes	No comment	Thank you.
University Hospitals of Leicester	Yes	No comment	Thank you.
UK Clinical Pharmacy Association (UKCPA)	No	We would like more guidance on the following: 1) 1.2.1 Offer a choice of prophylactic vaginal progesterone – Consider adding a dose regime (dose, frequency and maximum daily dose) as various dosing regimen are seen in practice. This standardises prescribing practice. 2) 1.4.2For women with P-PROM who cannot tolerate erythromycin or in whom erythromycin is contraindicated, consider an oral penicillin for a maximum of 10 days.... **[2015, amended 2019]** Consider advising on an oral penicillin and dose should give advice on drug and dose or options.	1) Prophylactic vaginal progesterone Thank you for your comment. Please note that according to the manual for Developing NICE guidelines NICE do not give dosages routinely in guidelines. Readers are expected to refer to a medicine's summary of product characteristics (SPC) for details of dosages for licensed indications. If off-label use is being recommended, check whether there is any relevant dosage information in the BNF or BNF for Children for the particular population or indication it is being recommended for. When the guideline was developed evidence was taken from a number of studies that used various doses of progesterone including 90mg daily, 100mg daily, 200mg daily, 400 mg daily and 200mg weekly. In the 2019 evidence review RCTs were included that compared progesterone with a placebo or no treatment for the prevention of preterm birth and a similar range of doses were considered. In the recent surveillance review no evidence was found to specify whether certain doses of progesterone are more

		3) 1.8.2 Consider nifedipine for tocolysis for women between 24^{+0} and 25^{+6} week…. **[2015].** Most studies are based on the capsules but some centres have switched over to using MR preparations; consider adding further information regarding which formulation may be used i.e. capsules or MR preps (making it clear that the latter is a divergence from most studies but increasingly being considered as accepted practice). Also add a maximum daily dose. 4) 1.9.2 Offer maternal corticosteroids to women between 24^{+0} and 33^{+6} weeks of pregnancy… **[2015, amended 2019].** Consider specifying which corticosteroid to use first-line and dose regime. Add a note to use an alternative agent and dose regime when either one experiences a supply problem. 5) In addition, some maternity units are administering maternal corticosteroids to all Caesaean sections and the rationale behind is that as babies are not going through the birth canal their lungs do not develop the same way as babies born vaginally. Are there any evidences for this practice?	beneficial than others. The guideline currently states that "although this use is common in UK clinical practice, at the time of publication (August 2019), vaginal progesterone did not have a UK marketing authorisation for this indication. The prescriber should see the summary of product characteristics (SPC) for the manufacturer's advice on use in pregnancy. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information". No further evidence was found during the surveillance review to contradict the guideline. Therefore NICE is currently unable to make a recommendation on dose regime. 2) Oral penicillin Thank you for your comment. In 2019 this recommendation was amended from "consider oral penicillin" to "consider AN oral penicillin" in order to make clear that the recommendation refers to a class of drug (oral penicillins) rather than a specific preparation. Please see previous point 1 above for information regarding medicine dosage in NICE guidelines. NICE has not found any evidence regarding the dose or preparation that should be used and therefore is unable to make a recommendation on dose options. 3) Nifedipine for tocolysis Thank you for your comment. Please see previous point 1 above for information regarding medicine dosage in NICE guidelines. NG25 states that "although this is common in UK clinical practice, at the time of publication (August 2019), nifedipine did not have a UK

			marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information. The suggested dose of nifedipine is a loading dose of 20 mg nifedipine orally, followed by 10–20 mg 3 to 4 times daily, adjusted according to uterine activity. At the time of publication, some brands of nifedipine were specifically contraindicated in pregnancy by the manufacturer in their SPC. Refer to individual SPCs for each preparation of nifedipine for further details". No further evidence was found during the surveillance review to contradict the guideline. Therefore NICE is currently unable to make further recommendations on formulation or dose regime. 4) Maternal corticosteroids Thank you for your comment. Please see previous point 1 above for information regarding medicine dosage in NICE guidelines. The full guideline for NG25 states that Betamethasone was the type of corticosteroid used in the studies. The course varied between the trials, with the most common course being 2 doses, 24 hours apart, of 12 mg betamethasone intramuscularly (IM), repeated weekly until 33 to 34 weeks or birth (5 trials). One trial used this course but repeated it fortnightly until 33+6 weeks or birth. In 3 trials the protocol allowed only 1 repeat course of 12 mg betamethasone IM (2 doses, 24 hours apart). No further evidence was found during the surveillance review regarding the first-line agent and dose regime and therefore it is not possible to give a firm recommendation on which drug or dose to use at this time.

			5) Caesarean section Thank you for your comment. No evidence was found during the surveillance review regarding administering corticosteroids during caesarean sections in preterm birth. NG25 does not recommend choosing a caesarean birth for preterm labour unless the woman presents with breech presentation. NICE guideline CG132 Caesarean Section (CS) recommendation 1.2.3.1 suggests that preterm birth is associated with higher neonatal morbidity and mortality, however the effect of planned CS in improving these outcomes remain uncertain and therefore CS should not routinely be offered outside a research context. If your comment refers to all caesarean sections for women who are delivering at term then this would need to be considered by the surveillance review for CG132 guideline Caesarean Section. NICE will log this comment for review at the next surveillance of CG132.
London Neonatal Operational Delivery Network (ODN)	No	For the reasons set out below, we strongly believe that the proposal not to update the guideline is wrong	Thank you for your comment. Evidence in the form of an individual participant data meta-analysis has been highlighted which states that prenatal corticosteroids given to women at ongoing risk of preterm birth after an initial course reduce the likelihood of their infant needing respiratory support after birth and leads to neonatal benefits. Additionally, the World Health Organisation now recommends repeat courses of maternal corticosteroids for women in suspected preterm labour based on an updated Cochrane review within this area. Therefore, in light of this new evidence, and the updated conclusions of the Cochrane review, we propose the guideline is updated to consider the safety and effectiveness of repeat courses of maternal corticosteroids.

British Maternal & Fetal Medicine Society	No comment	No comment	Thank you.
Royal College of Nursing	Yes	At this moment in time, yes.	Thank you for your comment.
Group B Strep Support (GBSS)	No	There should be an update to reference the fact in the 2017 Royal College of Obstetricians & Gynaecologists update to their Greentop Guideline Prevention of Early-onset Neonatal Group B Streptococcal Disease https://obgyn.onlinelibrary.wiley.com/doi/full/10.1111/1471-0528.14821 now recommends: - That intrapartum antibiotic prophylaxis (IAP) is recommended for all women who labour preterm (paragraph 7.3) That for women at more than 34 +0 weeks of gestation whose waters break prelabour, "it may be beneficial to expedite delivery if a woman is a known GBS carrier" (paragraph 8.1)	Thank you for your comment. NG25 recommendation 1.4.4 refers to NICE's guideline CG149 Neonatal infection (early onset): antibiotics for prevention and treatment. This guideline gives the following recommendations: 1.3.1.3 Consider intrapartum antibiotic prophylaxis using intravenous benzylpenicillin to prevent early-onset neonatal infection for women in preterm labour if there is prelabour rupture of membranes of any duration. 1.3.1.4 Consider intrapartum antibiotic prophylaxis using intravenous benzylpenicillin to prevent early-onset neonatal infection for women in preterm labour if there is suspected or confirmed intrapartum rupture of membranes lasting more than 18 hours. In January 2017 CG149 went through the surveillance process and the surveillance decision was to update the following sections of the guideline: • Risk factors for infection and clinical indicators of possible infection.

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			• Intrapartum antibiotics. • New area: maternal group B streptococcus status to guide the decision on timing of delivery in women with preterm prelabour rupture of membranes. This update is expected to publish in March 2021 and NICE will consider any amendments that will affect NG25 and amend accordingly.
Royal College of Paediatrics and Child Health	No	The reviewer strongly believes that the proposal not to update the guideline is wrong. Please see comments below for the rationale. 1) Would NICE be able to provide greater clarity of detail on the Impact statement for rescue cerclage? Page 14, 1.6 Rescue cerclage. Impact statement: 'There is not enough evidence to confirm that rescue cerclage combined with progesterone significantly prolongs pregnancy'. The evidence reviewed includes 'RCT identified through the surveillance review indicated that women who received rescue cerclage plus progesterone had significant pregnancy prolongation'. Could NICE clarify why this does not provide enough evidence (N=100 women)? 2) Regarding the decision not to add a section on In utero transfer (p.42) has the evidence below been considered, demonstrating an association between birth outside a tertiary neonatal unit and adverse outcomes? Although this does not address directly the issue of IUT it does provide cohort data relevant to the issue of place of	1) Thank you for your comment. The Ragab et al 2015 study does not provide confidence intervals for the results given in the abstract which lessens the usefulness of this study for decision making in surveillance. There is also no economic evidence provided to state whether rescue cerclage combined with progesterone would be cost effective for the NHS. Therefore, with this study alone, NICE is unable to make any change to the guideline recommendation at this time. 2) Thank you for your comment and for referencing the Helenius et al 2019 study. As this study was an observational cohort study NICE would not have considered it during our surveillance review as NICE were only considering randomised controlled trials and Cochrane Reviews due to the volume of evidence found. We have now considered this study through an assessment of the abstract. Place of birth and in-utero transfer was considered during the development and the surveillance of NG25. It was noted that in utero transfer to hospitals with appropriate care is important for the safety and wellbeing of mother and child. The British Association of Perinatal Medicine (BAPM) guideline on Perinatal Management of

