Stakeholder	Document	Page	Line	Comments	Developer's Response
Advanced Global Health Limited	Full	15	2	PAMG-1 is misspelt	Thank you for your comment. This is now corrected.
Advanced Global Health Limited	Full	23 24	41 1	We are concerned this statement infers the peer-reviewed publications relating to Placental alpha microglobulin-1 are inconclusive. Over 25 peer-reviewed publications exist outlining the very high accuracy of PAMG-1 in diagnosing P-PROM. Please contact us for full list, including: - Indigo carmine study (USA gold standard) vs PAMG-1= *Silva E, Martinez JC. Diagnosing ROM: a comparison of the gold standard, indigo carmine amnioinfusion, to the rapid immunoassay, the AmniSure ROM test. J Perinat Med 2009; 37(S1):956.* - IGFBP-1 vs PAMG-1 Meta-analysis = *Ramsauer et al. (2013) The diagnosis of rupture of fetal membranes (ROM): a meta analysis. J. Perinat. Med.* - IGFBP-1 vs PAMG-1 Blood study = *Ramsauer, B. (2012) Diagnosis of rupture of fetal membranes in patients with vaginal bleeding.*	Thank you for comment. We considered carefully the evidence you have provided and these references were not included in our evidence base for the following reasons: - Indigo carmine study: not a diagnostic study (a conference paper) - Meta analysis by Ramsauer et al (2013); this meta-analysis was excluded from our evidence base because the gestational age range of included population extended beyond the 37 weeks of pregnancy which was our age cut off point. However we considered carefully the individual studies for inclusion and studies were included when appropriate. - Blood study by Ramsauer et al (2012); we couldn't located this reference in any database. (Please refer to Appendix G for more details on reasons for excluded studies).
Advanced Global Health Limited	Full	102	1	We are concerned Table 23 does not reflect the most up to date publications comparing diagnostic tests for PPROM. Over 40 peer-reviewed publications have been produced analysing IGFBP-1 and PAMG-1 diagnostic	- Thank you for your comment. We excluded this meta-analysis from our evidence base because the gestational age range of included population extended beyond the 37 weeks of pregnancy which

				tests. The *Ramsauer et al. (2013) The diagnosis of rupture of fetal membranes (ROM): a meta-analysis. J. Perinat. Med. 41(3):233-40* peer reviewed publication is the most in-depth review of PPROM peer reviewed studies and reviewed more than 40 peer reviewed publications. The findings clearly outline the improved accuracy of PAMG-1 versus IGFBP-1.	was our age cut off point. However we considered carefully the individual studies for inclusion and studies were included when appropriate (Please refer to Appendix G for more details on reasons for excluded studies).
Advanced Global Health Limited	Full	102	1	Table 23 is formed of small-scale studies. We are concerned readers may believe larger sample sizes have not been reviewed or produced. More than 10 peer-reviewed publications have considered sample sizes greater than 150 patients when reviewing PAMG-1 as a useful biomarker. Examples include: - *Cousins et al. (2005) Amnisure placental a macroglobulin-1 rapid immunoassay versus standard diagnostic methods for detection of rupture of membranes. AM J Perinatol. 22:317-20 – Sample Size 203.* - *Lee et al. (2007) Measurement of placental a-microglobulin-1 in cervico-vaginal discharge to diagnose rupture of membranes. Obstet Gynecol. 109:634-640.* - *Hosli et al. (2011) Placental a-microglobulin-1 to detect uncertain rupture of membranes in a European cohort of pregnancies. Arch Gynecol Obstet. 285:21-25.*	Thank you for your comment. All of these references (Cousins et al, 2005, Lee et al, 2007, Hosli et al, 2011, Albayrak et al, 2011) were considered but excluded from our evidence base because they included a mixed population of women in term and preterm pregnancies without a subgroup analysis presented for women below 37 weeks of pregnancy. These studies along their exclusion reason are presented in the Appendix G.

				- *Albayrak et al. (2011) Comparison of the diagnostic efficiency of the two rapid bedside immunoassays and combined clinical conventional diagnosis in prelabour rupture of membranes. European Journal of Obstetrics & Gynecology and Reproductive Biology. 158:179-182.*	
Advanced Global Health Limited	Full	104	9	The clinical benefits section fails to consider how the tests perform in 'known' and 'unknown' scenarios. Our findings suggest that all hospitals consider using a diagnostic test following a speculum examination and review of history. This is categorised as usage in an 'unknown' scenario i.e. when amniotic pooling is not evident. The IGFBP-1 tests have been proven to substantially decrease in accuracy in 'unknown' scenarios. PAMG-1 tests remain high in all scenarios. The comments imply that IGFBP-1 tests maintain a high accuracy in all cases and thus hospitals experience false positives/negatives in 'unknown' cases. These findings are outlined in *Ramsauer et al. (2013) The diagnosis of rupture of fetal membranes (ROM): a meta-analysis. J. Perinat. Med. 41(3):233-40.*	Thank you for your comment. The Committee agree with your comment that a diagnostic test for P-PROM is only needed when pooling of amniotic fluid is not observed. The Committee recognised that the reviewed evidence showed that 2 tests (PAMG-1 and IGFBP-1) could be useful for correct identification for pPROM which was reflected in the wording of the recommendation (1.3.1 In a woman reporting symptoms suggestive of P-PROM, offer a speculum examination to look for pooling of amniotic fluid and: • if pooling of amniotic fluid is observed, do not perform any diagnostic test but offer care consistent with the woman having P PROM (see sections 1.4, 1.5 and 1.9) • if pooling of amniotic fluid is not observed, consider performing an insulin-like growth factor binding protein 1 test or placental alpha microglobulin 1 test of vaginal fluid.) The meta-analysis referenced was not included in our evidence base because this analysis included women with term and preterm pregnancies

					without subgroup analysis on results for women below 37 weeks of pregnancy. This reference along the exclusion reason is recorded in our excluded lists (Appendix G).
Advanced Global Health Limited	Full	104	24	We are concerned about the selection process of studies. The guidelines outline that small sample sizes have been selected and thus bias exists. This implies that larger scales do not exist or they have not been considered. As outlined, many large-scale studies have been completed, particularly concerning PAMG-1 diagnostic tests. The *Cousins et al. (2005) Amnisure placental a macroglobulin-1 rapid immunoassay versus standard diagnostic methods for detection of rupture of membranes. AM J Perinatol. 22:317-20* – Sample Size 203 publication was undertaken to achieve FDA status in the United States. It is the largest study and completed for FDA approval, a non-bias organisation. This publication is also quoted in the ***RCOG Green Top 44 Guidelines***. We believe all hospitals should be aware of this study and other large-scale studies as they eliminate bias.	Thank you for your comment. The Committee recognised that the studies which met the review protocol for this review question were of small size and its impact on the interpretation of results. The study by Cousins et al (2005) was excluded due to the wide gestational age range of its population (between 15-42 weeks) with no subgroup analysis on women below the age of 37 weeks of gestational age.
Advanced Global Health Limited	Full	163	31	We are concerned about the exclusion from the guidelines of PAMG-1 (The PartoSure test) for consideration as a PTL prediction tool. PAMG-1 has been proven to be a highly accurate biomarker for detecting imminent preterm birth. The test is likely to be part of the European Guideline, which will be released in 2016. The	Thank you for your comment. Placental alpha microglobulin-1 (PAMG-1) testing was not included in the protocol for the diagnostic review question for women with intact membranes at risk of preterm labour and the related evidence has not been reviewed. The references provided were not included in our

				PAMG-1 biomarker has been consistently shown in peer-reviewed publications to have an excellent negative predictive value and a very high positive predictive value. See: - *Nikolova et al. (2015) Comparison of a novel test for placental alpha microglobulim-1 with fetal fibronectin and cervical length measurement for the prediction of imminent spontaneous preterm delivery in patients with threatened preterm labor. J. Perinat Med. Jan 6 – (E-Pub ahead of print). – "PartoSure is the most accurate test compared to fFN and CL".* - *Di Renzo, G. C. et al. (2013) Evaluation of a novel placental alpha macroglobulin-1 (PAMG-1) test to predict spontaneous preterm delivery. J. Perinat. Med. 13:1-5.*	base as these didn't fit with our review protocol (Exclusion reason; not a diagnostic study).
Advanced Global Health Limited	Full	163	40	In head-to-head studies PAMG-1 has been proven to be more accurate than Fetal fibronectin (fFN). See *Nikolova et al. (2015) Comparison of a novel test for placental alpha microglobulim-1 with fetal fibronectin and cervical length measurement for the prediction of imminent spontaneous preterm delivery in patients with threatened preterm labor. J. Perinat Med. Jan 6 – (E-Pub ahead of print).*	Thank you for your comment. Placental alpha microglobulin-1 (PAMG-1) testing was not included in the protocol for the diagnostic review question for women with intact membranes at risk of preterm labour and the related evidence has not been reviewed. The reference provided was not included in our base as it didn't fit with our review protocol (Exclusion reason; not a diagnostic study).
Advanced Global Health Limited	Full	164	14	We are concerned the guidelines do not identify PAMG-1 as a useful tool when combined with cervical length. Peer reviewed publications have been released analysing cervical length and	Thank you for your comment. Placental alpha microglobulin-1 (PAMG-1) testing was not included in the protocol for the diagnostic review question for women with intact membranes at risk

				PAMG-1 test results. See *Bolotskikh, V. and Borisova, V. (2015) The role of PAMG-1 protein and ultrasound cervicometry in detection of spontaneous preterm labour. The International Academy of Human Reproduction Congress.* The findings indicate PAMG-1 and CL are a useful tool in determining spontaneous preterm delivery.	of preterm labour and the related evidence has not been reviewed. However, the Committee considered the evidence around the diagnostic value of cervical length to diagnose preterm labour for women with intact membranes and considered recommendations on its use in relation to women's gestational age. The reference provided was not included in our base as it didn't fit with our review protocol (Exclusion reason; not a diagnostic study).
Advanced Global Health Limited	Full	169	46	The guidelines imply that available diagnostic tests in the UK are not as good as the measurement of cervical length alone. PAMG-1 is the only biomarker proven to have a NPV > 95% and a PPV >75%. The head-to-head study with fetal Fibronectin and Cervical Length found that PAMG-1 test to be superior to both CL and fetal Fibronectin. See *Nikolova et al. (2015) Comparison of a novel test for placental alpha microglobulim-1 with fetal fibronectin and cervical length measurement for the prediction of imminent spontaneous preterm delivery in patients with threatened preterm labor. J. Perinat Med. Jan 6 – (E-Pub ahead of print). –* "PartoSure is the most accurate test compared to fFN and CL".	Thank you for your comment. Placental alpha microglobulin-1 (PAMG-1) testing was not included in the protocol for the diagnostic review question for women with intact membranes at risk of preterm labour and the related evidence has not been reviewed. However, the evidence we have included on cervical length measurement showed that a short cervical length (less than15mm) appears to have a moderately or very useful positive and negative likelihood ratio to diagnose women with preterm delivery at 48 hours and this clinical evidence along with the results of the health economic analysis drove the Committee to draft a recommendation on the use of cervical length measurement as a diagnostic test to determine likelihood of birth within 48 hours for women above 30 weeks of pregnancy.
Advanced Global Health Limited	Short	general	general	We are concerned fetal fibronectin is the only test mentioned as an aide to predict the likelihood of birth within 48 hours.	Thank you for your comment. The Committee selected to recommend the use of fetal fibronectin as a diagnostic test to determine likelihood of birth

					within 48 hours for women who are 30+0 weeks pregnant or more if transvaginal ultrasound measurement of cervical length is indicated but is not available or not acceptable. However, the Committee recognised that fibronectin was not as good a diagnostic tool as cervical length. No other diagnostic tool or combination of tools included in this evidence review were found useful in diagnosis of PTL for women with intact membranes. The Committee noted the importance of false positives and negatives and the associated harm with either missing women at risk of preterm birth who are deprived of the benefits of treatment, or identifying wrongly that women are at risk of preterm birth resulting in unnecessary management. Although the quality of evidence on fetal firbronectin was very low and the results were mixed, the Committee agreed that that this would be an option if ultrasound measurement of cervical length not available or acceptable.
Advanced Global Health Limited	Short	23	18	We are concerned the short version of the guideline states there is little evidence of the accuracy of PAMG-1 diagnostic tests for rupture of membranes, and that the results of available studies are inconclusive. The *Cousins et al. (2005) Amnisure placental a macroglobulin-1 rapid immunoassay versus standard diagnostic methods for detection of rupture of membranes. AM J Perinatol. 22:317-20* – Sample Size 203 publication was	Thank you for your comment. The Committee recognised that the studies which met the review protocol for this review question were of small size and its impact on the interpretation of results. The study by Cousins et al (2005) was excluded due to the wide gestational age range of its population (between 15-42 weeks) with no subgroup analysis on women below the age of 37 weeks of gestational age which is the focus of our guideline.