		delivery and adverse outcomes. The statement in 1.8.1 doesn't really reflect benefit: '1.8.1Take the following factors into account when making a decision about whether to start tocolysis: availability of neonatal care (need for transfer to another unit)' An amendment to the wording to indicate this would be helpful and/or an additional statement under IUT. Ref: 1. Helenius Kjell, Longford Nicholas, Lehtonen Liisa, Modi Neena, Gale Chris. Association of early postnatal transfer and birth outside a tertiary hospital with mortality and severe brain injury in extremely preterm infants: observational cohort study with propensity score matching BMJ 2019; 367 :l5678	Extreme Preterm Birth before 27 weeks of gestation gives specific advice in this area. It is also stated in the UK Preterm Clinical Network guideline for Commissioners and Providers on Reducing Preterm Birth that it is now a priority NHS England recommendation for local maternity systems (LMS) to take action to ensure that all women <27 weeks are delivered in centres with a neonatal intensive care unit and that LMS and corresponding Operational Delivery Networks have clear guidelines for antenatal transfer in the event of impending delivery <27 weeks. NG25 already mentions that clinicians should make an assessment on the need to transfer to another unit in recommendation 1.8.1. However, on review of the evidence, it is agreed that this recommendation could be refreshed to ensure that in utero transfer and place of birth are considered. Therefore NICE will add in an editorial amendment to ensure that clinicians consider the relevant NHS England guidance.
Royal College of Obstetricians and Gynaecologists (RCOG)	No	New evidence about the use of antenatal corticosteroids has been published since NG25, including an update of the Cochrane Review of antenatal corticosteroids, IPD meta-analysis of repeat courses of antenatal cortiostroids, a,new trials of late preterm (34-36+6 weeks gestation) antenatal corticosteroids. There has also been new BAPM guidelines for women at risk of preterm birth between 22+0 -23+6 weeks, RCOG guidance of women with PPROM and there is upcoming RCOG guidance on antenatal corticosteroids, which include this evidence.	Thank you for your comment. During the surveillance review 2 Cochrane Reviews were found which considered corticosteroids in preterm labour. One review looked at single courses (Robert et al 2017) and 1 looked at repeat doses (Crowther et al 2015). There was a significant reduction in perinatal death, neonatal death and respiratory distress syndrome in the group that were treated with single dose corticosteroids compared with the group who received placebo or no treatment and no adverse effects were recorded for the children later in life. This review also included the largest recent trial of late steroids (Gyamfi-Bannerman et al 2016) and

		NG25 now is outdated and thus conflicts with other national guidance. We would urge a revision of the guideline taking into account the latest evidence on antenatal corticosteroids so a consistent national approach can be applied.	while late steroids show some benefits to neonatal respiratory complications, there are also some harms in regard to hypoglycemia. Treatment with repeat doses of corticosteroid was associated with a reduction in mean birthweight however at early childhood follow up there were no significant differences between infants that had been exposed to prenatal corticosteroids compared with those not exposed. There were no significant adverse effects reported. NICE specifically asked at consultation whether the recommendation of "Do not routinely offer repeat courses of maternal corticosteroids" was still acceptable in practice. Evidence in the form of an individual participant data meta-analysis has been highlighted which states that prenatal corticosteroids given to women at ongoing risk of preterm birth after an initial course reduce the likelihood of their infant needing respiratory support after birth and leads to neonatal benefits. Additionally, the World Health Organisation now recommends repeat courses of maternal corticosteroids for women in suspected preterm labour based on an updated Cochrane review within this area. Therefore, in light of this new evidence, and the updated conclusions of the Cochrane review, we propose the guideline is updated to consider the safety and effectiveness of repeat courses of maternal corticosteroids. The BAPM guideline currently states that "administration of antenatal steroid and magnesium sulphate are associated with improved survival and neonatal outcomes as well as reduced risk of childhood impairment, even before 24 weeks of gestation". This does not contradict NICE's current recommendations which state that women at 23 weeks can discuss the use of steroids and magnesium sulphate in the context of individual circumstances and

			therefore this area of the recommendation will not be updated at this time.
British Association of Perinatal Medicine (BAPM)	No	The guideline needs to be reviewed to consider the gestational age limits for intervention (antenatal steroids, magnesium sulphate and antenatal monitoring) as they are currently at 24+0 weeks. There is evidence of improved outcomes if steroids are given even at extremely low gestations and the new BAPM framework for extreme preterm infants recommends considering intervention in babies as low as 22+0 weeks therefore the guideline should be brought into line with this. (https://www.bapm.org/resources/80-perinatal-management-of-extreme-preterm-birth-before-27-weeks-of-gestation-2019)	Thank you for your comment. The British Association of Perinatal Medicine (BAPM) guideline on Perinatal Management of Extreme Preterm Birth before 27 weeks of gestation gives information regarding the care of preterm neonates after birth which was a population excluded from the scope of this guideline. The BAPM guideline currently states that "administration of antenatal steroid and magnesium sulphate are associated with improved survival and neonatal outcomes as well as reduced risk of childhood impairment, even before 24 weeks of gestation". This does not contradict NICE's current recommendations which state that women at 23 weeks can discuss the use of steroids and magnesium sulphate in the context of individual circumstances and therefore this area of the recommendation will not be updated at this time. NICE found limited evidence for interventions pre-birth in babies before 23 weeks, such as steroids, magnesium sulphate and antenatal monitoring during this surveillance review and therefore we are unable to update this area of the guideline at this time. Xu Y-J et al 2015 was the only study to consider an intervention in women under 24 weeks pregnant and this was the use of atosiban. At the time of guideline development, the committee stated that atosiban had poor efficacy in reducing intraventricular haemorrhage and respiratory distress syndrome and a modest effect on perinatal mortality. Therefore, the committee decided that this should not be the first option of tocolytic treatment. No further evidence was found during the surveillance review and therefore this area of the guideline will not be updated at this time.

2. Do you have any comments on areas excluded from the scope of the guideline?			
Stakeholder	**Overall response**	**Comments**	**NICE response**
Besins Healthcare	Yes	1. We suggest "a stepwise approach in cervical shortening management, with the addition of cervical cerclage in women who do not respond to vaginal progesterone, or in those with a very short cervix during the initial evaluation" based on *Pergioltais* et al publication in AJOG 2019. (reference: Daskalakis G, et al. A stepwise approach for the management of short cervix: time to evolve beyond progesterone treatment in the presence of progressive cervical shortening. *Am J Obstet Gynecol.* 2019; 220(4):404-405) (DOI: https://www.ajog.org/article/S0002-9378(19)30251-0/fulltext 2. Based on state-of-the-art methods for indirect comparisons (*Conde Agudelo*, et al AJOG 2013), either vaginal progesterone or cerclage are equally efficacious in the prevention of preterm birth in women with a sonographic short cervix in the mid trimester, singleton gestation, and previous preterm birth. Selection of the optimal treatment needs to consider adverse events, cost and patient/clinician preferences. The current recommendation that patients with a short cervix and a	1) Thank you for your comment and for referencing the Daskalakis et al 2019 paper. This study was not considered in our surveillance review as it was a prospective study and NICE were only considering randomised controlled trials and Cochrane reviews due to the large volume of evidence found. There were also no confidence intervals provided for the results in the abstract which lessens the usefulness of the study for decision making in surveillance. We have now considered this study through an assessment of the abstract. Women in the study were treated with elective cervical cerclage, vaginal progesterone or progesterone plus cervical cerclage. There were no significant differences between the three groups in terms of perinatal outcomes and gestational latency periods, however there was a significant difference in terms of the frequency of P-PROM in the cerclage group. No further evidence was found regarding the safety and efficacy of cerclage and there were only 25 women in this cerclage group in this study. We also did not find any evidence regarding sequential approach to management of preterm labour during our surveillance review. Section 1.2 of the guideline will therefore remain and will not be updated. 2) Thank you for your comment and for referencing the Conde-Agudelo et al 2013 study. This study was excluded from the

		history of preterm birth should be treated with cervical cerclage must be revisited in light of the results of the present study. Medical treatment with vaginal progesterone can decrease the risks that are associated with anesthesia and a surgical procedure; therefore, it is important to disclose the availability of a non-surgical therapeutic choice to patients with a history of preterm birth and a short cervix (**reference:** Conde-Agudelo A, et al. A stepwise approach for the management of short cervix: time to evolve beyond progesterone treatment in the presence of progressive cervical shortening. *Am J Obstet Gynecol*. 2013; 208(1):42.e1-42.e18) (**DOI:** http://dx.doi.org/10.1016/j.ajog.2012.10.877)	surveillance review as NICE were only considering studies from January 2015 (when the last review was completed) until October 2019. We have now considered this study through an assessment of the abstract. The OPPTIMUM study was considered during the first surveillance review in 2017 and contributed to the update that published in 2016. NICE recommend in 1.2.1 offering women a choice of either prophylactic vaginal progesterone or prophylactic cervical cerclage if they have both a history of spontaneous preterm birth and a cervical length of 25 mm or less. It is recommended that women are informed of the risks and benefits of both options. If women only have a history of preterm birth OR a cervical length of 25 mm or less then they should consider prophylactic vaginal progesterone instead of cervical cerclage. NICE considered new evidence that has published since 2015. The new evidence indicates that cervical cerclage is effective at preventing preterm delivery. One RCT states that transabdominal cerclage is the most successful form. One NICE Interventional Procedures guideline IPG639 recommends the use of laparoscopic cerclage for cervical incompetence to prevent preterm birth. Laparoscopic cerclage was outside the scope of this guideline however this procedure is linked to NG25 through the Preterm labour and birth pathway. The guideline recommendations on the clinical effectiveness of prophylactic progesterone for the prevention of preterm labour were updated in 2019. The review at that time considered all current evidence and concluded that progesterone is safe and effective to use to prevent preterm labour. No evidence was found through the surveillance review to contradict current

			recommendations. Three randomised controlled trials (RCTs) were considered during the surveillance review. One of these did not fully complete. One RCT suggested that there was no difference between the 2 groups when using progesterone and the results of 1 RCT indicated that progesterone could decrease preterm birth when combined with other treatments such as indomethacin and treatment of bacterial vaginosis. No evidence was found during the surveillance review to contradict any of the current recommendations and therefore this section of the guideline on prophylactic vaginal progesterone and prophylactic cervical cerclage will not be updated at this time.
Neonatal Critical Care Clinical Reference Group	Yes	As above	Thank you for your comment.
Royal College of Pathologists	No	No comment	Thank you.
University Hospitals of Leicester	No	No comment	Thank you.
UK Clinical Pharmacy Association (UKCPA)	No	No comment	Thank you.