				undertaken to achieve FDA status in the United States. It is the largest study and completed for FDA approval, a non-bias organisation. This study, and there are many other available studies, provides evidence of the value of PAMG-1 as a tool in the diagnosis of rupture of membranes. This publication is also quoted in the ***RCOG Green Top 44 Guidelines***. We believe all hospitals should be aware of this study and other large-scale studies as they eliminate bias.	
Association for Improvements in the Maternity Services	Full	71	21-47	Information and Support We welcome the recommendations on information and support. However, we would point out that those who are having continuous care from the same midwife (where we would welcome a randomised trial of women at increased socio-economic risk with measurement of outcomes to include prematurity) are more likely to find this supportive, to understand information given, and to be able to communicate their wishes. Bearing in mind that a high proportion of women experiencing premature labour will be disadvantaged and with lower educational standards. , and that the qualitative studies quoted were not done on women in this higher risk group, there is insufficient information about their needs. Unfortunately we have years of hearing accounts of slanted information-giving by professionals (albeit unintentional) in the context of maternity care, even to well-educated women,	Thank you for your comment. The Committee understands the challenges they may occur in the communication of information and support for women at risk of preterm birth when they receive care from different health professionals or coming from lower socioeconomic backgrounds. The Committee reviewed carefully the population characteristics of each qualitative study and the impact on their conclusions. The population characteristics of each study are included in Table 7 (Chapter 3 in the full guideline) and these were considered when the overall assessment of transferability of results to our population of interest was made. A sentence has been also added in the Evidence to Recommendation Section in Chapter 3 of the full guideline. The Committee agrees with your comment that the different types of information provided to women (and their family members or carers as appropriate) depend on their personal

				and we have observed it in less well-educated clients when we have been with them. We are also receiving a continuous trickle of reports from parents of babies in neonatal care, that when they do not immediately agree with recommended treatments, they are faced with threats to call social services, and even a threat to call the police when a mother did not agree to a drug treatment for her baby. This does not bode well for communication in which mothers feel free to state honest views. RESUSCITATION Both information and decisions on this will be affected by gestation. We are aware of a number of cases where the mother's knowledge of when conception took place and clinical estimates of duration of pregnancy (based on early ultrasound) differed. When the pregnancy ended in a premature birth around 23-24 weeks, this led to serious problems, and anger in the parents. We would therefore add the following: when the mother's dating of the pregnancy differs, with sound reasons, her date should be accepted. We welcome the recommendation about "ongoing opportunities to talk about and state their wishes about resuscitation of the baby".. However, this is a complex issue which the qualitative research quoted does not cover and we can see many potential problems, e.g. What gestation is this to apply to? Pre-24 weeks? 24	circumstances. The Committee also agreed that information provision should be revisited over time, for example because of a changing clinical situation, or because information provided verbally may not be absorbed at the time it is given, and questions may come to woman's mind subsequently. The Committee considered that resuscitation is an important area of information provision which has been specified in the recommendation for women who are having a planned preterm birth or are offered treatment for preterm labour (please see chapter 3 in the full guideline). Consistency of information was also considered a key consideration. Inconsistencies in information provided to the woman by different members of the healthcare team as well as differences in the information given to each parent were acknowledged a source of anxiety that led to a reduction in trust. The Committee believed that improved communication between the healthcare team could help mitigate against this. In relation to the specific questions about resuscitation of the baby, the qualitative evidence reviewed revealed that this a complex topic and the Committee recommended that ongoing opportunities should be offered to talk about and state their wishes about resuscitation of the baby.

				weeks? 25 weeks? etc (b) What if the mother makes a decision which professionals disagree with? (c) Before birth it is the mother's decision. Once the child is born, the father also has a voice. What if they differ? We are well aware in maternity care where pressure was put on fathers to make mothers change their minds. We are aware of many factors which can affect choices – including needs of other children in the family, or conception following expensive multiple fertility treatments. This is an area where qualitative research is needed, covering problems of both parents and staff, This is ethical tiger country -	
Association for Improvements in the Maternity Services	Full	319	15-22	Cord Clamping We understand that evidence for delayed cord clamping in premature babies is weak. However, many women feel strongly about what they call "avoidance of premature cord clamping". We suggest that since no strong evidence of harm exists either, another recommendation should be added:	Thank you for your comment. The Committee agrees and this is reflected in the recommendation to "Wait at least 30 seconds, but no longer than 3 minutes, before clamping the cord of preterm babies if the mother and baby are stable". The Committee discussed that the evidence base for this recommendation was weak and this is noted in the Evidence to recommendations section for Chapter 15.
Asspciation for Improvements in the Maternity Services	Full	72	1-8	Prevention of preterm birth In view of the high costs to parents, children and society, of preterm birth, we are interested in primary prevention. There is a substantial literature showing many known socio-economic factors not mentioned here, including poverty, stress, lliving in a high crime area (1) living in an area of	Thank you for your comment. This area is outside the scope of the guideline.

				high pollution (2) , lower education levels,etc. One public health measure which has been suggested as reducing prematurity is smoke-free legislation (3). We realise that such associations, or observational studies, do not constitute NICE guideline evidence. But we believe that research recommendations (see below) should include such factors, as well as those increasing personal risk, such as pregnant women smoking – while also living in areas of high pollution about which no enquiries are made. .. We realise that there is a problem of many confounding factors, as one of the respondents to ref 3 pointed out. Nevertheless, we think that research recommendations should take a wider view. *(1) Messer L.C. et al (2006) Violent crime exposure classification and adverse birth outcomes: a geographically-defined cohort study. Int. Journal Health Geographics 5.22* http://www.ij-healthgeographics.com/content/5/1/22#B64 *(2) Kloog I (2012) Using new satellite based exposure methods to study the association between pregnancy pm2.5 exposure, premature birth and birth weight in Massachusetts. Environmental Health 11.40* *(3) Cox B. et al (2013) Impact of a stepwise introduction of smoke-free legislation on*	

				*the rate of preterm births: analysis of routinely collected birth data. BMJ 346:1441*http://www.bmj.com/content/346/bmj.f441.full.pdf+html Maternal underweight (4) We are particularly concerned that this is not mentioned as a risk factor since there is a possibility of it being addressed at the first antenatal visit. With the concentration on obesity as a risk factor for mother and child, , we are concerned that the women who diet, are underweight because of poverty and feeding children before themselves, and underweight teenagers are not given enough attention. . The last group, who may be still growing, are faced with a fetus which absorbs nutrients before their own nutritional needs for growth are met. Where special antenatal clinics exist for teenagers, this should be an important topic. There should be involvement of nutritionists in antenatal care for underweight women, since midwives, in our experience and as reported to us by midwives themselves, have insufficient training. We do not know if early advice would make a difference to outcomes: this again is a subject for research *(4) Han Z et al (2010) Maternal underweight and the risk of preterm birth and low birth weight: a systematic review and meta-*	

				analyses Int. J. Epidemiol. 40(1) 65-101 http://ije.oxfordjournals.org/content/40/1/65.long	
Besins Healthcare	Full	73-82	38-45	However we feel there is a point of contradiction with the draft guidelines which we describe below. "4 RCTs from the IPD review (Romero 2012) contributed to this section." "This IPD meta-analysis also showed no significant differences between the 2 treatment groups for perinatal mortality, intrauterine fetal death, neonatal death, preterm birth under 37 weeks, bronchopulmonary dysplasia or neonatal sepsis (moderate to low quality evidence from 2 to 4 RCTs with a couple of hundred women involved)." This is in contradiction with: "However, vaginal progesterone did not provide a significant benefit for the other neonatal outcomes (perinatal mortality, intrauterine fetal death, neonatal death, preterm birth under 37 weeks, bronchopulmonary dysplasia or neonatal sepsis)".	Thank you for your comment. We do not believe there is a contradiction between these two statements. The first sentence refers to the description of results in the meta-analysis which tested if there was any significant difference in the outcomes between the group of women who received prophylactic progesterone and the placebo group. The second sentence refers to the Committees' conclusions in the section of Evidence to recommendations. The Committee concluded that there was no significant benefit of the use of prophylactic progesterone on improving these outcomes as it didn't produced any added benefit compared to placebo.
Besins Healthcare	General	General	General	Question 1:. Which areas will have the biggest impact on practice and be challenging to implement? We are aware some units are already using	Thank you for your comment. This has been passed to the NICE implementation team to inform their support activities for this guideline.

				progesterone in appropriate patients. To ensure broad implementation of the guidelines, awareness, educational and training programmes will need to be held by professional societies. Regarding the research proposal which we support as a logical and important step forward, we foresee significant financial burden to execute it and suggest it should be recommended and/or proposed to the DoH, MRC or any other official research bodies in the UK to ensure adequate funding. Without allocating public money unfortunately this research is unlikely to take place.	
Besins Healthcare	General	General	General	Question 2: The following we believe would help prescribers and patients overcome any concerns about the use of progesterones for pre-term birth. To ensure alignment and aid implementation, the Royal College of Obstetrics and gogy recommendations for the use of progesterone in pre-term birth should be updated to reflect the draft NICE guidelines.	Thank you for your comment. This has been passed to the NICE implementation team to inform their support activities for this guideline.
Besins Healthcare	Short	9	5	Besins Healthcare supports the recommendations in sections 1.2.1 and 1.2.2 to offer vaginal progesterone as a prophylactic measure in the mentioned circumstances.	Thank you for your comment.
Besins Healthcare	Short	22	11	We support research recommendation no. 3.1 for prophylactic cervical cerclage alone compared with prophylactic vaginal progesterone alone and with both strategies together for	Thank you for your comment.

				preventing preterm birth in women with a short cervix and a history of spontaneous preterm birth. This is indeed a very relevant and important clinical and patient management topic.	
Bliss	Full	16	15	1.3 Information. We fully welcome the addition of the need to give mothers information about what may happen to their baby once it has been born preterm. This is a very vulnerable and scary time for families and it is incredibly important that this is supported by both maternity and neonatal staff. The communication needs to be well coordinated by both teams to ensure parents understand what may happen to their baby.	Thank you for your comment.
Bliss	Full	16	15	We recommend that you signpost to the Bliss Family Handbook and the Bliss Your Special Care Book for information that covers all the facts and stats in this section http://www.bliss.org.uk/Shop/bliss-family-handbook-admissions-pack http://www.bliss.org.uk/Shop/your-special-care-baby-a-guide-for-families	Thank you for your comment. The recommendations in this section were based on both the interpretation of qualitative evidence reviewed and on Committee's expert opinion. However, the Committee was aware of several reports that aligned with the findings of this review and with their own experience, including the report from the Bliss Organisation. The Committee discussed the information provided by the Bliss Report and this is referenced in the Evidence to recommendations section in the full guideline (section 3.1.5.5). However, because this is not NICE accredited patient information and access to it for the duration of this guideline is unclear, no specific reference or links would be provided in the text.
Bliss	Full	16	15	Also sign post to the NICE Neonatal Quality	Thank you for your comment. A reference has

				Standards	now been added in the Evidence to recommendations section of the chapter 3 in the full guideline.
Bliss	Short	9	16	As comment 1 above	Thank you for your comment. The Committee agrees with your comment on communication of both maternity and neonatal teams.
Bliss	Short	9	16	As comment 2 above	Thank you for your comment. The recommendations in this section were based on both the interpretation of qualitative evidence reviewed and on Committee's expert opinion. However, the Committee was aware of several reports that aligned with the findings of this review and with their own experience, including the report from the Bliss Organisation.
British Maternal & Fetal Medicine Society	Full	General	General	We remain concerned about the potential for Obstetricians to put sutures in when the patient is in PTL and thus causing iatrogenic cervical trauma,	Thank you for your comment. The Committee agrees that there is a possibility of harm such as cervical trauma associated with this procedure, but that the reviewed evidence suggested that benefits could outweigh harms in women who are not contracting. However, the Committee discussed that rescue cerclage would cause harm to women with signs of infection, active vaginal bleeding or uterine contractions and so they decided upon a strong recommendation of not offering 'rescue' cerclage to these groups of women.
British Maternal & Fetal Medicine Society	Full	General	General	The guideline does not appear to address use of cervical cerclage based on obstetric history alone – more guidance on this would be helpful.	Thank you for your comment. The Committee decided that a short cervix is a better indicator of whether cervical cerclage is beneficial or not and women who have a history of previous preterm birth but not a short cervix would not necessarily

					benefited from that intervention. The evidence reviewed showed that the benefits of prophylactic cervical cerclage, in terms of reduction in preterm birth, were more likely to be seen in the sub-group of women who had had both a previous preterm birth and a short cervix in the current pregnancy. Although the Committee reviewed the evidence on the comparison of prophylactic cerclage on the basis of obstetric history alone and as indicated by serial ultrasound-scanning of cervix measurement, the results were not very informative because the estimates of effects between the two groups were biased by the design limitations of the included studies. For these reasons, the Committee did not place confidence in these results and decided to recommend the choice of either prophylactic vaginal progesterone or prophylactic cervical cerclage to women with a history of spontaneous preterm birth or mid-trimester loss between 16^{+0} and 34^{+0} weeks of pregnancy **and** in whom a transvaginal ultrasound scan has been carried out between16^{+0} and 24^{+0} weeks of pregnancy that reveals a cervical length of less than 25 mm. This recommendation reflected both the evidence reviewed and the Committee's expert opinion.
British Maternal & Fetal Medicine Society	Full	General	General	The care pathway recommends cervical length scans, but doesn't give any guidance as to when to start them or how often to repeat (if at all), similarly with the vaginal progesterone there is no recommendation as to the dose, frequency or	Thank you for your comment. Screening for cervical length was outside the scope of this guideline and your comment will be passed to National Screening Committee. The care algorithm is a summary of the recommendations

				duration of treatment or when to start.	developed by the Committee. Its purpose is not to give detailed characteristics of each intervention. In addition, the guideline assumes that prescribers will use a medicine's summary of product characteristics to inform decisions made with individual patients.
British Maternal & Fetal Medicine Society	Full	General	General	There was much concern that many of the recommendations say that the risks and benefits of each option for treatment should be discussed with the patients which is fully supported. However, it was felt we would struggle to know what they were from reading this guideline. It would be very useful if these could be outlined clearly.	Thank you for your comment. The Committee discussed the specific risks and benefits for each of these interventions and the rationale behind each recommendation in the Evidence to recommendations section at the end of each chapter.
British Maternal & Fetal Medicine Society	Full	General	General	A general thought was with the evidence not being particularly convincing the committee seem to be coming down on the side of caution ie investigate more women and treat more women, which will have a significant effect on our current OP and IP services and the women themselves, without any additional funding/beds/scan slots etc. The Health Economics compare the costs of each of these treatments with the cost of caring for a premature neonate. Does it anywhere compare significant increase in the number of scans, treatments, admissions and possible transfers of women that would not have a premature delivery? Also, it appears to be looking at the health economy as a whole and it is not reflective of the current NHS pricing system	Thank you for your comment. The recommendations were based on both the clinical and cost effectiveness analysis of different diagnostic strategies. The Committee appreciates that these recommendations may involve change in clinical practice. In NICE guidelines the health economics analysis aims to assess whether an intervention (such as a diagnostic strategy) is cost-effective, representing good value for money for the NHS. The budget impact of guideline recommendations will be referred to NICE's Implementation team. The economic analyses undertaken for this guideline endeavoured to include all costs relevant to the intervention(s) being assessed. As a result of another stakeholder comment we have

				where these additional costs would probably be expected to be included in the current maternity tariffs and the savings will come from neonatal care and hopefully reduced lifetime costs for primary and secondary care.	undertaken an additional sensitivity analysis in the tocolytic model to reflect that some units might incur additional costs as a result of women transfers to other hospital units. The Committee reviewed the results of this sensitivity analysis but did not consider that these results changed the main model's results sufficiently to warrant a change in the action points of the recommendations.
British Maternal & Fetal Medicine Society	Full	14	General	It is not clear whether everyone with 1 LLETZ only should be offered Cx length surveillance – this is probably what is recommended and if such would in many units dramatically increase the number of TV scans required.	Thank you for your comment. This area is outside the scope of the guideline.
British Maternal & Fetal Medicine Society	Full	15	General	We are concerned that about the recommendations of MgSO4 and Ca++ channel blockers. Isn't there an interaction between these two?	Thank you for your comment. The Committee was aware that there may be a potential interaction between magnesium sulfate and calcium blockers of hypotension and neuromuscular blockade effects, although this is seldom reported in clinical practice. However, the Committee recommended regular monitoring of women who receive magnesium sulfate for magnesium toxicity at least every 4 hours and more frequently if symptoms of oliguria or signs of renal failure develop.
British Maternal & Fetal Medicine Society	Full	15	General	The guidance appears to suggest cerclage if there is threatened PTL. Does this not risk further cervical damage	Thank you for your comment. The Committee agrees that there is a possibility of harm such as cervical trauma associated with this procedure, but that the evidence we reviewed suggested that benefits could outweigh harms in women who are not contracting. However, the Committee discussed that rescue cerclage would cause harm

					to women with signs of infection, active vaginal bleeding or uterine contractions and so they decided upon a strong recommendation of not offering 'rescue' cerclage to these groups of women
British Maternal & Fetal Medicine Society	Full	17	14	It is unclear why someone would have a cervical length under these circumstances (if they had no recognised risk factors) – or is there a recommendation for cervical length screening in all	Thank you for your comment. Cervical screening in the general population is outside the scope of this guideline. However, in light of the reviewed evidence on women identified only with a short cervix (without necessarily having a history of previous preterm birth), the Committee decided to cover these circumstances in a separate recommendation.
British Maternal & Fetal Medicine Society	Full	17	34	If the tests are not to be used alone to make decisions, it is unclear what these add to the diagnosis – particularly as these are tests not used by many units at the moment.	Thank you for your comment. The Committee discussed the benefits of using different tests (CRP, white blood cell count, fetal heart rate and maternal temperature) in isolation for identification of different types of infection for women with P-PROM. The evidence did not show that any of these tests were helpful in identification of different types of infections (clinical and historical chorioamnionitis, funisitis and neonatal infection) for this group of women at risk of preterm birth that would be relevant in clinical practice. However, the Committee considered that if the results of the clinical assessment or any of the tests are not consistent with each other, tests should be considered if appropriate in order to avoid the serious complications of a missed intrauterine infection that can be life-threatening to the mother and to fetus in utero or the baby

					postnatally.
British Maternal & Fetal Medicine Society	Full	18	24	We could not follow the rationale for suture at 27+6. The evidence cited doesn't seem to support it. Section 8.1.2 suggests the highest gestation in the research was 27+0 so not clear why its 27+6 in the guidelines. By doing cerclage at 27+ weeks the undoubted success in terms of NN outcome is likely to cloud the poorer outcomes of cerclage at lower gestations. We are also concerned that there are fewer operators who can perform cervical cerclage. Let alone rescue cerclage – we are concerned about being able to provide such a service 24/7.	Thank you for your comment. The Committee recognised that both the randomised and observational evidence supported well a benefit of 'rescue' cerclage for the outcomes of reducing serious neonatal morbidity, preterm birth below 27, 32 and 34 weeks and increasing the interval between intervention and delivery. The upper limit of 27+6 days has been used from the reviewed evidence (reported in study by Curti 2012) and this is now corrected in section 8.1.2. The Committee's clinical opinion was that benefit of performing 'rescue' cerclage beyond 32 gestational weeks would be limited and may not outweigh the potential harms. It was agreed that the recommendation to perform 'rescue' cerclage for women with a dilated cervix and exposed, unruptured membranes should reflect both the quality of reviewed evidence (low to very low) and the gestational age of women included in these studies (of gestational age between 16 to 27+6 weeks).
British Maternal & Fetal Medicine Society	Full	19	20	We are concerned that there won't be many units that can provide Cx length scans out on normal working hours/on a weekend	Thank you for your comment. Your concern has been passed to the NICE implementation team to inform their support activities for this guideline.
British Maternal & Fetal Medicine Society	Full	19	34	The guidance suggest no FFN <30 weeks – it was unclear why the recommendations are not fir use at earlier gestation. We are concerned about the potential impact of the recommendation to treat all suspected PTL <30 weeks. This would cause a significant change in	Thank you for your comment. The Committee accept that that the recommendation to treat all suspected PTL < 30 will represent a significant change in practice for many units and that this recommendation will lead to an increase in costs. However, our analysis suggested that the

				practice as for many units, women are currently sent home, due to the confidence in the negative predictive value of fibronectin. Thye would now need admitting and treating. In addition it will increase in- utero transfers. With the excluded the HTA data relating to not in labour at 7 - 10 days post presentation it was difficult understand the health economics "what if" data, but it does not seem to be a valid comparison to just look at the diagnostic test costs vs an £20,000 cost for a false negative.	additional benefits were worth the additional costs resulting from implementation of this recommendation. Diagnostic tests usually have a false negative rate which has potential implications for 'missed cases'. At low gestational ages the absolute or baseline risk in the absence of treatment is high and therefore the absolute treatment benefits are relatively high in this group. This means that the implications of false negatives or missed cases (in terms of neonatal/perinatal mortality, respiratory distress syndrome and IVH) are relatively more important than at higher gestational ages. The diagnostic test accuracy evidence reviewed for this guideline was generally of low quality but suggested that fetal fibronectin didn't have sufficiently good diagnostic accuracy, especially at low gestational ages. In other words, although it would result in fewer women not in preterm labour being treated than treat all, it would do so at an unacceptably high level of increased adverse events – based on NICE's conventional threshold for cost-effectiveness (a willingness to pay £20,000 for each additional QALY gained).
British Maternal & Fetal Medicine Society	Full	22 292	1	IA vs CEFM. We have concerns that we recommend CEFM in term babies that are high risk and preterm labour is already high risk by definition. Whilst there are particular difficulties with interpretation and subsequent action the more preterm the gestation, it does appear to not be recommending CEFM would be a complete	Thank you for your comment. There was limited evidence in this review from only two studies. The evidence showed that that there were no significant differences in any of the outcomes between the group monitored by the CTG and the IA groups. Therefore, the Committee did not feel that they could recommend the use of one method

				shift in normal practice. P292 The trials reviewed all look at CTG's from 26 weeks gestation and this leaves a gap for the 25 - 25+6 weekers. Should the guidelines more advice that CTG's can be offered after 26 weeks and Consultant discretion before this?	over another. Although 26 weeks was the average gestational age included in one of these studies (the other study did not provide such information) the Committee has extended the use of these methods in earlier gestational ages following the rationale that the benefits found above the cut-off point of 26 weeks would be even more apparent for lower gestational ages. The Committee discussed in details the benefit and risks associated with each method in the Evidence to recommendations section of the chapter 13. However, in circumstances of very premature labour (below 26 weeks), the Committee decided that a senior clinician needs to be involved in discussions given that there is a high risk of neonatal morbidity and mortality and survival is dependant more on fetal weight and maturity rather than intrapartum hypoxia and mode of birth.
British Maternal & Fetal Medicine Society	Full	134	3-4	This reports that infection with group B strep or gram negative bacteria can spread to the fetus .....in the MBRRACE report 2014 pg 28 it is reported that it is Group A strep or coliforms	Thank you for your comment. We have amended this sentence to reflect that infection can be caused by different types of microorganisms (mainly due to Group A streptococcus or coliforms).
British Maternal & Fetal Medicine Society	Full	140	12 14	With regard to rescue cerclage what risks should be discussed as the evidence is poor. More specific guidance would be required what risks and benefits should be discussed at the relevant gestation ages.	Thank you for your comment. The Committee agrees that there is a possibility of harm such as cervical trauma associated with this procedure and these risks are highlighted in the Evidence to recommendations section of Chapter 8.
British Maternal & Fetal Medicine Society	Full	196	22	It's not clear where the 10 weeks interval was generated from for this statement.	Thank you for your comment. The Committee agrees that this specific time interval may be confusing and it has now been deleted from the

					recommendation.
British Maternal & Fetal Medicine Society	Full	197	4	We questioned it the recommendations are going to be 26-34 weekswhen the evidence is best for giving steroids and the recommendation to consider at 23-25+, should it also say consider for 34+1 – 35+6 weeks?	Thank you for your comment. A new recommendation has been added to reflect that the evidence base for the use of maternal corticosteroids was not very convincing for gestational ages from 24+0 to 26+0 and from 34+1 to 35+6. This lack of evidence was reflected in the wording of recommendations.
British Maternal & Fetal Medicine Society	Full	207/208	General	P207 11.1.6.2 The guidelines state Mg SO4 shows significant benefits only for babies <28 weeks, but the committee then recommend its use before 34 weeks in view of the potential benefit and no evidence of harm. This again would increase midwifery input with 1 :1 care for up to 24 hours (and use of delivery beds for women not in labour) which the women would not have if they were being observed on an AN Ward. Then on P208 line 17 it says "strong recommendation to start MgSO4 under 32 weeks – which does not seem to tally with the reported evidence.	Thank you for your comment. As a result of these stakeholder comments an additional sensitivity analysis in the health economics of magnesium sulfate at a gestational age of 34 weeks has been undertaken. This assumes that the relative treatment effect on cases of cerebral palsy would be the same at this gestational age but accepting that there is a much lower baseline risk of this adverse outcome. The committee considers that this sensitivity analysis supported the use of magnesium sulfate as a cost-effective intervention at gestational ages up to 34 weeks but that this should be a weaker ("consider") strength of recommendation than at earlier gestational ages when the recommendation is to "offer". The health economic model recognises that MgSo4 would require more intensive observation and the treatment cost includes an observation/hospitalisation cost of £1,036. Sensitivity analysis suggested that treatment was not very sensitive to treatment cost and would remain cost effective even if a much higher

					treatment cost was assumed. Whilst treatment cost is more important in determining cost-effectiveness at the higher gestational ages, tocolysis is also recommended and therefore the incremental treatment costs of MgSo4 are not so great as if administered as a standalone intervention. Furthermore, the Committee have now adopted a weaker strength of recommendation for MgSo4 at these higher gestational ages (between 30^{+0} and 33^{+6} weeks).
British Maternal & Fetal Medicine Society	Full	303	37	We are concerned with this statement - "there is some evidence that there may be a large reduction in perinatal mortality associated with caesarean section for preterm babies with breech presentation, but overall the evidence is inconclusive". How are patients supposed to understand this? They will hear large reduction in mortality but find it more difficult to understand why then its inconclusive. Guidance on this aspect counselling needs to be more detailed.	Thank you for your comment. The Committee considered a number of stakeholder comments regarding this recommendation. The Committee made several recommendations regarding information to be discussed with any woman in suspected, diagnosed or established preterm labour when the mode of birth is decided. The Committee considered important to explain to women the associated risks such as the increased likelihood of a vertical uterine incision and the implications of this for future pregnancies with CS for women at preterm labour which depend on gestational age with these women. However, the Committee agreed with your comments that this statement may create confusion to women and this is now deleted.
Central Manchester	Full	General	General	Our trust feels that it is disappointing to not see	Thank you for your comment. This area is outside

University Hospitals NHS Foundation Trust				any guidance regarding the use of Arabin pessaries or research recommendations regarding this.	the scope of the guideline. This will be noted in the next surveillance review and passed to the Surveillance Team.
Central Manchester University Hospitals NHS Foundation Trust	Full	19	39	Most units now use newer fetal fibronectin machines which give a quantitative value so it should clearly stipulate in the guideline what level constitutes a positive result.	Thank you for your comment. The Committee discussed the need for a quantitative value for the assessing the fibronectin results and decided upon the use of the threshold of 50ng/ml which was the most common cut-off value used across the studies.
Central Manchester University Hospitals NHS Foundation Trust	Full	21	10	The regimen for calcium channel blockers and oxytocin receptor antagonists for tocolysis should be clearly documented.	Thank you for your comment. The guideline assumes that prescribers will use a medicine's summary of product characteristics to inform decisions made with individual patients. For the use of calcium blockers, the Committee endorsed the dosage recommended by the RCOG Green-top guideline No 1B. Further information has been added in the Evidence to recommendations section of Chapter 10.
Cheshire & Merseyside Strategic Clinical Network – Maternity, Children & Young People	Short	General	General	The following comment has been put forward by our patient representative group who attend our Preterm birth special interest group ''Ensuring that relevant information is easily and readily available to patients and their families, for instance around car parking discounts, food vouchers, public transport discounts, help for patients on benefits etc."	Thank you for your comment. Although the Committee recognises that these topics of information may be important for women at risk of preterm birth, however, these areas of information were outside the scope of the guideline. This will be referred to the NICE Patient Involvement Team who are responsible for writing patient information to go with this guideline.
Cheshire & Merseyside Strategic Clinical Network – Maternity,	Short	18	1-5	There is concern about maternal and fetal side effects in clinical practice in relation to calcium channel blockers. Units have moved away from this practice to use oxytocin receptor antagonists	Thank you for your comment. The Committee decided upon the selection of calcium channel blockers for tocolysis for women from 24+1 to 34+0 weeks of pregnancy with intact membranes