London Neonatal Operational Delivery Network (ODN)	Yes	1) The guideline does not currently consider place of birth as a risk factor for poor outcome and in utero transfer as an intervention to improve outcomes in preterm birth. This is increasingly an untenable position for NICE to put itself in, with other national guidance placing this at the forefront of management of preterm labour. Evidence of improved outcomes in extremely preterm babies born in NICU centres is clear, including from the UK. For example: 1. Association of early postnatal transfer and birth outside a tertiary hospital with mortality and severe brain injury in extremely preterm infants: observational cohort study with propensity score matching. Helenius K, Longford N, Lehtonen L, Modi N, Gale C; Neonatal Data Analysis Unit and the United Kingdom Neonatal Collaborative. BMJ. 2019 Oct 16;367:l5678. doi: 10.1136/bmj.l5678. Perinatal outcomes for extremely preterm babies in relation to place of birth in England: the EPICure 2 study. Marlow N, Bennett C, Draper ES, Hennessy EM, Morgan AS, Costeloe KL. Arch Dis Child Fetal Neonatal Ed. 2014 May;99(3):F181-8. doi: 10.1136/archdischild-2013-305555. Epub 2014 Mar 6.	1) Thank you for your comment and for referencing the Helenius et al 2019 study and the Marlow et al 2014 study. These studies would not have been considered during the surveillance review as NICE were only looking at randomised controlled trials and Cochrane reviews due to the volume of evidence found. We have now considered these studies through an assessment of the abstract. Place of birth and in-utero transfer was considered during the development and the surveillance of NG25. It was noted that in utero transfer to hospitals with appropriate care is important for the safety and wellbeing of mother and child. The British Association of Perinatal Medicine (BAPM) guideline on Perinatal Management of Extreme Preterm Birth before 27 weeks of gestation gives specific advice in this area. It is also stated in the UK Preterm Clinical Network guideline for Commissioners and Providers on Reducing Preterm Birth that it is now a priority NHS England recommendation for local maternity systems (LMS) to take action to ensure that all women <27 weeks are delivered in centres with a neonatal intensive care unit and that LMS and corresponding Operational Delivery Networks have clear guidelines for antenatal transfer in the event of impending delivery <27 weeks. NG25 already mentions that clinicians should make an assessment on the need to transfer to another unit in recommendation 1.8.1. However, in light of the new evidence, it is agreed that this recommendation could be refreshed to ensure that in utero transfer and place of birth are considered. Therefore NICE will add in an editorial amendment to ensure that clinicians consider the relevant NHS England guidance. 2) Thank you for your comment. NG25 covers the care of women at increased risk of, or with symptoms and signs of, preterm labour.

		It is ridiculous that current guidelines do not reflect the quality improvement processes and recommendations that demonstrate improvement in outcomes for preterm infants. Why can't the NHS manage to join up its thinking? Place if birth has been identified as a modifiable factor in neonatal mortality reviews and not to consider this in national guidance does not support the drive to reduce neonatal mortality 2) I don't see how identifying women at high risk for premature labour can be outside the scope of a guideline on preterm labour & birth.	The recommendations are not covering the identification of women at increased risk of preterm labour as this is outside of the scope. Screening for preterm birth was considered during the development of CG62 Antenatal care for uncomplicated pregnancies and recommendation 1.9.3.1 states that routine screening for preterm labour should not be offered. This recommendation was given due to the need for future research investigating the value of tests that are cheap and easy to perform such as maternal serum human chorionic gonadotrophin (MSHCG), serum C-reactive protein (CRP) and cervico-vaginal fetal fibronectin levels. The diagnostic accuracy and cost effectiveness of transvaginal ultrasound to measure cervical length and funnelling to identify women at risk of preterm labour also needed to be more fully investigated. This recommendation is currently supported by the National Screening Committee guidance on preterm labour screening in pregnancy which state "systematic population screening programme is not recommended". Therefore, NICE is unable to consider adding any identification recommendations into the guideline at this time.
British Maternal & Fetal Medicine Society	No comment	No comment	Thank you.
Royal College of Nursing	No	All seems appropriate	Thank you for your comment.
Group B Strep Support (GBSS)	Yes	Additional comments below	Thank you.

Royal College of Paediatrics and Child Health	Yes	The guideline does not currently consider place of birth as a risk factor for poor outcome and in utero transfer as an intervention to improve outcomes in preterm birth. This is increasingly an untenable position for NICE to put itself in, with national guidance placing this at the forefront of management of preterm labour. Evidence of improved outcomes in extremely preterm babies born in NICU centres is clear, including from the UK. For example: 1. Association of early postnatal transfer and birth outside a tertiary hospital with mortality and severe brain injury in extremely preterm infants: observational cohort study with propensity score matching. Helenius K, Longford N, Lehtonen L, Modi N, Gale C; Neonatal Data Analysis Unit and the United Kingdom Neonatal Collaborative. BMJ. 2019 Oct 16;367:l5678. doi: 10.1136/bmj.l5678. 2. Perinatal outcomes for extremely preterm babies in relation to place of birth in England: the EPICure 2 study. Marlow N, Bennett C, Draper ES, Hennessy EM, Morgan AS, Costeloe KL. Arch Dis Child Fetal Neonatal Ed. 2014 May;99(3):F181-8. doi: 10.1136/archdischild-2013-305555. Epub 2014 Mar 6.	Thank you for your comment and for referencing two studies. These would not have been included in this surveillance review as they were observational studies and NICE were only considering RCTs and Cochrane reviews due to the large volume of evidence found. We have now considered these studies through an assessment of the abstract. Place of birth and in-utero transfer was considered during the development and the surveillance of NG25. It was noted that in utero transfer to hospitals with appropriate care is important for the safety and wellbeing of mother and child. The British Association of Perinatal Medicine (BAPM) guideline on Perinatal Management of Extreme Preterm Birth before 27 weeks of gestation gives specific advice in this area. It is also stated in the UK Preterm Clinical Network guideline for Commissioners and Providers on Reducing Preterm Birth that it is now a priority NHS England recommendation for local maternity systems (LMS) to take action to ensure that all women <27 weeks are delivered in centres with a neonatal intensive care unit and that LMS and corresponding Operational Delivery Networks have clear guidelines for antenatal transfer in the event of impending delivery <27 weeks. NG25 already mentions that clinicians should make an assessment on the need to transfer to another unit in recommendation 1.8.1. However it is agreed in light of the new evidence that this recommendation could be refreshed to ensure that in utero transfer and place of birth are considered. Therefore NICE will add in an editorial amendment to ensure that clinicians consider the relevant NHS England guidance.

Royal College of Obstetricians and Gynaecologists (RCOG)	Yes	1) The use of antenatal corticosteroids in women having caesarean birth both at late preterm and term gestations is an area of uncertainty with emerging evidence, where clear clinical guidance would be valuable. It is not clear where these women sit within current NICE guidance. NG25 "Includes women having planned preterm birth" and "Excludes women in labour at term " but makes no comment on women who have planned CS around term. There is no mention of steroids in CG132 Caesarean section. It would be extremely valuable to have evidence clearly reviewed and explicit guidance made in either or both NG25 or CG132 with consistent approach (in reality evidence around late preterm and term el CS is often combined so needs to be considered together). 2) NG137 (twin and triplets) references NG25 on use of antenatal corticosteroids for planned birth even though NG25 does not review evidence for twins OR review use of steroids at late gestation planned birth. This inconsistency should be rectified – either with inclusion of twins in NG25 , or proper review of the evidence of antenatal corticosteroids in twins in NG137.	1) Thank you for your comment. Section 1.9 gives clear recommendations on the use of maternal corticosteroids for women having a planned preterm birth. CG132 Caesarean Section had a surveillance review in 2017 and evidence around the use of antenatal corticosteroids was not found, however we will note this area of concern for the next surveillance review which should take place in 2 years' time. 2) During the development of NG137 on Twin and Triplet pregnancy it was noted that limited evidence was identified for the effectiveness of routine (elective) corticosteroids for reducing perinatal morbidity in twin and triplet pregnancies. The evidence compared different aspects of treatment and was mostly very low in quality however the studies considered did refer to women with multiple pregnancy. The recommendations for timing of birth were updated in 2019 and the full evidence review states that "The evidence for women with uncomplicated monochorionic diamniotic twin pregnancies indicated that planned birth from 36+0 weeks' gestation does not appear to be linked to an increased risk of neonatal mortality or morbidities. For women with uncomplicated monochorionic diamniotic twin pregnancy planned birth should be offered after a course of antenatal corticosteroids has been considered. The committee was reassured that this is also in line with the findings from the Cheong-See 2016 systematic review for this group and acknowledged also that it was consistent with the timing of birth recommended for this type of pregnancy in 2011". After consideration, the NG25 recommendations were then confirmed to be relevant to this population and the recommendations were referred to in the NG137 guideline to avoid duplication.

British Association of Perinatal Medicine (BAPM)	No	No comment	Thank you.

3. Do you have any comments on equalities issues?

Stakeholder	Overall response	Comments	NICE response
Besins Healthcare	No	No comment	Thank you.
Neonatal Critical Care Clinical Reference Group	No	No comment	Thank you.
Royal College of Pathologists	No	No comment	Thank you.
University Hospitals of Leicester	No	No comment	Thank you.
UK Clinical Pharmacy Association (UKCPA)	No	No comment	Thank you.

London Neonatal Operational Delivery Network (ODN)	No	No comment	Thank you.
British Maternal & Fetal Medicine Society	No comment	No comment	Thank you.
Royal College of Nursing	No	No comment	Thank you.
Group B Strep Support (GBSS)	No comment	No	Thank you.
Royal College of Paediatrics and Child Health	No	No comment	Thank you.
Royal College of Obstetricians and Gynaecologists (RCOG)	No	No comment	Thank you.
British Association of Perinatal Medicine (BAPM)	No	No comment	Thank you.