Children & Young People				only for the purpose of administrating corticosteroids and in utero transfers. Further clarification is needed on the use of calcium channel blockers in clinical practice.	which was based on both the clinical and cost effectiveness analysis of the evidence. Although oxytocin receptor blockers were also found effective for some other outcomes (such as reduction of maternal side effects and increasing gestational age), the Committee decided that their use has to be balanced against its poor efficacy in reducing IVH and RDS and its modest effect on perinatal mortality. Therefore the Committee decided that based on the available clinical and economic evidence, it would be reasonable to recommend calcium channel blockers as a first line tocolytic treatment. The Committee discussed that this would not deviate from current practice in many settings providing care for women at risk of preterm labour. In addition the Committee thought that oxytocin receptor blockers should be offered to those in whom calcium channel blockers were contraindicated as the model provided evidence that they were the most cost-effective treatment option after calcium channel blockers. This rationale for the Committee's discussion is captured in the Evidence to Recommendations section (10.1.10) of the full guideline.
Cheshire & Merseyside Strategic Clinical Network – Maternity, Children & Young People	Short	21	1-15	The fact that we tell women that there may be a large reduction in perinatal mortality will be enough for them to request C sections with the associated risks and as you stipulate lack of evidence. The last statements are contradictory and most units feel that the RCOG guidance on management of breech presentation would	Thank you for your comment. The Committee considered a number of stakeholder comments regarding this recommendation. The Committee agreed with your comments that

				enable them to offer vaginal delivery in an otherwise uncomplicated preterm labour. Please can this paragraph be made clearer for ease of conveying the information to the woman and her family.	these statements may create confusion to women and there are now deleted.
Department of Health	General	General	General	I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Thank you for your comment.
Ferring Pharmaceuticals Ltd.	Full	371	1	Table 126: Summary of tocolytic treatment costs. It is not clear how the cost of managing adverse events is factored into the treatment costs? This is particularly important as two recent Cochrane reviews have concluded that oxytocin receptor agonists result in fewer maternal adverse effects as compared to calcium channel blockers. 1. In a recent Cochrane review, oxytocin receptor agonists were associated with less maternal adverse effects than treatment with the calcium channel blockers (Flenady V1, Reinebrant HE, Liley HG, Tambimuttu EG, Papatsonis DN. Oxytocin receptor antagonists for inhibiting preterm labour. Cochrane Database Syst Rev. 2014 Jun 6;6:CD004452). 2. Another recent Cochrane review to evaluate calcium channel blockers for inhibiting preterm labour also concluded that oxytocin receptor agonists (ORAs) result in fewer maternal adverse effects (Flenady V1, Wojcieszek AM, Papatsonis DN, Stock OM, Murray L, Jardine LA, Carbonne B. Calcium	Thank you for your comment. Maternal adverse events were not explicitly factored into the health economic analysis - with the reasons outlined in 16.4.2.1. This decision was made *a priori* to model development. Discontinuation of treatment due to adverse maternal effects was considered to be a proxy for other outcomes influencing health related quality of life. The NMA on discontinuation due to adverse maternal events failed to reject a null hypothesis of no difference between oxytocin channel blockers an oxytocin receptor blockers (see 10.1.5). The Cochrane Database Syst Rev. 2014 Jun 6;6:CD004452 discussing the evidence on ORA versus CCB notes "The studies were considered as having high risk of bias as neither study blinded the intervention and in one study it was not known if allocation was blinded." The results on which SH makes their observation about fewer maternal adverse effects is: "ORA (atosiban) resulted in less maternal adverse effects (RR 0.38, 95% CI 0.21 to 0.68; NNTB 6,

				channel blockers for inhibiting preterm labour and birth. Cochrane Database Syst Rev. 2014 Jun 5;6:CD002255).	95% CI 5 to 12; two studies, 225 women) but not maternal adverse effects requiring cessation of treatment (RR 0.36, 95% CI 0.01 to 8.62; one study, 145 women)." Therefore, in addition to our reasons for not including maternal adverse events in the health economic model, we consider that the evidence on maternal adverse events is uncertain with respect to costs and health related quality of life.
Ferring Pharmaceuticals Ltd.	Full	21	10-12	Ferring is pleased to note that NICE has included the statement - Although this use is common in UK clinical practice, at the time of consultation (June 2015), calcium channel blockers 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 It is suggested documentation of this informed consent is included as a Quality Standard measure to drive measurable quality improvements within the area of management of preterm labour.	Thank you for your comment. Quality Standards are developed separately from this guidance but your comment has been noted.
Ferring Pharmaceuticals Ltd.	Full	21	10-16	We would ask for clarification as to why NICE would recommend use of calcium channel blockers for tocolysis to women between 24+1 and 34+0 weeks of pregnancy, when there is an absence of evidence about all tocolytic medicines before 26+0 weeks of pregnancy.	Thank you for your comment. The recommendations were drafted based on the review of clinical and cost effectiveness analysis of different treatments for tocolysis. Although the studies included in the network meta-analyses did not include women at gestational ages below 26

					weeks, the Committee considered it would be reasonable to extrapolate relative treatment effects to women with a gestational age between 24-26 weeks. The baseline risks are large for gestational ages 24+1 to 26+0 weeks and therefore large benefits would potentially be forgone by excluding these women from tocolysis. This was discussed in details in the Section 16.4.4 (Chapter on Health Economics) in the full guideline.
Ferring Pharmaceuticals Ltd.	Full	21	13-14	Ferring Pharmaceuticals would request that NICE specifically define the contraindications for the use of calcium channel blockers in preterm labour. The contraindications stated in the Summary of Product Characteristics are for licenced indications and may not be the same for preterm labour.	Thank you for your comment. The Committee discussed this and concluded that the contraindications for the use of calcium channel blockers would be the same for preterm labour.
Ferring Pharmaceuticals Ltd.	Full	255	19-23	The general reason for lack of support for oxytocin receptor antagonists, particularly atosiban, is that it is not more clinically or cost effective than other available, and non-licenced products. However, atosiban is a licenced product with a good and well documented, long term safety record as compared to available non-licenced products, and greater focus should be given to atosiban in this regard. Ferring requests that in the complex environment of preterm labour, the licensed status of atosiban should have greater significance in consideration of benefit and this should be reflected in the guidelines.	Thank you for your comment. Drugs are frequently used off licence in pregnancy. The Committee are of the view that calcium channel blockers are frequently used as a tocolytic in the NHS and that the evidence reviewed and economic model support their use. The Committee did not believe that the licensed status of atosiban should take precedence over clinical and cost effectiveness considerations.

Ferring Pharmaceuticals Ltd.	Full	260	43	In a network meta-analysis, probabilities can be fragile when the network is sparse, and the ranking of treatments may change drastically when a new trial is introduced into a network. For this reason, less emphasis should be placed on the probabilities of a network meta-analysis output and greater emphasis on the treatment effects and their uncertainty. Ferring suggest that this is highlighted in the key conclusions of the guidelines as a limitation associated with the interpretation of a network meta-analysis performed for a condition such as preterm labour.	Thank you for your comment. Whilst considering the clinical evidence for tocolytic treatments, the Committee looked at both the treatment effects and their uncertainty (presented as 95% credible intervals), as well as the probabilities of different treatment rankings. The decision-making for this review question was based primarily on the health economic model, which was not based on the probabilities from the NMA, but on the estimates for treatment effects that were also the output from the model. As the ranking of treatments contributed relatively little information towards the final decision we do not feel that it is necessary to elaborate on this as a limitation.
Ferring Pharmaceuticals Ltd.	Full	366	8-9	It is not clear if the dose of nifedipine used for the purpose of the costing analysis is also the dose recommended by NICE for management of preterm labour, rather than only an assumption for the purposes of costing as stated in the guidelines. Ferring believes that it is very important to specify this because the calculated cost provides the estimates of treatment effectiveness for the network metaanalysis and thus the choice of tocolytic.	Thank you for your comment. Recommended dosages are not usually included in the NICE recommendations. The guideline assumes that prescribers will use a medicine's summary of product characteristics to inform decisions made with individual patients. However, we appreciate that given that calcium channel blockers have an unlicensed indication, guidance on the most optimal dose of this treatment has been included in the Evidence to recommendations section (Chapter 10) in the full guideline. The cost of calcium channel blockers is not an important driver of the results in the cost-effectiveness analysis and is cost-effective even if a much higher treatment cost is assumed. This is noted in the discussion in the health economics

					chapter whereas a discussion is made on the fact that the model's results would not be particularly sensitive to differences in treatment costs, especially at the lower gestational ages, as the treatment cost represents only a small proportion of the difference in net mean benefit between the various treatment alternatives.
Ferring Pharmaceuticals Ltd.	Full	386	36-38	The economic model used in the guideline provides reasonably strong evidence that calcium channel blockers can be considered as a cost-effective tocolytic treatment for women with diagnosed or suspected preterm labour between a gestational age of 24-34 weeks. However, it has been suggested that a cost-minimisation analysis, rather than a cost-effectiveness analysis may be conducted to compare treatments with similar efficacy for tocolytic treatments (J. Wex et al. / European Journal 132 of Obstetrics & Gynecology and Reproductive Biology 157 (2011) 128–135). We would ask for clarification as to why a more suitable cost-minimisation analysis was not conducted to compare the costs of nifedipine with oxytocin receptor agonists?	Thank you for your comment. Most health economists would agree that cost minimisation is rarely appropriate - see Briggs, A.H. and O'Brien, B.J. (2001) The death of cost-minimization analysis? Health Economics 10(2):pp. 179-184. The authors argue in this paper that a cost minimisation is only legitimate (but not more suitable) when an RCT has tested a hypothesis of equivalence, as opposed to the usual case where a null hypothesis of no difference is tested. Furthermore, the NMA results demonstrated there were some statistically significant differences for treatment alternatives included in the health economic analysis for some outcomes (e.g. IVH).
Ferring Pharmaceuticals Ltd.	General	General	General	Which areas will have the biggest impact on practice and be challenging to implement? Ferring is of the opinion that in the current environment, with increasing patient awareness and litigation issues, recommendation of an unlicensed product for first-line use in a complex	Thank you for your comment. This has been passed to the NICE implementation team to inform their support activities for this guideline. The guideline assumes that prescribers will use a medicine's summary of product characteristics to inform decisions made with individual patients. However, we appreciate that given that calcium

				condition like preterm labour, where other licenced products are available, is unwise and may be challenged legally, as an unwarranted increase to the risk /benefit of pharmacological treatment of preterm labour with calcium channel blockers. NICE states on its own website; Evidence summaries: unlicensed or off-label medicines summarise the best available evidence for selected unlicensed or off-label medicines. Unlicensed or off-label medicines have a valuable role in the care of certain patients when there are no suitable licensed medicines available which meet their needs.	channel blockers have an unlicensed indication, guidance on the most optimal dose of this treatment (specifically on nifedipine as it was the selected channel calcium blocker) has been included as a footnote in the recommendation and more information was given in the Evidence to recommendations section (Chapter 10) in the full guideline.
Ferring Pharmaceuticals Ltd.	General	General	General	What would help users overcome any challenges? The general reason for lack of support for oxytocin receptor antagonists, particularly atosiban, is that it is not more clinically or cost effective than other available, and non-licenced products. However, atosiban is a licenced product with a good and well documented, long term safety record as compared to available non-licenced products, and greater focus should be given to atosiban in this regard. Ferring requests that in the complex environment of preterm labour, the licensed status of atosiban should have greater significance in consideration of benefit and this should be reflected in the	Thank you for your comment. Drugs are frequently used off licence in pregnancy. The Committee are of the view that calcium channel blockers are frequently used as a tocolytic in the NHS and the evidence reviewed and economic model support their use. The Committee did not think that the licensed status of atosiban trumped these other considerations.

				guidelines.	
Ferring Pharmaceuticals Ltd.	General	General	General	Ferring would request that NICE take into consideration the results from the following publications: 1. Roos C, Vis JY, Scheepers HC, Bloemenkamp KW, Duvekot HJ, van Eyck J, de Groot C, Kok JH, Opmeer BC, Oudijk MA, Papatsonis DN, Porath MM, Sollie K, Spaanderman ME, Lotgering FK, van der Post JA, Mol BW. Fetal fibronectin status and cervical length in women with threatened preterm labor and the effectiveness of maintenance tocolysis. J Matern Fetal Neonatal Med. 2015 Jun 24:1-6. The study concludes that maintenance tocolytic therapy with nifedipine is ineffective and not dependent on fetal fibronectin or cervical length status. 2. de Heus R, Mol BW, Erwich JJ, van Geijn HP, Gyselaers WJ, Hanssens M, Härmark L, van Holsbeke CD, Duvekot JJ, Schobben FF, Wolf H, Visser GH. Adverse drug reactions to tocolytic treatment for preterm labour: prospective cohort study. BMJ. 2009 Mar 5;338:b744. In women treated with a single tocolytic, the incidence of serious adverse drug reactions was 0.9% for nifedipine. No serious adverse	Thank you for your comment. The study by Roos et al. (2015) was published after the rerun searches were performed, so it was not possible to include this study. It may be included in updates to the guideline. The study by de Heus et al. (1999) is a cohort study and therefore would not have been included, as these studies are lower in the hierarchy of evidence and there is already a sufficient body of evidence on adverse events from RCTs. This will be noted in the next surveillance review and passed to the NICE Surveillance Team.

				drug reaction was observed after treatment with a single course of atosiban.	
Ferring Pharmaceuticals Ltd.	General	254	General	Vis,J.Y., Wilms,F.F., Oudijk,M.A., Porath,M.M., Scheepers,H.C., Bloemenkamp,K.W., Bolte,A.C., Cornette,J., Derks,J.B., Duvekot,J.J., van,Eyck J., Kwee,A., Opmeer,B.C., van Pampus,M.G., Lotgering,F.K., Scherjon,S.A., Sollie,K.M., Spaanderman,M.E., Willekes,C., van der Post,J.A., Mol,B.W., Cost-effectiveness of fibronectin testing in a triage in women with threatened preterm labor: alleviation of pregnancy outcome by suspending tocolysis in early labor (APOSTEL-I trial) (BMC Pregnancy and Childbirth, 9, 38-, 2009). This study has been excluded from the analysis as the publication related to the study protocol, and no results were available. We would advise that the results have now been published and conclude that in symptomatic women with preterm labour, a shortened cervix, and negative fibronectin test, placebo treatment is not inferior to tocolysis with nifedipine. Moreover, in the nifedipine group, three pregnancies (8.1%), including two twin pregnancies, had poor neonatal outcomes, and none in the placebo group. One intrauterine death of a twin occurred 35 days after randomization; the foetus had developed subcutaneous oedema. One neonatal death of a singleton pregnancy occurred 28 days after birth due to multisystem organ failure after	Thank you for your comment. The published paper cited is reporting the results of the RCT and not the economic evaluation and so would not be included as part of the review of economic evidence. Furthermore, this results paper was published (April 2015) after the date of our re-run searches.

				necrotizing enterocolitis (JY. Vis, G van Baaren, F. Wilms et al. Am J Perinatol. 2015 Apr;32(5):451-60).	
Ferring Pharmaceuticals Ltd.	General	288	General	Husslein,P., Cabero,Roura L., Dudenhausen,J.W., Helmer,H., Frydman,R., Rizzo,N., Schneider,D., Atosiban versus usual care for the management of preterm labor (Journal of Perinatal Medicine, 35, 305-313, 2007). We would ask for clarification as to why this study has been excluded from the analysis for tocolysis – the reason for exclusion is stated as – "A short report with limited data available", but the study is a randomised controlled trial with nearly 600 patients.	Thank you for your comment. This study was not excluded from our analysis for tocolysis. This reference was wrongly included in the list of excluded studies and this has now been corrected.
Ferring Pharmaceuticals Ltd.	General	293	General	Romero,R., Sibai,B.M., Sanchez-Ramos,L., Valenzuela,G.J., Veille,J.C., Tabor,B., Perry,K.G., Varner,M., Goodwin,T.M., Lane,R., Smith,J., Shangold,G., Creasy,G.W., An oxytocin receptor antagonist (atosiban) in the treatment of preterm labor: a randomized, double-blind, placebo-controlled trial with tocolytic rescue (American Journal of Obstetrics and Gynecology, 182, 1173-1183, 2000). We would ask for clarification as to why this study has been excluded from the analysis for tocolysis – the reason for exclusion is stated as – "No tocolytic used" whereas this was a multicentre, double-blind, placebo-controlled trial where 531 patients were randomized and 246 received intravenous atosiban.	Thank you for your comment. This study was not excluded from our analysis for tocolysis. This reference was wrongly included in the list of excluded studies and this has now been corrected.