4. Do you have any comments on the implementation of recommendation 1.9.5? Is this recommendation of "Do not routinely offer repeat courses of maternal corticosteroids" still acceptable in practice?			
Stakeholder	**Overall response**	**Comments**	**NICE response**
Besins Healthcare	No	No comments	Thank you.
Neonatal Critical Care Clinical Reference Group	Yes	Agree that this recommendation is still acceptable in practice	Thank you for your comment.
Royal College of Pathologists	No	No comment	Thank you.
University Hospitals of Leicester	Yes	No comment	Thank you.
UK Clinical Pharmacy Association (UKCPA)	Yes, to the first part of the question No to the second part	No comment	Thank you.

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees

London Neonatal Operational Delivery Network (ODN)	Yes	1) Because the guidance currently recommends a 'treat all' approach to threatened preterm labour <30 weeks gestation, it will result in many more women than necessary being given steroids. This then will result in many more women being potentially considered for repeated steroid doses. 2) The is increasing evidence for harm (growth and neurodevelopmental outcome), for babies exposed to antenatal steroids, as well theoretical scientific animal evidence for an effect on neuronal growth, which should raise concerns about widespread antenatal steroid use in women who do not end up delivering prematurely. 3) We agree with the recommendation "Do not routinely offer repeat courses of maternal corticosteroids". However, we think the guideline should be offer a more nuanced approach to giving the first course of steroids, based on an appropriate assessment of risk of preterm delivery in the 1-2 weeks following presentation.	1) Thank you for your comment. At the time of guideline development, it was noted that the additional costs of 'treat all' are worth the reduction in adverse outcomes at lower gestational ages. The committee felt that there was not a sufficiently large impact on the diagnostic accuracy threshold to justify using a diagnostic test at gestational age lower than 30 weeks. NG25 therefore recommends not offering diagnostic testing to women under 30 weeks gestation and that tocolysis and maternal corticosteroids is the most cost-effective option for all women at this point. NICE currently recommend that women should not routinely be given repeat steroid doses, however no evidence was found during the surveillance review to state that single use and/or repeat use of steroid doses was harmful to women or to their child, and this included the consideration of long term adverse effects. During the surveillance review 2 Cochrane Reviews were found which considered corticosteroids in preterm labour. One review looked at single courses (Robert et al 2017) and 1 looked at repeat doses (Crowther et al 2015). There was a significant reduction in perinatal death, neonatal death and respiratory distress syndrome in the group that were treated with single dose corticosteroids compared with the group who received placebo or no treatment and no adverse effects were recorded for the children later in life. It was suggested that treatment with repeat dose of corticosteroid was associated with a reduction in mean birthweight however at early childhood follow up there were no significant differences between infants that had

			been exposed to prenatal corticosteroids compared with those not exposed. There were no significant adverse effects reported. NICE only consider studies which have been conducted in humans. Evidence in the form of an individual participant data meta-analysis has been highlighted which states that prenatal corticosteroids given to women at ongoing risk of preterm birth after an initial course reduce the likelihood of their infant needing respiratory support after birth and leads to neonatal benefits. Additionally, the World Health Organisation now recommends repeat courses of maternal corticosteroids for women in suspected preterm labour based on an updated Cochrane review within this area. Therefore, in light of this new evidence, and the updated conclusions of the Cochrane review, we propose the guideline is updated to consider the safety and effectiveness of repeat courses of maternal corticosteroids. As we have found no evidence to suggest that the use of single course corticosteroids is unsafe in this population we will not be updating this recommendation within the guideline.
British Maternal & Fetal Medicine Society	No comment	No comment	Thank you.
Royal College of Nursing	Yes	This seems to be in line with the Good clinical practice advice: Antenatal corticosteroids for fetal lung maturation,	Thank you for your comment. Evidence in the form of an individual participant data meta-analysis has been highlighted which states that prenatal corticosteroids given to women at ongoing risk of

		(International Journal of Obstetrics and Gynecology) which is set out below……. "Because of concerns for maternal and fetal harm and the balance of risk and benefits, planned multiple courses are not recommended. The National Institute of Child Health and Human Development 2000 Consensus Panel noted that, although there is a suggestion of possible benefit from repeated courses (especially in the reduction and severity of respiratory distress), some animal and human data suggest deleterious effects on the fetus regarding cerebral myelination, lung growth, and function of the hypothalamic–pituitary–adrenal axis.10 Regularly scheduled repeat courses or serial courses (more than two) are not currently recommended.11" With the addition of: "WHO recommends that a single repeat course of steroids may be considered if preterm birth does not occur within 7 days after the initial course and subsequent assessment demonstrates that there is a high risk of preterm birth in the next 7 days.**5** The American College of Obstetricians and Gynecologists recommends a single repeat course of antenatal corticosteroids in women who are at less than 34 weeks of gestation with a risk of preterm delivery within 7 days, and whose prior course of antenatal corticosteroids was administered more than 14 days previously.**9"**	preterm birth after an initial course reduce the likelihood of their infant needing respiratory support after birth and leads to neonatal benefits. Additionally, the World Health Organisation now recommends repeat courses of maternal corticosteroids for women in suspected preterm labour based on an updated Cochrane review within this area. Therefore, in light of this new evidence, and the updated conclusions of the Cochrane review, we propose the guideline is updated to consider the safety and effectiveness of repeat courses of maternal corticosteroids.
Group B Strep Support (GBSS)	No comment	No	Thank you.

Royal College of Paediatrics and Child Health	Yes	The wording 'consider offering a repeat course taking into account…' would reflect evidence of benefit with minimal known harm and encourage greater discussion around benefit/risk with the neonatal team. Because the guidance currently recommends a 'treat all' approach to threatened preterm labour <30 weeks gestation, it will result in many more women than necessary being given steroids. This then will result in many more women being potentially considered for repeated steroid doses. There is increasing evidence for harm (growth and neurodevelopmental outcome), for babies exposed to antenatal steroids, as well theoretical scientific animal evidence for an effect on neuronal growth, which should raise concerns about widespread antenatal steroid use in women who do not end up delivering prematurely. The reviewer agrees with the recommendation "Do not routinely offer repeat courses of maternal corticosteroids". However, the guideline should offer a more nuanced approach to giving the first course of steroids, based on an appropriate assessment of risk of preterm delivery in the 1-2 weeks following presentation.	Thank you for your comment. At the time of guideline development, it was noted that the additional costs of 'treat all' are worth the reduction in adverse outcomes at lower gestational ages. The committee felt that there was not a sufficiently large impact on the diagnostic accuracy threshold to justify using a diagnostic test at gestational age lower than 30 weeks. NG25 therefore recommends not offering diagnostic testing to women under 30 weeks gestation and that tocolysis and maternal corticosteroids is the most cost-effective option for all women at this point. During the surveillance review 2 Cochrane Reviews were found which considered corticosteroids in preterm labour. One review looked at single courses (Robert et al 2017) and 1 looked at repeat doses (Crowther et al 2015). There was a significant reduction in perinatal death, neonatal death and respiratory distress syndrome in the group that were treated with single dose corticosteroids compared with the group who received placebo or no treatment and no adverse effects were recorded for the children later in life. It was suggested that treatment with repeat dose of corticosteroid was associated with a reduction in mean birthweight however at early childhood follow up there were no significant differences between infants that had been exposed to prenatal corticosteroids compared with those not exposed. There were no significant adverse effects reported. NICE only consider studies which have been conducted in humans. NICE currently recommend that women should not routinely be given repeat steroid doses. Evidence in the form of an individual participant data meta-analysis has been highlighted which states that prenatal corticosteroids given to women at ongoing risk of preterm birth after an initial course reduce the likelihood of their

			infant needing respiratory support after birth and leads to neonatal benefits. Additionally, the World Health Organisation now recommends repeat courses of maternal corticosteroids for women in suspected preterm labour based on an updated Cochrane review within this area. Therefore, in light of this new evidence, and the updated conclusions of the Cochrane review, we propose the guideline is updated to consider the safety and effectiveness of repeat courses of maternal corticosteroids.
Royal College of Obstetricians and Gynaecologists (RCOG)	Yes	With new evidence on antenatal corticosteroids including an IPD meta-analysis now published, we think that this recommendation should be reviewed.	Thank you for your comment. NICE currently recommend that women should not routinely be given repeat steroid doses. Evidence in the form of an individual participant data meta-analysis has been highlighted which states that prenatal corticosteroids given to women at ongoing risk of preterm birth after an initial course reduce the likelihood of their infant needing respiratory support after birth and leads to neonatal benefits. Additionally, the World Health Organisation now recommends repeat courses of maternal corticosteroids for women in suspected preterm labour based on an updated Cochrane review within this area. Therefore, in light of this new evidence, and the updated conclusions of the Cochrane review, we propose the guideline is updated to consider the safety and effectiveness of repeat courses of maternal corticosteroids.
British Association of Perinatal Medicine (BAPM)	No	No comment	Thank you.

5. Do you have any comments on whether there are any gaps in the guideline that haven't been addressed that should be considered further?			
Stakeholder	**Overall response**	**Comments**	**NICE response**
Besins Healthcare	Yes	Please see above	Thank you for your comment.
Neonatal Critical Care Clinical Reference Group	Yes	See 1. Above 1. The current guideline does not consider place of birth and in-utero transfer for threatened preterm labour <27 weeks gestation. We understand that this is because it was considered to be outside of the scope of the guideline. We strongly disagree with this and urge reconsideration of place of birth as part of the guideline as this has a significant influence on mortality and other outcomes for babies born <27 weeks.	Thank you for your comment. Place of birth and in-utero transfer was considered during the development and the surveillance of NG25. It was noted that in utero transfer to hospitals with appropriate care is important for the safety and wellbeing of mother and child. The British Association of Perinatal Medicine (BAPM) guideline on Perinatal Management of Extreme Preterm Birth before 27 weeks of gestation gives specific advice in this area. It is also stated in the UK Preterm Clinical Network guideline for Commissioners and Providers on Reducing Preterm Birth that it is now a priority NHS England recommendation for local maternity systems (LMS) to take action to ensure that all women <27 weeks are delivered in centres with a neonatal intensive care unit and that LMS and corresponding Operational Delivery Networks have clear guidelines for antenatal transfer in the event of impending delivery <27 weeks. NG25 already mentions that clinicians should make an assessment on the need to transfer to another unit in recommendation 1.8.1. However it is agreed that this recommendation could be refreshed to ensure that in utero transfer and place of birth are considered. Therefore NICE will add in an editorial amendment to ensure that clinicians consider the relevant NHS England guidance.