Ferring Pharmaceuticals Ltd.	General	295	General	van Vliet,E.O., Schuit,E., Heida,K.Y., Opmeer,B.C., Kok,M.,Gyselaers,W., Porath,M.M., Woiski,M., Bax,C.J., Bloemenkamp,K.W., Scheepers,H.C., Jaquemyn,Y., van,Beek E., Duvekot,H.J., Franssen,M.T., Bijvank,B.N., Kok,J.H., Franx,A.,Mol,B.W., Oudijk,M.A., Nifedipine versus atosiban in the treatment of threatened preterm labour (Assessment of Perinatal Outcome after Specific Tocolysis in Early Labour: APOSTEL III-Trial). (BMC Pregnancy and Childbirth, 14, 93, 2014). This study has been excluded from the network analysis as the publication related only to the protocol. The study was stopped due to the results of an interim analysis that demonstrated non-significant, but possibly clinically relevant increase in mortality in the nifedipine group, thus questioning the safety of nifedipine. The interim results have been presented at an oral presentation (35th meeting of the Society for Maternal Fetal Medicine, San Diego, USA, February 2015; van Vliet EOG: Nifedipine versus atosiban for tocolysis of preterm labour); the abstract is published (Mol BWJ, van Vliet EOG, Oudijk MA: Journal of Paediatrics and Child Health 51 (Suppl. 1):2015, 35).	Thank you for your comment. Only peer reviewed publications were considered for inclusion in the evidence base of NMA.
Ferring Pharmaceuticals Ltd.	Short	4	7-9	Ferring is pleased to note that NICE has included the statement - This guideline recommends some medicines for indications for which they do not have a UK marketing	Thank you for your comment.

				authorisation at the date of publication, if there is good evidence to support that use.	
Ferring Pharmaceuticals Ltd.	Short	18	1	Ferring Pharmaceutical would suggest that in order to enable clinicians to make well-informed decisions based on a full recommendation from NICE about the choice of drug therapy for preterm labour, the recommended doses of all tocolytic agents should be included, particularly so for the unlicensed pharmaceutical agents such as calcium channel blockers, for which no recommended doses will be available for use in unlicensed indications in the Summary of Product Characteristics.	Thank you for your comment. Recommended dosages are not usually included in the NICE recommendations. The guideline assumes that prescribers will use a medicine's summary of product characteristics to inform decisions made with individual patients. However, the Committee appreciated that given that calcium channel blockers have an unlicensed indication, guidance on the most optimal dose of this treatment has been included in the Evidence to recommendations section (Chapter 10) in the full guideline. Following further advice from NICE's MPC about the contraindications of different calcium channel blockers the recommendations have been amended so that just nifedipine is recommended rather than the whole class for tocolysis. Additional analysis demonstrated that removing evidence derived from studies involving nicardipine would not affect direction of the results of the health economic analysis and its conclusions.
Group B Strep Support	Full	General	General	Group B Strep Support is disappointed that the topic of testing for group B Strep carriage is not covered by this guideline. Group B Strep Support notes that knowledge of group B Strep carriage status has usefulness in terms of how to manage both the mother and baby's care, and is	Thank you for your comment. Testing for Group B streptococcus is outside the scope of this guideline.

				saddened NICE has missed an opportunity to cover the issue.	
Group B Strep Support	Full	118	13-17	It is disappointing that while quoting from Colbourn 2007, the authors do not acknowledge that the paper also concluded that "In the absence of vaccination, culture-based testing of women in groups 11 and 12, combined with treatment for the rest, would be the most cost-effective strategy."	Thank you for your comment. Vaccination is outside the scope of this guideline. Furthermore, Groups 11 & 12 were term babies and therefore also outside the scope because of gestational age.
Guys and St Thomas' Trust	Full	General	General	Given that the fibronectin manufacturers are no longer offering qualitative fetal fibronectin testing kits, in favour of quantitative tests, we feel that reference to positive/negative tests should be replaced with explanation regarding risk thresholds (eg <10 ng/ml and >200 ng/ml, which have been validated in symptomatic women, and offer more information than the traditional qualitative test. Hologic are replacing for free all qualitative machines for the more accurate quantitative one, and the old test is therefore no longer available.	Thank you for your comment. The Committee agreed with your comment and discussed the need for a quantitative value for assessing the fibronectin results. Given that the majority of studies included in the evidence review used the threshold of 50ng/ml, the Committee considered this quantitative cut-off point of assessing positive results in fibronectin (more than 50ng/ml) or negative results (50ng/ml or less).This is now added in the recommendation.
Guys and St Thomas' Trust	Full	98	17	There is no mention of prophylactic cerclage in women with a history of multiple preterm births (e.g. x 3, as in RCOG guidelines)	Thank you for your comment. The results of the review showed that the benefits of prophylactic cerclage, in terms of reduction in preterm birth, were more likely to be seen in the sub-group of women who had had both a previous preterm birth and a short cervix in the current pregnancy. This also reflected the Committee's clinical experience. The Committee noted that in women with a previous preterm birth, the comparison of a policy of prophylactic cerclage on the basis of clinical

					history versus a policy of cerclage indicated by serial ultrasound-scanning was not very informative because the estimates of effects between the two groups were biased by the design limitations of the trial. For these reasons, the Committee did not place confidence in these results. The RCOG distinguishes the recommendations on prophylactic cerclage based on the number of previous preterm births which was not the focus of our review question. Furthermore, the RCOG does not routinely recommend the use of history only indicated cerclage for women with two or less previous preterm births which will account for the majority of women presented with symptoms of preterm labour.
Guys and St Thomas' Trust	Full	136	29	Whilst one small study included women for rescue cerclage up to 27 weeks, we are concerned re the recommendation that rescue cerclage should be considered up to 27 weeks (especially given that the mean gestation in all the studies reported was 22 weeks. Given the concerns surrounding rescue cerclage (rupture of membranes, infection), exposing a viable fetus to these risks >24 weeks is controversial. Perhaps the committee should recognise that studies included women up to 27 weeks, but that this is rarely performed in practice and should therefore not be classified as a NICE recommendation.	Thank you for your comment. The Committee agrees that there is a possibility of harm such as cervical trauma associated with this procedure, but that the evidence we reviewed suggested that benefits could outweigh harms in women who are not contracting. However, the Committee discussed that rescue cerclage would cause harm to women with signs of infection, active vaginal bleeding or uterine contractions and so they decided upon a strong recommendation of not offering 'rescue' cerclage to these groups of women. The order of recommendations in this section has now changed to reflect the emphasis on the risk associated with this procedure for specific group of women. However, the

					Committee agreed that the recommendation to consider performing 'rescue' cerclage for women with a dilated cervix and exposed, unruptured membranes was justifiable by both the quality of reviewed evidence and the gestational age of women included in these studies (from 16+0 to 27+6 weeks).
Guys and St Thomas' Trust	Full	170	26	It is concerning that transvaginal ultrasound cervical length measurement and fetal fibronectin should not be offered until 30 weeks, and that all women under 30 weeks with symptoms and uncertain diagnosis should be treated as if in true preterm labour. This recommendation appears to be based on an economic evaluation which suggests that "a treat all strategy was a cost-effective approach at lower gestational ages..." based on the cost of false negatives being untreated, even when "90% of those treated might not derive any treatment benefit". Although their review does not seem to have found evidence of harm of repeated steroid use, my understanding is that the body of evidence suggesting harm of unnecessary steroid therapy and potential need for repeat doses is growing. It is particularly concerning that, as they acknowledge, "some studies were terminated early on the basis of possible harm" (see section 10.3.6.2).. Aside from the potentially dangerous and unpleasant side effects of drugs, hospitalisation and especially in-utero transfers have significant	Thank you for your comment. The Committee recognises that the recommendations to treat all women in suspected preterm labour below a gestational age of 30 weeks will increase costs but our analysis suggested that this additional cost is justified by the additional benefits. The Committee agrees that fetal fibronectin is predictive at less than 30 weeks but ther analysis did not suggest it was sufficiently so to be cost-effective when the absolute treatment effects were large, as a result of the false negative rate associated with fetal fibronectin.

				impacts on women and the NHS, and the potential costs of over-treating 90% of women with symptoms must be enormous. Given we have good evidence of the efficacy of fFN and CL in ruling out TPTL from 24 weeks, it is unclear why use at these gestations is not recommended.	
Guys and St Thomas' Trust	Full	196	22	Given that steroids are most effective between 24 hours and 7 days, should this read 10 days rather than 10 weeks? Also, consider rephrasing the final bullet point to 'if the likelihood of imminent birth <48 hours remains high	Thank you for your comment. The Committee agrees that this specific time interval may be confusing and it has now been deleted from the recommendation.
HQT Diagnostics	Full	General	General	There is evidence that increased levels of Vitamin D 25(OH)D reduce the incidence of preterm birth At first presentation, GP should measure 25(OH)D and supplement to achieve 100-150 nmol/L If blood tests are not taken, advise or prescribe the mother to take 100 micrograms (4,000IU) of Vitamin D3 each day during the full term of the pregnancy and for 3 months afterwards If the woman asks for advice before conceiving, both she and the potential father should be advised to take 100 micrograms of Vitamin D3 each for 3 months before conception. If they do not want to take supplements, then a holiday in the sunshine should be suggested	Thank you for your comment. Increased levels of Vitamin D during pregnancy is an area outside the scope of the guideline. Recommendations of Vitamin D supplementation during pregnancy can be found in the NICE guideline on Antenatal Care.

				These levels of 25(OH)D may appear high according to current practice, but RCT evidence shows that higher levels reduce the incidence of pre-term birth, gestational diabetes, pre-eclampsia and emergency C-sections. Higher levels of 25(OH)D during the whole pregnancy produce larger babies and reduce the risk of diabetes in the child European Food Safety Agency (www.efsa.europe.eu) has issued a formal Opinion that 100 micrograms (4,000IU) of Vitamin D3 each day is safe for pregnant women Evidence: http://www.vitamindwiki.com/4000+IU+Vitamin+D+Safe+and+Effective+For+Healthy+Pregnant+Women+%E2%80%93+June+2011 http://www.vitamindwiki.com/Overview+Pregnancy+and+vitamin+D http://www.grassrootshealth.net/media/download/scientists_call_to_daction_020113.pdf http://www.efsa.europa.eu/en/efsajournal/doc/2813.pdf http://greenvits.eu/blogs/news/31767747-how-	

				much-vitamin-d-do-i-need	
HQT- Diagnostics	Full	General	General	There is evidence that increased levels of Omega-3 reduce the incidence of preterm birth At first presentation, GP should measure Fatty Acids and advise diet, lifestyle and supplements if necessary to achieve: • Omega-3 Index >8% of total Fatty Acids • Omega-6/3 Ratio <3:1 If blood tests are not taken, advise the mother to eat at least 2 portions of fatty fish each week or prescribe 2 grams of Omega-3 each day during the full term of the pregnancy and for 3 months afterwards If the woman asks for advice before conceiving, both she and the potential father should be advised to eat at least 2 portions of fatty fish each week or take 2 grams of Omega-3 each day for 3 months before conception. They should also be referred to a dietitian about how to reduce intake of Omega-6. RCT evidence shows that improving both the Omega-3 Index and the Omega-6/3 Ratio has multiple benefits for both mother and baby. It reduces the incidence of preterm birth, gestational diabetes, pre-eclampsia and post-	Thank you for your comment. Omega-3 levels is an area outside the scope of the guideline.