Royal College of Pathologists	No	No comment	Thank you.
University Hospitals of Leicester	No	No comment	Thank you.
UK Clinical Pharmacy Association (UKCPA)	Yes	We have noted that as Green-top guidelines from RCOG are being archived and incorporated within NICE, many useful information such as specific drug choices, dose regime had been removed	Thank you for your comment. Please note that according to the manual for Developing NICE guidelines NICE do not give dosages routinely in guidelines. Readers are expected to refer to a medicine's summary of product characteristics (SPC) for details of dosages for licensed indications. If off-label use is being recommended, check whether there is any relevant dosage information in the BNF or BNF for Children for the particular population or indication it is being recommended for. Therefore NICE will not be providing any information regarding the dose regime in this guideline. NICE specifies the drug choice in areas where there is evidence to suggest the most benefit. NICE also does not regularly incorporate other guidelines into its recommendations.
London Neonatal Operational Delivery Network (ODN)	Yes	1. The guideline fails to address the evidence for place of birth for extreme preterm babies and the impact on outcomes of in utero transfer. 2. In assessing the evidence for 'Diagnostic testing for women under 30 weeks' gestation', the authors fail to	1) Thank you for your comment. Place of birth and in-utero transfer was considered during the development and the surveillance of NG25. It was noted that in utero transfer to hospitals with appropriate care is important for the safety and wellbeing of mother and child. The British Association of Perinatal Medicine (BAPM) guideline on Perinatal Management of Extreme Preterm Birth before 27 weeks of gestation gives specific advice in this area. It is also

		sufficiently take into account potential for harm from a 'treat all' approach, including: a. Potential harm from widespread, indiscriminate use of antenatal steroids b. In utero transfer to NICU centres of women at inadequately assessed, potentially low, risk of premature delivery, leading to worsening capacity constraints in the antenatal wards of NICU centres. This then risks leading to failure to successfully secure in utero transfer for women who need it. There is substantial evidence across the country of poor rates of in utero transfer for babies <27 weeks gestation, which is affecting neonatal outcomes c. The cost effectiveness analysis for comparing diagnostic testing and 'treat all' uses tocolysis as "the output of the health economic model" "that is a treatment that could be offered as the result of a diagnostic assessment for women with suspected preterm labour and intact membranes". The only other potential beneficial treatments assessed in the guideline in this context are steroids and magnesium sulphate. The far more important intervention, that has not been assessed or discussed, is in utero transfer, which is more likely to produce benefits, both in terms of number of transfers, but also reduction in neonatal mortality and morbidity.	stated in the UK Preterm Clinical Network guideline for Commissioners and Providers on Reducing Preterm Birth that it is now a priority NHS England recommendation for local maternity systems (LMS) to take action to ensure that all women <27 weeks are delivered in centres with a neonatal intensive care unit and that LMS and corresponding Operational Delivery Networks have clear guidelines for antenatal transfer in the event of impending delivery <27 weeks. NG25 already mentions that clinicians should make an assessment on the need to transfer to another unit in recommendation 1.8.1. However it is agreed that this recommendation could be refreshed to ensure that in utero transfer and place of birth are considered. Therefore NICE will add in an editorial amendment to ensure that clinicians consider the relevant NHS England guidance. 2) Thank you for your comment. At the time of guideline development, it was noted that the additional costs of 'treat all' are worth the reduction in adverse outcomes at lower gestational ages. The committee felt that there was not a sufficiently large impact on the diagnostic accuracy threshold to justify using a diagnostic test at gestational age lower than 30 weeks. NG25 therefore recommends not offering diagnostic testing to women under 30 weeks gestation a) During the development of the guideline and the surveillance review NICE found no evidence to suggest that the use of single course corticosteroids is unsafe in this population and therefore we will not be updating this recommendation of the guideline. We will be partially updating the guideline to reconsider the recommendation on repeat courses of maternal corticosteroids due to evidence highlighted that suggests it is safe and effective.

		3. There is currently further evidence that will be published in the near future that is likely to provide additional evidence around assessment of risk of preterm delivery. 4. Since the last update, BAPM has produced a framework for practice for care of preterm babies <27 weeks gestation, https://hubble-live-assets.s3.amazonaws.com/bapm/attachment/file/182/Extreme_Preterm_28-11-19_FINAL.pdf. This suggests that consideration should be given to active care in babies from 22 weeks gestation. NICE needs to review the implications for their guidance from this framework, in particular for the consideration of IUT, antenatal steroids and magnesium sulphate use. 5. I think the suggestion that there is insufficient evidence to support the use of foetal fibronectin in diagnosing preterm labour is wrong as is the comment that all women presenting <30 weeks should be subject to a 'treat all' approach and that it is more cost effective is fundamentally wrong. There is a significant problem with bed and cot capacity which means that unnecessary admission or transfer of all women presenting <30 weeks with threatened preterm labour is far from cost effective. Where is the cost analysis behind this statement?	b) It is stated in the UK Preterm Clinical Network guideline for Commissioners and Providers on Reducing Preterm Birth that it is now a priority NHS England recommendation for local maternity systems to take action to ensure that all women <27 weeks are delivered in centres with a neonatal intensive care unit and that LMS and corresponding Operational Delivery Networks have clear guidelines for antenatal transfer in the event of impending delivery <27 weeks. Recommendation 1.7.2 suggests offering a clinical assessment to women reporting symptoms of preterm labour who have intact membranes. It is agreed that this recommendation could be refreshed to ensure that in utero transfer and place of birth are considered. Therefore NICE will add in an editorial amendment to ensure that clinicians consider the relevant NHS England guidance. Recommendation 1.7.3 suggests that if the woman is in suspected preterm labour and she is 29 weeks pregnant or less she should receive tocolysis or corticosteroids and it is for the clinician to decide whether transfer to another unit is required. c) The full guideline states. "There is also a concern that the implications of a 'treat all' strategy might require some units to transfer women out of their hospital and therefore a sensitivity analysis was undertaken where the treatment cost was increased by £300 per woman to allow for the costs of such transfers. As expected this change lowers the threshold for diagnostic accuracy to be considered cost effective relative to 'treat all' and increases the threshold for diagnostic accuracy to be considered cost effective relative to 'no diagnosis and no treat'. At the lowest gestational ages the higher treatment cost has a relatively small impact on the diagnostic threshold (see Figure 43) but this increases with increasing gestational age. The overall impact of this sensitivity analysis would be to tend to push down the gestational age at which

			the cost-effective strategy would change from 'treat all' to treatment based on a diagnostic test. However, given the uncertainty with respect to the diagnostic accuracy of the tests reviewed, the committee, on balance, did not consider that this sensitivity analysis had a sufficiently large impact on the diagnostic accuracy threshold to justify using a diagnostic test at gestational age lower than 30 weeks" . No further evidence was identified through the surveillance review to change this view. In utero transfer is considered in recommendation 1.8.1. 3) Thank you for your comment. Please send through any evidence once published that you feel is relevant to this guideline to CFGSurveillanceTeam@nice.org.uk and NICE will assess its impact. 4) Thank you for your comment. NICE considered the content of the BAPM Perinatal Management of Extreme Preterm Birth Before 27 Weeks of Gestation in the surveillance review. Please note that the care of preterm neonates is outside of the scope of this guideline. The BAPM guideline currently states that "administration of antenatal steroid and magnesium sulphate are associated with improved survival and neonatal outcomes as well as reduced risk of childhood impairment, even before 24 weeks of gestation". This does not contradict NICE's current recommendations which state that women at 23 weeks can discuss the use of steroids and magnesium sulphate in the context of individual circumstances and therefore this area of the recommendation will not be updated at this time. Transfer to another unit is also mentioned within the NICE guidelines as noted earlier in our response. 5) Thank you for your comment. NICE guideline DG33 Biomarker tests to help diagnose preterm labour in women with intact membranes states that "there is currently insufficient evidence to

			recommend the routine adoption of the Rapid Fetal Fibronectin (fFN) 10Q Cassette Kit to help diagnose preterm labour in women with intact membranes". During the surveillance review 1 Cochrane review found insufficient evidence to support the use of fetal fibronectin for diagnosing preterm labour. Chapter 16 of the full guideline on Health Economics states that "the base-case model did not address the possible costs of diagnosis which can cause the costs of achieving particular outcomes to be underestimated. Nor did it include the costs of hospitalisation because, with the possible exception of standard care, this cost would be identical across the different treatment alternatives. However, this model was used to inform the model that did consider the diagnosis of preterm labour in women with suspected preterm labour and intact membranes (see Section 16.2). That model found that treatment remained cost effective even when including diagnostic costs, hospitalisation costs and the treatment of false positives". The full guideline also shows the relevant review questions that were considered during the development of NG25 and having the patient in a neonatal intensive care unit is a common outcome that is considered throughout the guideline.
British Maternal & Fetal Medicine Society	No comment	No comment	Thank you.
Royal College of Nursing	Yes	The Midwifery Forum considers that the guideline remains comprehensive.	Thank you for your comment. During the surveillance review NICE contacted previous guideline committee members and clinicians working in this field to ask them if they believed the guideline

		We are also aware that some trusts are currently updating their guidelines and in due course we consider would wish to report on their findings, evidence and the way forward. It would be helpful to know if NICE have approached the original 'guideline committee members' for their views on this proposal? Finally, the flow charts are helpful to practitioners.	needed updating and to request further information in this area. This feedback has been used to inform the surveillance decision.
Group B Strep Support (GBSS)	Yes	1. There should be an update to reference the fact in the 2017 Royal College of Obstetricians & Gynaecologists update to their Greentop Guideline Prevention of Early-onset Neonatal Group B Streptococcal Disease https://obgyn.onlinelibrary.wiley.com/doi/full/10.1111/1471-0528.14821 now recommends: - That intrapartum antibiotic prophylaxis (IAP) is recommended for all women who labour preterm (paragraph 7.3) That for women at more than 34 +0 weeks of gestation whose waters break prelabour, "it may be beneficial to expedite delivery if a woman is a known GBS carrier" (paragraph 8.1) *2. From Page 123 of the guideline:* *6.1.6.2 Consideration of clinical benefits and harms (of prophylactic antibiotics for PPROM)* *"In summary, although antibiotics given to mothers with P-PROM seem to have little effect on the long-term health*	1) Intrapartum antibiotic prophylaxis Thank you for your comment. NG25 recommendation 1.4.4 refers to NICE's guideline CG149 Neonatal infection (early onset): antibiotics for prevention and treatment. This guideline gives the following recommendations: 5.3.1.3 Consider intrapartum antibiotic prophylaxis using intravenous benzylpenicillin to prevent early-onset neonatal infection for women in preterm labour if there is prelabour rupture of membranes of any duration. 5.3.1.4 Consider intrapartum antibiotic prophylaxis using intravenous benzylpenicillin to prevent early-onset neonatal infection for women in preterm labour if there is suspected or confirmed intrapartum rupture of membranes lasting more than 18 hours.

		outcomes of children, the short-term advantages (reducing neonatal infection and delaying birth) are such that the committee decided that antibiotics should be offered routinely to all women with P-PROM. *Although the evidence base for this section was not robust, the committee concluded that this recommendation should be strong."* *P124:* *"The Committee noted that although there was little evidence of benefit to the baby, there was no evidence of harm."* To make a *strong* recommendation to give erythromycin on the basis of *non-robust* evidence seems perverse. It would make more sense to check for group B Strep and treat for that if present than to give prophylaxis to all cases (Tajik P, van der Ham DP, Zafarmand MH, Hof MH, Morris J, Franssen MT et al. Using vaginal Group B Streptococcus colonisation in women with preterm premature rupture of membranes to guide the decision for immediate delivery: a secondary analysis of the PPROMEXIL trials. *BJOG* 2014; 121(10):1263-1272). Furthermore, extracted from the editorial by two of the members of the charity's Medical Advisory Panel: Bedford	In January 2017 CG149 went through the surveillance process and the surveillance decision was made to update the following sections of the guideline: • Risk factors for infection and clinical indicators of possible infection. • Intrapartum antibiotics. • New area: maternal group B streptococcus status to guide the decision on timing of delivery in women with preterm prelabour rupture of membranes. This update is expected to publish in March 2021 and NICE will consider any amendments that will affect NG25 and update accordingly. 2. Oral erythromycin Thank you for your comment and for referencing the Tajik et al 2014 study. This would not have been considered by the surveillance review as NICE were only looking at studies published between 2015 and 2019 after the last review was published. We have now considered this study through an assessment of the abstract. The study suggests that women would benefit from immediate delivery if they have GBS vaginal colonisation and NICE's guideline CG149 on Neonatal infection is currently being updated to consider the timing of delivery in women with preterm prelabour rupture of membranes. This update is expected to publish in March 2021 and NICE will consider any amendments that will affect NG25 and amend accordingly. No evidence around testing for group B strep was found during the surveillance review and no evidence or intelligence was found to

		Russell AR, Steer P. The ORACLE has spoken. Lancet, 2008;372:1276-8: "In ORACLE II, the administration of antibiotics to women in spontaneous preterm labour produced no benefit, and indeed the difficulty of diagnosing preterm labour accurately was shown by the fact that 63·5% of women delivered after 37 weeks' gestation (1). The positive finding of a small benefit from erythromycin in PROM in singletons may have been due to chance (2). The intention-to-treat analysis including multiple pregnancies did not show a statistically significant benefit from erythromycin (12·7% had the composite adverse outcome *vs* 15·2% with placebo, p=0·08). The singleton subgroup analysis was not pre-specified, and an interaction between treatment group and type of pregnancy was not tested for (3). The clinical significance of the short-term benefits (less oxygen dependence at 28 days, fewer major cerebral abnormalities on cerebral ultrasound, and fewer positive blood cultures) was also debatable (4) Co-amoxiclav produced no such benefit and was associated with an increase in necrotising enterocolitis. In the 7-year ORACLE follow-up study, the short-term gains from giving erythromycin in PROM were not obviously counter balanced by any long-term disadvantage (5,6). Neither was there any persisting advantage.	contradict our recommendation regarding oral erythromycin. The full guideline for NG25 states that "although the evidence base for this section was not robust, the committee concluded that this recommendation should be strong. Giving antibiotics to women with P-PROM is currently standard clinical practice in the UK and the review of evidence in this question showed no reason to change this practice. More specifically, the evidence of no harm for the baby in terms of cerebral palsy or for the mother in terms of major maternal adverse drug reaction further confirmed the direction and the strength of the recommendation". In regard to choosing other available antibiotics, the committee considered that, in addition to the benefits of erythromycin shown in the evidence summary above, there are additional potential benefits of erythromycin as the choice of antibiotic in women with P-PROM. Firstly, erythromycin is not reported to increase the risk of necrotising enterocolitis. Secondly, it can be administered orally to target group B streptococcus, other streptococcal and staphylococcal infections, bacteria relevant to early-onset sepsis, and other micro-organisms affecting the woman and baby before labour. Thirdly, erythromycin offers a theoretical advantage (for the woman, rather than the baby) in that it can counteract mycoplasma infection that is implicated in the early stages of chorioamnionitis – this effect is not seen with penicillins). Finally, the absorption of erythromycin across the gastrointestinal tract and the placenta is limited, which suggests a potential benefit in terms of minimising the baby's exposure to antibiotics. It has been noted that a 'treat all' process for this population is cost effective. Therefore screening would not be cost effective and would be unnecessary as the drug prescribed targets group B

		Meanwhile there has been a substantial increase in prescriptions for peripartum erythromycin (4) unfortunately with no specific microbiological surveillance of the consequences. Nationally collected data in that time showed a large rise in the number of isolates of erythromycin-resistant group-B streptococcus, from 6·4% in 2002 to 11·2% in 2006 (7, 8). Although it is well established that antibiotic resistance is driven by antibiotic pressure, this increase in the number of isolates of erythromycin-resistant group-B streptococcus cannot be linked specifically to increased peripartum erythromycin use, as these data have not been collected. More worryingly, in the follow-up, the administration of either co-amoxiclav or erythromycin to women in threatened preterm labour increased the risk of cerebral palsy significantly (erythromycin: 53 [3·3%] of 1611 *vs* 27 [1·7%] of 1562, odds ratio 1·93, 95% CI 1·21–3·09; co-amoxiclav: 50 [3·2%] of 1587 *vs* 30 [1·9%] of 1586, 1·69, 1·07–2·67); the number needed to harm with erythromycin was 64 (95% CI 37–209) and with co-amoxiclav 79 (42–591). The number of children with cerebral palsy was greater when both antibiotics were given together (35 of 769, 4·55%) compared with erythromycin alone (18 of 785,	streptococcus and other streptococcal and staphylococcal infections. Please note that NICE recommendation 1.4.3 states "Do not offer women with P-PROM co-amoxiclav as prophylaxis for intrauterine infection". Thank you for referencing the Kenyon et al 2001 study. This would not have been considered by the surveillance review as NICE were only looking at studies published between 2015 and 2019 after the last review was published. We have now considered this study through an assessment of the abstract. The study suggests that antibiotics for women in preterm labour with intact membranes did not help to lower neonatal death, chronic lung disease, or major cerebral abnormality. There are no confidence intervals provided for the results in the abstract which lessens the usefulness of the study for decision making in surveillance. The study did suggest there were lower occurrences of maternal infection for those who received antibiotics. The use of antibiotics for women in labour with intact membranes is considered by the guideline CG149 Neonatal Infection and this guideline is currently being updated. Thank you for referencing Assmann et al 2000. This would not have been considered by the surveillance review as it does not specifically refer to preterm labour. Therefore it will not be reconsidered during surveillance. Thank you for referencing Kenyon et al 2008. This would not have been considered by the surveillance review as NICE were only looking at studies published between 2015 and 2019 after the last review was published. This study was considered and appraised

		2·29%), co-amoxiclav alone (15 of 763, 1·97%) or placebo alone (12 of 735, 1·63%). The mechanism of this effect is unclear but, when subclinical infection is provoking labour, treatment with low doses of oral antibiotic (250 mg erythromycin and 325 mg co-amoxiclav, both four times a day) might only suppress rather than eradicate infection from the amniotic fluid and uterine cavity. Suppression without eradication might prolong the pregnancy, thus allowing continued fetal exposure to a damaging environment. The association between definite perinatal infection and neurological damage is well described (9, 10), but ORACLE did not recruit mothers who required antibiotic treatment for clinical indications such as chorioamnionitis. Such mothers would have received antibiotics in substantially higher doses, given intravenously to achieve bactericidal concentrations in amniotic fluid. The doses of antibiotic used in ORACLE were too small and the route inappropriate for proper treatment of in-utero infection. Antibiotics can affect gut flora, and the development of the naive immune system depends crucially on the gut flora of the newborn baby. Use of perinatal antibiotic can thus alter immune tolerance, which could have contributed to the substantial increase in the incidence of allergic and autoimmune disease in young children over the past three decades in resource-rich countries.16	during the development of NG25 and therefore it will not be reconsidered by this surveillance review. Thank you for referencing Kenyon et al 2008. This would not have been considered by the surveillance review as NICE were only looking at studies published between 2015 and 2019 after the last review was published. We have now considered this study through an assessment of the abstract. The study suggests that erythromycin and/or amoxicillin–clavulanate (co-amoxiclav) given to women in preterm labour with intact membranes had no significant effect on neonatal death, medical conditions, behavioural patterns or educational attainment. There were significantly more cases of cerebral palsy in the children of those mothers who took antibiotics however compared to those who did not. The use of antibiotics for women in labour with intact membranes is considered by the guideline CG149 Neonatal Infection and this guideline is currently being updated. Thank you for referencing Jacobsson et al 2001, Inder et al 2000 and Bedford et al 2006. These would not have been considered by the surveillance review as NICE were only looking at studies published between 2015 and 2019 after the last review was published. They would also not have been considered during the development of NG25 as they are not clinical studies and therefore we will not consider them during the surveillance review. This is also the same for the Health Protection Report 2007. NICE could not access the abstracts for Hannah et al 2001, Tan et al 2003 nor Pearson et al 2004 and therefore we were unable to include these in our surveillance review. As noted above, NICE guideline CG149 is expected to update in March 2021 and NICE will consider any amendments that will affect