				natal depression and improves both the chance of conception and the neurological development of the baby. Evidence: http://www.expertomega3.com/omega-3-study.asp?id=21 http://www.expertomega3.com/omega-3-study.asp?id=38 http://www.omegametrix.eu/gynaekologie.html http://www.omegaquant.com/omega-3-index/ http://greenvits.eu/blogs/news/26072707-learn-more-about-vitamin-d-and-omega-3 (Omega-3 Literature List)	
King's College London (Division of Women's Health)	Full	23	3	"this practice is based on an extrapolation of evidence of best management for breech presentation for babies born at term" We are concerned that this recommendation may imply all preterm breech babies should be born by caesarean section. The 2 yr follow up of the Term Breech Trial (Whyte et al 2004) shows a 6% increase in medical problems in babies who were born by elective caesarean section.	Thank you for your comment. The Committee agrees with your concern and this recommendation has now been amended without including the bullet points. However, the Committee acknowledged in the Evidence to Recommendation section (14.1.6) of this chapter in the full guideline that they were s aware that in current clinical practice the selection of the mode of birth for preterm babies is often extrapolated from full-term babies as described in the NICE Guideline for Caesarean section (CS). For example if the baby has a breech presentation then CS would be the most favoured mode of

					birth. No evidence was found in this review to suggest that following current practice for term babies (e.g. delivery by CS for breech presentation) would be harmful to the baby. However, this recommendation does not preclude the option of a vaginal birth. The follow up study of the Term Breech Trial was not included because of its non-randomized design. Only RCTs were considered as this study design provides the strongest evidence base to answer this review question.
King's College London (Division of Women's Health)	Full	98	17	The RCOG guideline recommends history indicated cerclage for women with 3 preterm births, but there is no mention of history indicated cerclage this is in this draft.	Thank you for your comment. The results of the review showed that the benefits of prophylactic cerclage, in terms of reduction in preterm birth, were more likely to be seen in the sub-group of women who had had both a previous preterm birth and a short cervix in the current pregnancy. This also reflected the Committee's clinical experience. The Committee noted that in women with a previous preterm birth, the comparison of a policy of prophylactic cerclage on the basis of clinical history versus a policy of cerclage indicated by serial ultrasound-scanning was not very informative because the estimates of effects between the two groups were biased by the design limitations of the trial. For these reasons, the Committee did not place confidence in these results. The RCOG distinguishes the recommendations on prophylactic cerclage based on the number of previous preterm births which

					was not the focus of our review question. Furthermore, the RCOG does not routinely recommend the use of history only indicated cerclage for women with two or less previous preterm births which will account for the majority of women presented with symptoms of preterm labour.
King's College London (Division of Women's Health)	Full	100	36	The guideline states that "No studies were found that examined the diagnostic accuracy of ….the diagnostic panty-liner with polymer-embedded strip…" It is not clear how the committee came to this conclusion because NICE guidance has already been published on the use of this test, and is referred to in section 2.1.6.1. as "related NICE guidance" - "Vision Amniotic Leak Detector to assess unexplained vaginal wetness in pregnancy (2013) 22 NICE medical technology guidance MTG15". The first conclusion of this guidance is: "The Committee concluded that the Vision Amniotic Leak Detector (ALD) test is sufficiently accurate to exclude amniotic fluid leak as a cause of wetness in pregnancy and that its use in the correct clinical setting would avoid unnecessary speculum examinations." This was based on evidence from three studies that included participants with gestation ranges from 16, 18 and 20 weeks, and therefore did not exclude women with PPROM. In any case, I would question whether the chemical constitution of amniotic fluid and urine at term and preterm is likely to be different enough to affect the	Thank you for your comments. A search was performed for the evidence on the diagnostic use of panty-liner with polymer-embedded strip for the diagnosis of P-PROM and no studies were included according to the review protocol. The three studies that were included in NICE MTG15 (https://www.nice.org.uk/guidance/mtg15/chapter/3-Clinical-evidence) were excluded mainly because they referred to older gestational ages (more than 37 weeks) or they included results on different gestational ages without a subgroup analysis on women below 37 weeks (please refer to Appendix G.3 for further details).However, this research recommendation has now been withdrawn from the final version of full and NICE guideline.

				reliability of the results at earlier gestations. The NICE PTB committee recommends further research is needed, but how much more, above and beyond an already published NICE guideline, would be sufficient to recommend this non-invasive, cheap test in practice?	
King's College London (Division of Women's Health)	Full	136	29	Rescue cerclage over 24 weeks is not usually performed in practice because the risks (of infection and rupture of membranes) may outweigh the benefits and at 24 weeks the baby is viable. Although one study included women up to 27 weeks, the majority were much earlier.	Thank you for your comment. The Committee agrees that there is a possibility of harm such as cervical trauma associated with this procedure, but that the evidence we reviewed suggested that benefits could outweigh harms in women who are not contracting. However, the Committee discussed that rescue cerclage would cause harm to women with signs of infection, active vaginal bleeding or uterine contractions and so they decided upon a strong recommendation of not offering 'rescue' cerclage to these groups of women. The order of recommendations in this section has now changed to reflect the emphasis on the risk associated with this procedure for specific group of women. However, the Committee agreed that the recommendation to consider performing 'rescue' cerclage for women with a dilated cervix and exposed, unruptured membranes was justifiable by both the quality of reviewed evidence and the gestational age of women included in these studies (from 16+0 to 27+6 weeks).
King's College London (Division of Women's Health)	Full	170	26	It is concerning that transvaginal ultrasound cervical length measurement and fetal fibronectin should not be offered until 30	Thank you for your comment. The Committee recognises that the recommendations to treat all women in suspected preterm labour below a

				weeks, and that all women under 30 weeks with symptoms and uncertain diagnosis should be treated as if in true preterm labour. This recommendation appears to be based on an economic evaluation which suggests that "a treat all strategy was a cost-effective approach at lower gestational ages..." based on the cost of false negatives being untreated, even when "90% of those treated might not derive any treatment benefit". Although their review does not seem to have found evidence of harm of repeated steroid use, my understanding is that the body of evidence suggesting harm of unnecessary steroid therapy and potential need for repeat doses is growing. It is particularly concerning that, as they acknowledge, "some studies were terminated early on the basis of possible harm" (see section 10.3.6.2).. Aside from the potentially dangerous and unpleasant side effects of drugs, hospitalisation and especially in-utero transfers have significant impacts on women and the NHS, and the potential costs of over-treating 90% of women with symptoms must be enormous. We have a lot of evidence that fFN is predictive at less than 30 weeks.	gestational age of 30 weeks will increase costs but our analysis suggested that this additional cost is justified by the additional benefits. The Committee agrees that fetal fibronectin is predictive at less than 30 weeks but the analysis did not suggest it was sufficiently so to be cost-effective when the absolute treatment effects were large, as a result of the false negative rate associated with fetal fibronectin.
King's College London (Division of Women's Health)	Full	171	18	The committee conclude that TVS CL should be offered first (at 30+/40) and fFN only if that is not available. Although they say not to use TVS CL and fFN in combination, in section 9.1.6.2 - in relation to combination of either bishops score or	Thank you for your comment. The Committee discussed that the evidence on the diagnostic accuracy of a combination of transvaginal ultrasound measurement and fetal fibronectin was not useful, therefore a "do not use"

				fFN and CL - they say that "Although the committee chose not to make a research recommendation, they commented that further research may be necessary because looking at individual tests would only be part of the full assessment for diagnosis of preterm labour and so combining them might be useful".... So I do not understand why the guideline appears to strongly discourage it with the wording “do not use…”	recommendation on the combination of these tests was made. The Committee also noted that the clinical relevance of the use of the combination of these two tests is limited and of no more use in the current clinical context than the use of cervical length measurement alone. However, the note on further research was made not only for the combination of cervical length measurement and use of fetal fibronectin but every other possible combination of the diagnostic tests for preterm labour such as aspects of clinical assessment, fetal fibronectin, IGF-BP1 insulin-like-growth factor binding protein 1 and cervical ultrasound features.
King’s College London (Division of Women’s Health)	Full	196	22	Given that steroids are most effective between 24 hours and 7 days, should this read 10 days rather than 10 weeks?	Thank you for your comment. The Committee agrees that this specific time interval may be confusing and it has now been deleted from the recommendation.
King’s College London (Division of Women’s Health)	Short	19	29	“…advise her that if she does decide to go home, she should return if symptoms suggestive of preterm labour recur”. This is assuming the symptoms have settled. Does this mean that if she is still symptomatic, despite negative tests, she should be admitted? Ditto for line 43, same page.	Thank you for your comment. The Committee does not necessarily suggest that symptomatic women over 30 weeks should be admitted to hospital despite negative tests given that measuring cervical length using transvaginal ultrasound was found the most accurate way to diagnose preterm labour for women over 30 weeks in pregnancy. The Committee suggests that there should be discussion with the women about the interpretation of the results to guide possible subsequent management strategies and the benefits and risks of going home compared with continued monitoring and treatment in

					hospital.
Leeds Teaching Hospitals Trust	Full	14	2	Clarity needed over pathway – implication that if previous PROM (or if cervical trauma) should only recommend suture and not progesterone – surely insufficient evidence for guideline to be so proscriptive. Why not incorporate all three entry criteria with recommendation to carry out TV scans and consider progesterone or cerclage? We're concerned this will stop people thinking about aetiologic pathways and lead to inappropriate and on occasions unnecessary treatment	Thank you for your comment. The difference in the criteria for recommending either preventive progesterone or cerclage or both of them as prophylactic measures for preterm birth is driven by both the evidence review and Committee's clinical experience. The evidence we have included did not demonstrate a common aetiological pathway for both preventive interventions and this is reflected in the care algorithm.
Leeds Teaching Hospitals Trust	Full	14	2	Need to define 'cervical trauma' – previous LLETZ or cone? Previous Cx tear? Multiple cervical dilatations? Previous operative hysteroscopy? Very difficult to quantify. May be interpreted differently by different people, including pregnant women and their families	Thank you for your comment. Cervical trauma is further defined in the scope under groups that will be covered. However, the Committee appreciate that a definition could have been made clearer and this has been updated in the glossary of the full guideline. Pregnant women with cervical trauma are defined as those who are considered to be at risk of preterm labour and birth because they have a history of cervical trauma (including surgery – for example, previous cone biopsy [cold knife or 29 laser], large loop excision of the transformation zone [LLETZ – any number] and radical 30 diathermy).
Leeds Teaching Hospitals Trust	Full	14	4	Implications of offering care for all <30wks women with suspected PTL is that 50% will receive inappropriate interventions (evidence from placebo controlled tocolytic trials); why not use a bedside rapid test or TVS to triage?	Thank you for your comment. We reviewed the evidence on combinations of tests and the results did not show these combinations to be useful tools for diagnosis of preterm labour. The Committee acknowledges that that the

					recommendation to treat all women in suspected preterm labour who are below 30 weeks will represent a significant change in practice for many units and that this recommendation may lead to an increase in costs. However, the analysis suggested that the additional costs resulting from implementation of this recommendation were worth the additional health benefits. Diagnostic tests usually have a false negative rate which has potential implications for 'missed cases'. At low gestational ages the absolute or baseline risk in the absence of treatment is high and therefore the absolute treatment benefits are relatively high in this group. This means that the implications of false negatives or missed cases (in terms of neonatal/perinatal mortality, respiratory distress syndrome and IVH) are relatively more important at lower than at higher gestational ages. The diagnostic test accuracy evidence reviewed for this guideline was generally of low quality but suggested that they didn't have sufficiently good diagnostic accuracy, especially at low gestational ages. In other words although tests to triage would result in fewer women who are not in preterm labour being treated than under a treat all strategy, it would do so at an unacceptably high level of increased adverse events. This rationale was based on NICE's conventional threshold for cost-effectiveness (a willingness to pay £20,000 for each additional QALY gained)

Leeds Teaching Hospitals Trust	Full	14	4	Why only fibronectin quoted? There are alternatives on the market with equivalent NPVs such as Actim Partus and Partosure which may be cheaper.	Thank you for your comment. Although other tests were examined in this review, fibronectin was found to be useful to rule out preterm delivery based on the evidence reviewed. In addition, further sensitivity analysis suggested that the cost of the diagnostic test (within plausible ranges) was not an important driver of cost-effective thresholds for the decisions to treat all, treat based on diagnostic test and no diagnosis and no treatment. The Committee discussed that fetal fibronectin should be used for the preterm delivery diagnosis only if transvaginal ultrasound measurement of cervical length is indicated but is not available or not acceptable. The care algorithm reflects the decisions made in the recommendations that's why only fibronectin is included at this section.
Leeds Teaching Hospitals Trust	Full	14	4	CL of 15mm sounds quite low to rule out PTL – our last memory suggested 30mm provided an equivalent NPV	Thank you for your comment. The cut of point of 15 mm of cervical length is based on the evidence reviewed and this is presented in details in Chapter 9 of the full guideline. In summary, the evidence showed that a short cervical length (<15mm) appears to have a moderately or very useful positive and negative likelihood ratio to diagnose women with preterm delivery at 48 hours whereas the other cut off points of cervical length used in the included studies did not.
Leeds Teaching Hospitals Trust	Full	14	4	Need exit from 'woman unlikely to be in PTL' box suggest 'consider alternative diagnoses'	Thank you for your comment. The relevant recommendation and the care algorithm have

					been amended to include alternative diagnoses.
Leeds Teaching Hospitals Trust	Full	15	1	The implications of using Actim PROM and/or Amnisure as diagnostic tests leading to treatment are not yet known – there may be subclinical leaks or transudates which are of no clinical significance. Implementation as is will certainly lead to rising intervention – either of antibiotics/steroids/hospitalisation or for women greater than 34 wks induction of labour. There is likely to be a knock-on effect on delivery suite and neonatal resources with no proven clinical benefit for mother or baby if this guideline is adopted as is.	Thank you for your comment. The Committee reviewed the evidence and decided to consider using these tests in the diagnosis of P-PROM but highlighted with another recommendation that the care of women, in light of positive results of these tests, should be interpreted with caution ("do not use the test results alone to decide care") allowing for the option of waiting and reassessing the situation. In relation to the issue of implementation of these recommendations, this has been passed to the NICE implementation team to inform their support activities for this guideline.
Leeds Teaching Hospitals Trust	Full	15	3	Recommend removing the rescue cerclage bubble – and at any rate strongly reconsider the upper limit of 27+6 weeks; we know that McDonald in his seminal paper did, but surely this is too high in contemporary practice. Suggest 24wks instead.	Thank you for your comment. The care algorithm reflects the content of recommendations. The Committee based the upper limit of gestational age for this recommendation on the reviewed evidence. However, the Committee acknowledge in the recommendations made that the decision for rescue cerclage must be made only after discussion with a consultant obstetrician by taking into account of the woman's gestation and her own stated wishes after a full discussion.
Leeds Teaching Hospitals Trust	Full	15	4	Need more guidance on the timing of corticosteroid administration; evidence is so much more in favour of near-delivery benefit on more important outcomes such as IVH and death acw historical ones such as RDS – ie benefit for IVH/death is gone 3 days post-administration	Thank you for your comment. The protocol was set up to assess the effectiveness of maternal corticosteroids in terms of two aspects; when a single course is given at different gestations to improve preterm neonatal outcomes and whether a repeated or single course is the most effective treatment. Timing of corticosteroid administration

					was not prioritised to be included for this question. The Committee agrees that IVH and death are important negative outcomes for this question that's why these were included in our presentation of evidence. Evidence from the Cochrane review suggests that, the optimal timing of corticosteroid administration is within 24h and 7 days of delivery (to reduce the risk of RDS or cerebro-ventricular haemorrhage) or within 7 days of delivery to reduce neonatal death.
Leeds Teaching Hospitals Trust	Full	17	14-24	Real concern about women with past history of LLETZ who are more likely to fall into this grouping but for whom a suture or progesterone may be inappropriate/not required/harmful. We need more studies before 'offer' used	Thank you for your comment. The Committee decided to consider cervical cerclage in women with a history of cervical trauma (including LLETZ) and who have a short cervix defined as less than 25mm. The evidence base for this recommendation was on meta-analyzed data where LLETZ was one of the inclusion criteria for the studies in the meta-analysis, and a reduction in preterm birth is shown. We do not mention the use of progesterone specifically in women with cervical trauma, but we have a recommendation "Offer prophylactic vaginal progesterone to women with no history of spontaneous preterm birth or mid-trimester loss in whom a transvaginal ultrasound scan has been carried out at 16+0 to 24+0 weeks of pregnancy that reveals a cervical length of less than 25 mm". Some of these women may have had a LLETZ, and they would not be excluded from this recommendation.
Leeds Teaching Hospitals Trust	Full	17	24	Need to define 'cervical trauma' – previous LLETZ or cone? Previous Cx tear? Multiple	Thank you for your comment. Cervical trauma is further defined in the scope under groups that will

				cervical dilatations? Previous operative hysteroscopy? Very difficult to quantify. May be interpreted differently by different people, including pregnant women and their families	be covered. However, the Committee appreciate that a definition could have been made clearer and this has been now updated in the glossary of the full guideline. Pregnant women with cervical trauma are defined as those who are considered to be at risk of preterm labour and birth because they have a history of cervical trauma (including surgery – for example, previous cone biopsy [cold knife or 29 laser], large loop excision of the transformation zone [LLETZ – any number] and radical 30 diathermy).
Leeds Teaching Hospitals Trust	Full	17	31-41	The implications of using Actim PROM and/or Amnisure as diagnostic tests leading to treatment are not yet known – there may be subclinical leaks or transudates which are of no clinical significance. Implementation as is will certainly lead to rising intervention – either of antibiotics/steroids/hospitalisation or for women greater than 34 wks induction of labour. There is likely to be a knock-on effect on delivery suite and neonatal resources with no proven clinical benefit for mother or baby if this guideline is adopted as is especially as false +ve more likely at higher gestations in 'normal' pregnancies; real risk of increasing intervention without proven benefit – we feel that too much latitude given here which will be open to interpretation by aggressive marketing by commercial drivers	Thank you for your comment. The Committee reviewed the evidence and decided to consider using these tests in the diagnosis of P-PROM but highlighted with another recommendation that the care of women, in light of positive results of these tests, should be interpreted with caution ("do not use the test results alone to decide care") allowing for the option of waiting and reassessing the situation. In relation to the issue of implementation of these recommendations, this has been passed to the NICE implementation team to inform their support activities for this guideline.
Leeds Teaching Hospitals Trust	Full	18	24	Recommend removing the rescue cerclage bubble – and at any rate strongly reconsider the upper limit of 27+6 weeks; we know that	Thank you for your comment. The care algorithm reflects the content of recommendations. The Committee based the upper limit of gestational

				McDonald in his seminal paper did, but surely this is too high in contemporary practice. Suggest 24wks instead	age for this recommendation on the reviewed evidence. However, the Committee acknowledges in the recommendations that the decision for rescue cerclage must be made only after discussion with a consultant obstetrician by taking into account of the woman's gestation and her own stated wishes after a full discussion..
Leeds Teaching Hospitals Trust	Full	18	27-28	Suggest 'use caution' rather than 'do not' when the descriptors are so vague 'signs of infection' could be interpreted many different ways!	Thank you for your comment. The Committee decided that, in their clinical opinion, rescue cerclage would cause harm to women with signs of infection, active vaginal bleeding or uterine contractions and so they decided upon a strong recommendation of not offering 'rescue' cerclage to these groups of women rather than using with caution this intervention.
Leeds Teaching Hospitals Trust	Full	18	7-9	What about women with concurrent GB strep carriage?	Thank you for your comment. Women with concurrent GS strep carriage are outside the scope of this guideline.
Leeds Teaching Hospitals Trust	Full	19	17-19	Implications of offering care for all <30wks women with suspected PTL is that 50% will receive inappropriate interventions (evidence from placebo controlled tocolytic trials); why not use a bedside rapid test or TVS to triage?	Thank you for your comment. We reviewed the evidence on combinations of tests and the results did not show these combinations to be useful tools for diagnosis of preterm labour. The Committee acknowledges that that the recommendation to treat all women in suspected preterm labour who are below 30 weeks will represent a significant change in practice for many units and that this recommendation may lead to an increase in costs. However, the analysis suggested that the additional costs resulting from implementation of this

					recommendation were worth the additional health benefits. Diagnostic tests usually have a false negative rate which has potential implications for 'missed cases'. At low gestational ages the absolute or baseline risk in the absence of treatment is high and therefore the absolute treatment benefits are relatively high in this group. This means that the implications of false negatives or missed cases (in terms of neonatal/perinatal mortality, respiratory distress syndrome and IVH) are relatively more important at lower than at higher gestational ages. The diagnostic test accuracy evidence reviewed for this guideline was generally of low quality but suggested that they didn't have sufficiently good diagnostic accuracy, especially at low gestational ages. In other words although tests to triage would result in fewer women who are not in preterm labour being treated than under a treat all strategy, it would do so at an unacceptably high level of increased adverse events. This rationale was based on NICE's conventional threshold for cost-effectiveness (a willingness to pay £20,000 for each additional QALY gained)
Leeds Teaching Hospitals Trust	Full	19	34	Why only fibronectin quoted? There are alternatives on the market with equivalent NPVs such as Actim Partus and Partosure which may be cheaper.	Thank you for your comment. Although other tests were examined in this diagnostic review, fibronectin was found to be useful to rule out preterm delivery based on the evidence reviewed. In addition, further sensitivity analysis suggested that the cost of the diagnostic test (within plausible ranges) was not an important driver of cost-

					effective thresholds for the decisions to treat all, treat based on diagnostic test and no diagnosis and no treatment. The Committee discussed that fetal fibronectin should be used for the preterm delivery diagnosis only if transvaginal ultrasound measurement of cervical length is indicated but is not available or not acceptable. The care algorithm reflects the decisions made in the recommendations that's why only fibronectin is included at this section.
Leeds Teaching Hospitals Trust	Full	21	17	Can we include NO donors in this list, and also NSAIDs at gestations greater than 30 weeks	Thank you for your comment. The list to which you refer is unclear from the information sent from NICE, however, it presumed that this comment refers to the recommendations regarding tocolysis and why nitrates and NSAIDs are not recommended for use. As discussed in the Evidence to recommendations section in this chapter and in the corresponding Health Economics discussion section (16.4.4), although nitrates performed well for some outcomes considered in the NMA and the Health Economic analysis, the Committee did not recommend its use because: 1) only 6 trials examined the effect of nitrates, 2) no evidence on this drug contributed to the NMA for the outcome of respiratory distress syndrome and 3) nitrates were not found to be significantly better than placebo at reducing chronic lung disease in pair-wise comparisons. Therefore there was uncertainty regarding the effectiveness of

					nitrates and results were interpreted with caution. Further the Committee considered that the benefits from nitrates needed to be balanced against the potential harm to the fetus. Similarly for prostaglandin inhibitors (NSAIDs), although these performed well for some outcomes (delaying birth by more than 48 hours, for increasing estimated gestational age and for reducing perinatal mortality), they were not found to be significantly better than calcium channel blockers at delaying birth by more than 48 hours. In addition, prostaglandins inhibitors were not found to improve the 'harder' outcomes such as neonatal mortality, respiratory distress syndrome and neonatal sepsis in all of which they scored very low in the ranking of best treatments. The Committee was also aware of other harms thought to be associated with prostaglandin inhibitors such as premature closure of the ductus arteriosus. Therefore they did not consider them as a tocolytic option for women in suspected or diagnosed preterm labour.
National Childbirth Trust	Full	54	General	It would help readers if you can explain the reasoning as to why only one of these studies (Guptan & Heaman 1994) was considered 'Likely to be transferrable'. Also, In particular, we are familiar with the Sawyer 2013 study and see no reason why this study is considered 'unlikely' to be transferrable.	Thank you for your comment. This was reconsidered in response to the points made and the quality assessment for these two studies and this table has now been updated.
National Childbirth	Full	57	General	We feel that providing reassurance (as well as	Thank you for your comment. The first

Trust				explaining what to expect) needs to be highlighted in the recommendations to staff.	recommendation of this guideline refers to the information and support that women at risk at preterm birth or diagnosed or planned preterm birth should be provided following the principles as described in the NICE guideline on patient experience in adult NHS services. In addition, the committee discussed that women at risk or diagnosed at preterm birth and their families or carers may be particularly anxious and this has been added in the recommendation to draw attention to the healthcare providers that this should be taking into account when information and support is provided for this group of women and their families.
National Childbirth Trust	Full	57	General	We also think that consistency of information is important to parents and we believe there should be a recommendation to ensure this.	Thank you for your comment. The recommendations number 1 and 2 in the full guideline aim to provide consistency on the content of information and support given to women at increased risk, diagnosed, established or planned preterm birth.
National Childbirth Trust	Full	58	General	We think it would be important to recommend that neonatologists focus on building trust with parents – similarly for other staff.	Thank you for your comment. Reassurance and trust in health professionals were recurring themes in the qualitative evidence were reviewed as part of this review question. The Committee has interpreted this as requiring the provision of honest and realistic information about a woman's individual situation. More details are given in the Evidence to recommendations section of Chapter 3 in the full guideline.
National Childbirth Trust	Full	58	General	Support strategies are also important and we believe should be a recommendation.	Thank you for your comment. Although the Committee recognised the importance of provision

					of support to women at risk of preterm birth or at planned preterm birth and this was reflected in all recommendations saying both 'information and support', the review protocol for this question was not set up to look at the difference between different support strategies for women at risk of preterm labour, therefore no further indications about this were included in the recommendations.
National Childbirth Trust	Full	58	General	Women spoke volumes of the tour around NICU and the opportunity to speak with the neonatologist, and we feel this needs to be emphasised in the recommendations.	Thank you for your comment. The Committee agrees and the recommendation on information provision and support for women with planned preterm birth (recommendation 1.1.2 in the short guideline and 2 in the full guideline) included an opportunity to tour to a neonatal unit and an opportunity to speak with a neonatologist or paediatrician.
National Childbirth Trust	Full	69 71 9	15 16 5	We believe this statement from the full draft guideline is really important: “As a first principle, the Committee agreed that kindness, compassion and empathy were crucial principles in all interactions between clinicians and the pregnant woman and her partner because otherwise the content of any information imparted becomes redundant.” (p 69 line 15) We believe this should form the basis of the first recommendation in the section on ‘Support and information.’	Thank you for your comment. The first recommendation of this guideline refers to the information and support that women at risk at preterm birth or diagnosed or planned preterm birth should be provided following the principles as described in the NICE guideline on patient experience in adult NHS services. In addition, the Committee discussed that women at risk or diagnosed at preterm birth and their families or carers may be particularly anxious and this has been added in the recommendation to draw attention to the healthcare providers that this should be taking into account when information and support is provided for this group of women and their families.

				We suggest something like this for the first recommendation in this section: "When giving support to women at increased risk of preterm labour, with suspected, diagnosed or established preterm labour, or having a planned preterm birth (and their family members or carers as appropriate): • be aware that kindness, compassion and empathy are crucial principles in all interactions with the pregnant woman and her partner because otherwise the content of any information imparted becomes redundant • build trust with both the woman and her partner • provide reassurance that support is there for both the woman and her partner • offer a tour round the NICU and provide an opportunity for parents to speak with the neonatologists • develop strategies to provide support and ensure that information given by staff is consistent "	
National Childbirth Trust	Full	71,9	22,5	1.1.1 would then become 1.1.2 and begin "When giving information to women…"	Thank you for your comment. The Committee do not believe that the order of these recommendations should change.
National Childbirth Trust	Full	9,71	21	These recommendations are really about giving information and we would like to see much more focus on giving support. The evidence is clear that support is of real benefit to women and	Thank you for your comment. The Committee agrees that support is as important as provision of information and this is reflected in all the recommendations in this section.

				parents, and support seems even more important than information. Women in preterm labour (and partners) are often very worried and frightened for their baby, and need real kindness, compassion and support. These draft recommendations seem to be all about providing information, but we believe the evidence reported in the Full guideline shows that support is very important to parents of premature babies. This comes across in all the studies assessed. In particular also support for the partner is very important but often missing – he has his own support needs and yet his role is also to support the woman too – a really difficult role. We would like to see the first recommendations in this section on supporting women and their partners with understanding, kindness and compassion. See 10 below for specific suggestion.	
National Childbirth Trust	Full	72	17	We know that the Cochrane review (Sandall 2013) showed a significant reduction in preterm birth with midwifery-led continuity of care models care compared with other models of care (average RR 0.77, 95% CI 0.62 to 0.94). Why has this been missed in this draft guideline? We believe this is very important information which needs to be included. Our understanding is that this review has been updated and is	Thank you for your comment. Examination of models of care was outside the scope of this guideline.

				currently in the editorial process, and we request the GDG contacts the Cochrane Pregnancy & Childbirth Group for further information. 'Sandall J, Soltani H, Gates S, Shennan A, Devane D. Midwife-led continuity models versus other models of care for childbearing women. Cochrane Database of Systematic Reviews 2013, Issue 8.	
National Childbirth Trust	Full	209,17	26,7	It would help to list the clinical signs of magnesium toxicity in brackets in this recommendation..	Thank you for your comment. The Committee discussed the importance of monitoring for clinical symptoms of magnesium toxicity in the Evidence to recommendations in section 12.1.6. Monitoring for magnesium toxicity was the focus of the following two recommendations: For women on magnesium sulfate, monitor for clinical signs of magnesium toxicity at least every 4 hours by recording pulse, blood pressure, respiratory rate and deep tendon (for example, patellar) reflexes. If a woman has or develops oliguria or other signs of renal failure: • monitor more frequently for magnesium toxicity • think about reducing the dose of magnesium sulphate.
National Childbirth Trust	Full	292	17	We think that women should be informed of the lack of mobility that comes with CTG assessment of the fetal heart and that women	Thank you for your comment. The issue of woman's mobility during fetal monitoring if continuous cardiotocography is needed has been

				should also be informed of the frequency of the IA if that is used, so they can make a better informed decision.	covered by the NICE IPC guideline (http://www.nice.org.uk/guidance/cg190/evidence/cg190-intrapartum-care-full-guideline3) and recommendations in this guideline cross refer to the relevant sections of the IPC guideline. The Evidence to recommendations section has now been updated to clarify this.
National Childbirth Trust	Full	300	34	We are concerned about the statement "The evidence from 1 SR of 3 RCTs (n=105) showed no significant difference in the incidence of postpartum haemorrhage in women whose babies were born by caesarean section compared with those whose babies were born by vaginal birth. The evidence across all studies was of very low quality." The RCT evidence around PPH after CS and vaginal birth is clearly insufficient with only 105 women in this SR. We are aware, however, that amongst clinicians it is general knowledge that there is higher blood loss at CS than at vaginal birth, so we believe that this information should be included otherwise the statement is misleading. The evidence may not be there specifically around preterm birth but we think some of the general evidence about higher blood loss and PPH at CS compared with vaginal birth should be included and referred to. We understand that some countries define PPH differently between CS and vaginal birth,	Thank you for your comment. The Committee agreed that there was a very serious imprecision around this effect estimate for the outcome of postpartum haemorrhage and this is reflected in downgrading the overall quality of evidence.