		The lessons to be learned seem clear: contrary to popular opinion ("might as well give them, they don't do any harm"), antibiotics are not risk free. There are extremely good and increasing reasons not to give antibiotics in association with threatened preterm labour unless there is clear evidence of infection." References 1. Kenyon SL, Taylor DJ, Tarnow-Mordi W, for the ORACLE Collaborative Group. Broad-spectrum antibiotics for spontaneous preterm labour: the ORACLE II randomised trial. *Lancet* 2001; 357: 989–94. 2. Hannah M. Antibiotics for preterm prelabour rupture of membranes and preterm labour? *Lancet* 2001; 357: 973–74. 3. Assmann SF, Pocock SJ, Enos LE, Kasten LE. Subgroup analysis and other (mis)uses of baseline data in clinical trials. *Lancet* 2000; 355: 1064–69. 4. Tan S, Holliman R, Bedford Russell AR. Hazards of widespread use of erythromycin for preterm prelabour rupture of membranes. *Lancet* 2003;361: 437. 5. Kenyon S, Pike K, Jones DR, et al. Childhood outcomes after prescription of antibiotics to pregnant women with preterm rupture of the membranes: 7-year follow-up of the ORACLE I trial. *Lancet* 2008; published online Sept 18. DOI:10.1016/S0140-6736(08)61202-7. 6. Kenyon S, Pike K, Jones DR, et al. Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous preterm labour: 7-year follow-up of the	NG25 and update accordingly. One of the review questions for CG149 is "What is the effectiveness of intrapartum antibiotic prophylaxis in the prevention of early-onset neonatal infection (compared to no treatment)"? During the surveillance review for CG149 a difference was identified between the Royal College of Obstetricians and Gynaecologists Green-top Guideline 36 ('The prevention of early-onset neonatal group B streptococcal disease') and NICE's guideline on neonatal infection. The Green-top Guideline 36 says 'Antibiotic prophylaxis for group B streptococcus is unnecessary for women with preterm rupture of membranes'. It further notes 'Antibiotic administration specifically for group B streptococcus colonisation is not necessary prior to labour and should not be given 'just in case'. If these women are known to be colonised with group B streptococcus, intrapartum antibiotic prophylaxis should be offered.' The CG149 NICE guideline says 'Consider intrapartum antibiotic prophylaxis using intravenous benzylpenicillin to prevent early-onset neonatal infection for women in preterm labour if there is prelabour rupture of membranes of any duration.' Topic experts agreed there is a discrepancy and that local practice is split. They noted that there is not good evidence in this area and it has been interpreted differently by the Royal College and NICE. Given the current differences between the 2 guidelines, it would be useful to look again at the evidence. Therefore, once CG149 is updated in March 2021 NG25 will consider referencing the new

		ORACLE II trial. *Lancet* 2008; published online Sept 18. DOI:10.1016/S0140-6736(08)61203-9. 7. Pearson A. Pyogenic and non-pyogenic streptococcal bacteraemias, England, Wales, and Northern Ireland: 2004. *CDR Weekly* 2004; 15: 4. 8. Health Protection Agency. Health protection report. Nov 16, 2007; 1: 9. http://www.hpa.org.uk/hpr/archives/2007/hpr4607.pdf (accessed Sept 10, 2008). 9. Jacobsson B, Hagberg G. Antenatal risk factors for cerebral palsy. *Best Pract Res Clin Obstet Gynaecol* 2004; 18: 425–36. 10. Inder TE, Volpe JJ. Mechanisms of perinatal brain injury. *Semin Neonatol* 2000; 5: 3–16. 11. Bedford Russell AR, Murch SH. Could peripartum antibiotics have delayed health consequences for the infant? *BJOG* 2006; 113: 758–65. Nationally collected data in that time and since have shown a large rise in the number of isolates of erythromycin-resistant group-B streptococcus in the UK, from 6·4% in 2002 to 11·2% in 2006 (7, 8) and to 15% in 2010 (Lamagni T et al Clin Infect Dis 2013 57, 682-8). In even more recent data from other parts of the world, the resistance rate is even higher - for example 36% in Taiwan (Teatero S et al, J Clin Microbiol 2017, 55:412-422) and 63% in China (Guo Y	update and the recommendations in this section on intrapartum antibiotics in NG25 may change. 3. <u>Cord Milking/Delayed cord clamping</u> Thank you for your comment and for referencing Katheria et al 2019. The searches were completed for this review in October 2019 and therefore this study was not included. We have now considered this study through an assessment of the abstract. Evidence was found during the surveillance review in the form of 3 RCTs which corroborated with the current recommendations on cord milking. Therefore this new study will not have an effect on the recommendations at this time. In regard to delayed cord clamping NG25 recommends waiting for a period of time before clamping the cord if the mother and baby are stable. It is presumed that the baby would cry during this time and be considered stable enough for cord clamping to commence. There was no evidence found in the surveillance review to suggest that delayed cord clamping for longer than 3 minutes was unsafe. Out of 10 RCTs, 6 of them indicated significant benefits of delayed cord clamping between either 30 seconds or 2 minutes. The other 4 RCTs showed no differences between the 2 groups. During the development of the guideline the committee noted that some evidence cast doubt on the assumption that the position of the baby in relation to the uterus is important, but noted that this has not been tested in preterm babies, so no further conclusions can be made. No new evidence has been presented to NICE to suggest that the position of the baby before clamping the cord is or is not

		et al Ann Clin Microbiol Antimicrob. 2018;17(1):28.), a trend which is likely to be seen in the UK as well. It is disappointing that the NICE CGC do not seem to understand the global issues and concerns in relation to the necessity to actively promote robust antibiotic stewardship, within every aspect of healthcare. The following statement in the guideline is extremely alarming from a committee of such high standing, who would be anticipated to advocate for antibiotic stewardship: *P124: The Committee noted that although there was little evidence of benefit to the baby, there was no evidence of harm.* 3. Delayed cord clamping page 319: There have been a number of published studies which prompt review of the recommendations as they stand: *15.1.8 Recommendations* *59. If a preterm baby needs to be moved away from the mother for resuscitation, or there is significant maternal bleeding:* □ *consider milking the cord*	important and therefore the recommendation will remain as it is at this time.

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		→ this is not recommended following the Premature Infants Receiving Milking or Delayed Cord Clamping: PREMOD2 trial Following a predefined interim assessment, the Data and Safety Monitoring Board (DSMB) recommended stopping recruitment based on the safety outcome of increased severe IVH in infants randomized to umbilical cord milking in the lower GA strata (23-27 weeks). Katheria A, Reister F, Essers J, Mendler M, Hummler H, Subramaniam A, Carlo W, Tita A, Truong G, Davis-Nelson S, Schmölzer G, Chari R, Kaempf J, Tomlinson M, Yanowitz T, Beck S, Simhan H, Dempsey E, O'Donoghue K, Bhat S, Hoffman M, Faksh A, Arnell K, Rich W, Finer N, Vaucher Y, Khanna P, Meyers M, Varner M, Allman P, Szychowski J, Cutter G. Association of Umbilical Cord Milking vs Delayed Umbilical Cord Clamping With Death or Severe Intraventricular Hemorrhage Among Preterm Infants. JAMA. 2019 Nov 19;322(19):1877-1886. doi: 10.1001/jama.2019.16004. PubMed PMID: 31742630. *60. Wait at least 30 seconds, but no longer than 3 minutes, before clamping the cord 20 of preterm babies if the mother and baby are stable.* → more recent data demonstrates that the important "event" is for the baby to breathe or cry before clamping	

		the cord. The time this takes is highly variable and time is therefore not the ideal marker for when the cord should be clamped to obtain maximum benefit. *61. Position the baby at or below the level of the placenta before clamping the cord.* → more recent evidence suggests that this is not necessary	
Royal College of Paediatrics and Child Health	Yes	1) Please see above comment regarding In utero transfer and place of delivery. The guideline fails to address the evidence for place of birth for extreme preterm babies and the impact on outcomes of in utero transfer. 2) In assessing the evidence for 'Diagnostic testing for women under 30 weeks' gestation', the authors fail to sufficiently take into account potential for harm from a 'treat all' approach, including: - Potential harm from widespread, indiscriminate use of antenatal steroids - In utero transfer to NICU centres of women at inadequately assessed, potentially low, risk of	1) Thank you for your comment. Place of birth and in-utero transfer was considered during the development and the surveillance of NG25. It was noted that in utero transfer to hospitals with appropriate care is important for the safety and wellbeing of mother and child. The British Association of Perinatal Medicine (BAPM) guideline on Perinatal Management of Extreme Preterm Birth before 27 weeks of gestation gives specific advice in this area. It is also stated in the UK Preterm Clinical Network guideline for Commissioners and Providers on Reducing Preterm Birth that it is now a priority NHS England recommendation for local maternity systems (LMS) to take action to ensure that all women <27 weeks are delivered in centres with a neonatal intensive care unit and that LMS and corresponding Operational Delivery Networks have clear guidelines for antenatal transfer in the event of impending delivery <27 weeks. NG25 already mentions that clinicians should make an assessment on the need to transfer to another unit in recommendation 1.8.1. However it is agreed that this recommendation could be refreshed to

		premature delivery, leading to worsening capacity constraints in the antenatal wards of NICU centres. This then risks leading to failure to successfully secure in utero transfer for women who need it. There is substantial evidence across the country of poor rates of in utero transfer for babies <27 weeks gestation, which is affecting neonatal outcomes - The cost effectiveness analysis for comparing diagnostic testing and 'treat all' uses tocolysis as "the output of the health economic model" "that is a treatment that could be offered as the result of a diagnostic assessment for women with suspected preterm labour and intact membranes". The only other potential beneficial treatments assessed in the guideline in this context are steroids and magnesium sulphate. The far more important intervention, that has not been assessed or discussed, is in utero transfer, which is more likely to produce benefits, both in terms of number of transfers, but also reduction in neonatal mortality and morbidity. There is currently further evidence that will be published in the near future that is likely to provide additional evidence around assessment of risk of preterm delivery. 3) Since the last update, BAPM has produced a framework for practice for care of preterm babies <27 weeks gestation, https://hubble-live-assets.s3.amazonaws.com/bapm/attachment/file/182/Extreme_Preterm_28-11-19_FINAL.pdf. This suggests that consideration should be given to active care	ensure that in utero transfer and place of birth are considered. Therefore NICE will add in an editorial amendment to ensure that clinicians consider the relevant NHS England guidance. 2) Thank you for your comment. At the time of guideline development, it was noted that the additional costs of 'treat all' are worth the reduction in adverse outcomes at lower gestational ages. The committee felt that there was not a sufficiently large impact on the diagnostic accuracy threshold to justify using a diagnostic test at gestational age lower than 30 weeks. NG25 therefore recommends not offering diagnostic testing to women under 30 weeks gestation and that tocolysis and maternal corticosteroids is the most cost-effective option for all women at this point. The full guideline states. "There is also a concern that the implications of a 'treat all' strategy might require some units to transfer women out of their hospital and therefore a sensitivity analysis was undertaken where the treatment cost was increased by £300 per woman to allow for the costs of such transfers. As expected this change lowers the threshold for diagnostic accuracy to be considered cost effective relative to 'treat all' and increases the threshold for diagnostic accuracy to be considered cost effective relative to 'no diagnosis and no treat'. At the lowest gestational ages the higher treatment cost has a relatively small impact on the diagnostic threshold but this increases with increasing gestational age. The overall impact of this sensitivity analysis would be to tend to push down the

		in babies from 22 weeks gestation. NICE needs to review the implications for their guidance from this framework, in particular for the consideration of IUT, antenatal steroids and magnesium sulphate use. In addition, the Saving Babies' Lives Version Two care bundle for reducing perinatal mortality, released by NHS England places an emphasis on improving preterm outcomes by focusing on place of birth. It is inconceivable in this context that this NICE guideline does not address this issue in its recommendations. 4) Increasingly maternity and neonatal units across the country are ignoring the advice of this NICE guideline, specifically around assessment of risk of preterm delivery and the use of diagnostic testing for decision-making around in utero transfer. The report of Better Newborn Care, the recent national review of neonatal critical care, accords place of birth and the use of in utero transfer to ensure best care for extremely preterm babies, one of its highest priorities. This is otherwise a really comprehensive and helpful review of the evidence.	gestational age at which the cost-effective strategy would change from 'treat all' to treatment based on a diagnostic test. However, given the uncertainty with respect to the diagnostic accuracy of the tests reviewed, the committee, on balance, did not consider that this sensitivity analysis had a sufficiently large impact on the diagnostic accuracy threshold to justify using a diagnostic test at gestational age lower than 30 weeks". No further evidence was identified through the surveillance review to change this view. Therefore, we will not be updating the guideline's current recommendations at this time. 3) Place of birth and in-utero transfer was considered during the development and the surveillance of NG25. It was noted that in utero transfer to hospitals with appropriate care is important for the safety and wellbeing of mother and child. The British Association of Perinatal Medicine (BAPM) guideline on Perinatal Management of Extreme Preterm Birth before 27 weeks of gestation gives specific advice in this area. It is also stated in the UK Preterm Clinical Network guideline for Commissioners and Providers on Reducing Preterm Birth that it is now a priority NHS England recommendation for local maternity systems (LMS) to take action to ensure that all women <27 weeks are delivered in centres with a neonatal intensive care unit and that LMS and corresponding Operational Delivery Networks have clear guidelines for antenatal transfer in the event of impending delivery <27 weeks. NG25 already mentions that clinicians should make an assessment on the need to transfer to another unit in recommendation 1.8.1. However it is agreed that this

			recommendation could be refreshed to ensure that in utero transfer and place of birth are considered. Therefore NICE will add in an editorial amendment to ensure that clinicians consider the relevant NHS England guidance. The BAPM guideline currently states that "administration of antenatal steroid and magnesium sulphate are associated with improved survival and neonatal outcomes as well as reduced risk of childhood impairment, even before 24 weeks of gestation". This does not contradict NICE's current recommendations which state that women at 23 weeks can discuss the use of steroids and magnesium sulphate in the context of individual circumstances and therefore this area of the recommendation will not be updated at this time. . Transfer to another unit is also mentioned within the NICE guidelines. 3) Thank you for your comment. We are not aware of any issues around implementation of the guideline. We will inform our implementation team so they can investigate in more detail and if there are any issues we will feed this into the next surveillance.
Royal College of Obstetricians and Gynaecologists (RCOG)	Yes	Risk factors for preterm birth and screening for preterm birth and care of women in high risk groups.	Thank you for your comment. NG25 covers the care of women at increased risk of, or with symptoms and signs of, preterm labour. The recommendations are not covering the identification of women at increased risk of preterm labour as this is outside of the scope. Screening for preterm birth was considered during the development of CG62 Antenatal care for uncomplicated pregnancies and recommendation 1.9.3.1 states that routine screening for preterm labour should not be offered. This recommendation was given due

			to the need for future research investigating the value of tests that are cheap and easy to perform such as maternal serum human chorionic gonadotrophin (MSHCG), serum C-reactive protein (CRP) and cervico-vaginal fetal fibronectin levels. The diagnostic accuracy and cost effectiveness of transvaginal ultrasound to measure cervical length and funnelling to identify women at risk of preterm labour also needed to be more fully investigated. This recommendation is currently supported by the NSC recommendation on preterm labour screening in pregnancy for which the recommendation is "systematic population screening programme is not recommendation". Therefore, NICE is unable to consider adding any identification recommendations into the guideline at this time. The scope for NG25 states that routine screening for preterm labour in all pregnant women is outside of the scope. Risk factors for preterm labour are also outside of the scope. CG62 Antenatal care for uncomplicated pregnancies considers lifestyle considerations for women in pregnancy. The guideline Saving Babies' Lives Version Two: A care bundle for reducing perinatal mortality also considers risk factors for preterm labour.
British Association of Perinatal Medicine (BAPM)	No	No comment	Thank you.

Additional comments			
Stakeholder	**Overall response**	**Comments**	**NICE response**

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London Neonatal Operational Delivery Network (ODN)	No comment	Increasingly maternity and neonatal units across the country are ignoring the advice of this NICE guideline, specifically around assessment of risk of preterm delivery and the use of diagnostic testing for decision-making around in utero transfer. The report of Better Newborn Care, the recent national review of neonatal critical care, accords place of birth and the use of in utero transfer to ensure best care for extremely preterm babies, one of its highest priorities. In addition, the Saving Babies' Lives Version Two care bundle for reducing perinatal mortality, released by NHS England places an emphasis on improving preterm outcomes by focusing on place of birth. It is inconceivable in this context that this NICE guideline does not address this issue in its recommendations.	Thank you for your comment. We are not aware of any issues around implementation of the guideline. We will inform our implementation team so they can investigate in more detail and if there are any issues we will feed this into the next surveillance. NICE hope that clinicians will use this NG25 guideline alongside other evidence-based reports such as the BAPM Perinatal Management of Extreme Preterm Birth Before 27 weeks of Gestation, the UK Preterm Clinical Network guideline for Commissioners and Providers on Reducing Preterm Birth and NHS England Saving Babies' Lives to give advice on the safest and most effective ways of caring for women and babies at risk of and during preterm labour. NICE will add in an editorial amendment to recommendation 1.8 to ensure that clinicians consider the NHS England guidance regarding place of birth and in utero transfer.
British Maternal & Fetal Medicine Society	No comment	Consideration should be given to the recent BAPM Framework for Practice on Perinatal Management of Extreme Preterm Birth Before 27 weeks of Gestation (2019) and the evidence contained within it to ensure synergy across practice. **https://www.bapm.org/resources/80-perinatal-management-of-extreme-preterm-birth-before-27-weeks-of-gestation-2019**	Thank you for your comment. The British Association of Perinatal Medicine (BAPM) guideline on Perinatal Management of Extreme Preterm Birth before 27 weeks of gestation gives information regarding the care of preterm neonates after birth which was a population excluded from the scope of this guideline. The BAPM guideline currently states that "administration of antenatal steroid and magnesium sulphate are associated with improved survival and neonatal outcomes as well as reduced risk of childhood impairment, even before 24 weeks of gestation". This does not contradict NICE's current recommendations which state that women at 23 weeks can discuss the use of steroids and magnesium sulphate in the context of individual circumstances and therefore this area of

			the recommendation will not be updated at this time. NICE hope that clinicians will use NG25 alongside other evidence-based reports such as the BAPM Perinatal Management of Extreme Preterm Birth Before 27 weeks of Gestation, the UK Preterm Clinical Network guideline for Commissioners and Providers on Reducing Preterm Birth and NHS England Saving Babies' Lives to give an holistic review on the safest and most effective ways of caring for women and babies at risk of and during preterm labour. NICE will add in an editorial amendment to recommendation 1.8 to ensure that clinicians consider the NHS England guidance regarding place of birth and in utero transfer.