				although this is not done in the UK, it illustrates the knowledge of higher blood loss following CS. (Knight 2012. 'Trends in postpartum hemorrhage in high resource countries: a review and recommendations from the International Postpartum Hemorrhage Collaborative Group.' BMC Pregnancy and Childbirth 2009, 9:55	
National Childbirth Trust	Full	304	General	We are surprised that the additional study to the one in the Cochrane review (Rabe 2012) on cord milking was March 2011. March et al have published in 2013 a study on cord milking on preterm infants (probably the same study but with more women and babies included) however we would expect a draft guideline in 2015 to include a 2013 paper. We are however, unsure of the quality of this trial as they exclude many women and babies after randomisation, so this may the reason for exclusion - but this is not clear in the full guideline March MI, Hacker MR, Parson AW, Modest AM, De M. The effects of umbilical cord milking in extremely preterm infants: A randomized controlled trial. Journal of Perinatology 2013;33(10):763-7.	Thank you for your comment. The March 2013 study was not included in our evidence base because it compared umbilical cord milking (more placental transfusion) with immediate cord clamping (less placental transfusion) in extremely preterm births which was not covered in the protocol. The protocol focused on the comparison of 'later' (more placental transfusion) versus 'earlier' (less placental transfusion) types of cord clamping. The March 2013 study is noted in the excluded list (Appendix G).
National Childbirth Trust	Full	319	16	We believe the above on cord milking is a good example of where wording 'consider' does not really reflect the poor quality evidence and can be misleading.	Thank you for your comment. The Committee agrees that the evidence base of this recommendation is weak and the word "consider" has been selected to reflect this following NICE standard terminology on translating the quality of evidence in the strength of recommendations.

National Childbirth Trust	Full	319	General	We agree with this research recommendation: "*Is there any advantage to preterm babies from delayed versus early cord clamping, or cord milking?"* – and believe it is very important as the current evidence is poor on timing of cord clamping in preterm birth.	Thank you for your comment.
National Childbirth Trust	Full	319,21	16,18	In the next recommendation: *"If a preterm baby needs to be moved away from the mother for resuscitation, or there is significant maternal bleeding:* • *consider milking the cord and* • *clamp the cord as soon as possible"* we think there is too much emphasis on "*clamp the cord as soon as possible*" though we recognise that resuscitation should take priority. There are skills being developed to give resuscitation at the bedside with the cord intact (Schoonakker 2013) and using a specially designed trolley (Thomas 2014; Weeks 2014) – so we think the wording should be modified. We are also concerned about the lack of evidence to support cord milking. The included study in the Cochrane review (Rabe 2012) involved just 40 babies and the March 2011 study reports involving only 38 babies, so this	Thank you for your comment. Resuscitation of the baby as a type of intervention was outside the scope of this guideline. The evidence derived by Rabe 2014 study related to cord clamping was considered of very low quality in our evidence profile unless bedside resuscitation is possible.

				means there is evidence on only 78 babies in all, with only 41 babies having cord milking. We believe this is insufficient to be comfortable about the safety of this procedure. We think the recommendation would be clearer as: "If a preterm baby needs to be moved away from the mother for resuscitation, or there is significant maternal bleeding • • clamp the cord to enable resuscitation or attend to the mother's PPH • cord milking prior to cord clamping should only be considered within the context of a well conducted RCT Refs Rabe H, Diaz-Rossello JL, Duley L, Dowswell T. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. *Cochrane Database of Systematic Reviews* 2012, Issue 8 Schoonakker B, . Dorling, J,. Oddie, S,. Batra, D,. Grace, N,. Duley, L. Bedside resuscitation of preterm infants with cord intact is achievable	

				using standard resuscitaire. Available at p430 of https://www.eiseverywhere.com/file_uploads/9206db9fe962868d47f709b38365ec5e_9349_abstract_book_-_25sett13-it-it.pdf. European Society for Pediatric Research 2013. Thomas M, Yoxall C, Weeks A, Duley L. Providing newborn resuscitation at the mother's bedside: assessing the safety, usability and acceptability of a mobile trolley. BMC Pediatrics 2014;14:135. Weeks AD WP, Hutchon DJR, Yoxall CW, Gallagher A, Burleigh A, Bewley S, Heuchan AM, Duley L. Innovation in immediate neonatal care: development of the Bedside Assessment, Stabilisation and Initial Cardiorespiratory Support (BASICS) trolley. http://www.nottingham.ac.uk/nctu/documents/preterm-birth/basicsdevelopment- report-29april2014.pdf	
National Childbirth Trust	Full	319,21	20,22	We believe it is better to begin with recommendations for babies where mother and baby are stable as this should be the 'norm' unless the baby is poorly. So we suggest Recommendation 60 should come before Recommendation 59.	Thank you for your comment. The Committee disagrees with this suggestion given the emphasis on the first action needs to be placed on the premature babies due to the high risk of further complications.
National Childbirth Trust	Full	319,21	20,22	We also believe the wording in this recommendation: *"Wait at least 30 seconds, but no longer than 3*	Thank you for your comment. The Committee noted that the majority of the included studies defined delayed cord clamping as being between 30 to 60 seconds after birth. In some studies the

				minutes, before clamping the cord of preterm babies if the mother and baby are stable." is far too strong when it says "…but no longer than 3 minutes…". There is no evidence that waiting more than 3 minutes causes any harm. Three minutes is here only because this was the cut-off that researchers chose to study. Contact between baby and mother at this time can be really important to help with bonding and this will begin at the moment of birth if facilitated by staff. Also, there is evidence that placental transfusion lasts 2-5 minutes in term babies (Farrar 2011) and theoretically may last longer in preterm infant (Pushpa-Rajah 2014). According to Unwins 2014 (Pediatric Health, Medicine and Therapeutics 26 September 2014) "…*most international guidelines suggest a delay of one to three minutes…*". We suggest the first recommendation in this section on Timing of cord clamping would be better as: "In preterm babies, where baby and mother are stable, wait at least 30 seconds, but consider waiting for one minute or more, before clamping the cord. If the mother wishes to wait longer she should be supported in her choice."	cord was clamped after a longer interval (up to 180 seconds after birth). The Committee felt that in clinical practice, delayed cord clamping is generally conducted within the 30-60 second time limit and although they felt the same benefits might be seen at other timings, decided that the recommendations should reflect the 30-60 second interval. Regarding the two references provided; Farrar 2011 study was excluded as it was related to term babies and Pushpa-Rajah 2014 is an ongoing trial with results not yet published.

				Refs: Farrar D, Airey R, Law G, Tuffnell D, Cattle B, Duley L. Measuring placental transfusion for term births: weighing babies with cord intact. BJOG 2011;118:70–75. Pushpa-Rajah 2014. *Cord pilot trial - immediate versus deferred cord clamping for very preterm birth (before 32 weeks gestation): study protocol for a randomized controlled trial. Trials 2014, 15:258*	
National Childbirth Trust	NICE	5	1	We would like this section to be 'Woman centred care' rather than 'Patient centred care', and for 'woman' to be used throughout the document. A woman in preterm labour is not necessarily a patient – though her baby may well be.	Thank you for your comment. This wording is standardised text that is applied to all NICE guidance however this section will be removed in the final version at publication.
National Childbirth Trust	NICE	6	1-99	It is very unclear to us why NICE uses wording to represent the strength of evidence behind a recommendation. The previous NICE system, which we found clearer and much more transparent, gave a score for the quality of the evidence and clearly marked where a recommendation was a 'Good practice point' [GPP] meaning there was no clear evidence to support the recommendation but instead this was the opinion of the GDG. It is very unclear now when a recommendation is based on good evidence, limited evidence or opinion. The WHO system reports on the strength of the recommendation and the quality of the evidence.	Thank you for your comment. There is a standard method of wording the recommendations in NICE guidelines which reflects the evidence base. Please see more details in the NICE Manual 2014 (https://www.nice.org.uk/Media/Default/About/what-we-do/our-programmes/developing-NICE-guidelines-the-manual.pdf).

				We would find either the WHO or the previous NICE systems much more acceptable and more transparent than this current NICE system using wording. We understand that this is unlikely to change for this guideline, but we ask NICE to re-consider and to look at either ways of reporting on the strength of the evidence in its guidelines.	
National Childbirth Trust	Short	3	22	These research recommendations are all very clinical. There is recently published a James Lind Alliance methodology gathering research recommendations – including suggestions from the public forming a large input. From this list we would suggest the following are important areas for research in preterm birth: • What emotional and practical support improves attachment and bonding, and does the provision of such support improve outcomes for premature babies and their families? • What type of support is most effective at improving breast feeding for premature babies? • Does specialist antenatal care for women at risk of preterm birth improve outcomes for mother and baby? • What are the best ways to optimise the environment (such as light and noise) in order to improve outcomes for premature babies?	Thank you for your comment. Although the Committee recognises the importance of these topics for women at risk of preterm birth, it was felt that the majority of these referred to postnatal care of preterm babies which was outside the scope of this guideline. However, a reference has been made to both NICE quality standards on specialist neonatal care (QS4) and the report developed by the Bliss Organisation.

				*Lelia Duley, Seilin Uhm, Sandy Oliver. 2014. *Top 15 UK research priorities for preterm birth*. Lancet Vol 383 June 14, 2041	
National Childbirth Trust	Full	21,303	12,30	We are very concerned about this recommendation: • there is some evidence that there may be a large reduction in perinatal mortality associated with caesarean section for preterm babies with breech presentation, but overall the evidence is inconclusive. We believe there is such poor evidence on this that telling women this will be very misleading, frightening and completely inappropriate, and may turn out to be incorrect. The data is from a subgroup analysis in a Cochrane review with only 51 babies (where 7 died). This is clearly not only insufficient data on which to make such a statement but the difference was not statistically significant (this was for breech, vertex or both), and such data on small sample sizes can change very easily when more data is gathered. The Cochrane authors report: "Given that very few women have been recruited to trials of planned immediate caesarean section versus planned vaginal delivery for preterm birth, and that the quality of the trials conducted is generally unclear, we recommend that firm conclusions regarding the relative merits of	Thank you for your comment. The Committee considered a number of stakeholder comments regarding this recommendation. The Committee made several recommendations regarding information to be discussed with any woman in suspected, diagnosed or established preterm labour when the mode of birth is decided. The Committee considered important to explain to women the associated risks such as the increased likelihood of a vertical uterine incision and the implications of this for future pregnancies with CS for women at preterm labour which depend on gestational age with these women. However, the Committee agreed with your comments that this statement may create confusion to women and this is now deleted.

				planned immediate caesarean section versus planned vaginal delivery should not be drawn from this evidence to guide practice for preterm births." We suggest this recommendation is removed.	
NHS Choices, Digital Assessment Services	Full	General	General	The Digital Assessment Service welcome the guidance and have no comments as part of the consultation	Thank you for your comment.
NHS England	Full	General	General	Thank you for the opportunity to comment on the above Clinical Guideline. I wish to confirm that NHS England has no substantive comments to make regarding this consultation.	Thank you for your comment.
Royal College of General Practitioners	Full	General	General	The College feels the draft guideline is not of great relevance to GPs, except to make sure the woman gets into the hospital. The assessment of whether women are in PTL should also be made in the hospital and not by a GP. [redacted] This guidance is primarily for midwives and maternity departments, obstetricians and paediatricians. It gives hope to GPs that progress is being made in the difficult diagnoses of Premature Rupture of Membranes, and whether labour is commencing early with no membrane rupture! It helped explain how one of my patients, who had a Caesarean section at 32 weeks because the baby was not growing, is bringing the baby home soon! Both are well.	Thank you for your comment. The Committee agree that this guideline is mainly directed to provide guidance to midwives, obstetricians and paediatricians who care for women at risk of preterm labour. Additional outputs of this guidance will be related to the implementation of the guideline along with information to the public.

				The guidance educates primary care on foetal fibronectin, the placental macroglobulin and insulin like growth factor protein tests which may be used to help difficult judgements. The cost analysis is found to be quite scary; most GPs don't have to price up the cost of saving a baby and the mother. It was relieving to find standard treatments affirmed. We would be pleased to see a shorter section for implications for patients and for primary care – the guidance is very relevant but most of the time we hope not to need it. The message is refer in? [redacted]	
Royal College of Midwives	Full	General	General	RCM welcomes the draft of this important guideline which includes strong recommendations on interventions that should no longer be used.	Thank you for your comment.
Royal College of Midwives	Full	General	General	We disagree with the exclusion of women with a multiple pregnancy as this group is at such a high risk of preterm birth.	Thank you for your comment. Women with a multiple pregnancy were not included as the populations to be covered by the scope of the guideline. However, we agree that this needs to be covered by a NICE guidance and it will be referred to our Surveillance Team for potential inclusion in the update of the NICE Guideline on Multiple Pregnancy.
Royal College of Midwives	Full	General	General	We are particularly pleased to see such a high focus in the guideline on detailed information giving to women and their families at all stages of pregnancy with the risk of prematurity, as lack of access to this information has remained an important and disturbing issue for a long	Thank you for your comment. Staff training is outside the scope of this guideline however, we will raise that as an issue for implementation of the guideline with the NICE Implementation Team.

				time. There must be consistency in the information given which will mean that all staff giving it must be up to date with current evidence and local policy - this will present a challenge in the context of the lack of evidence in many of the key areas as outlined in the research recommendations.	
Royal College of Midwives	General	1.13	21	We are pleased to see the recommendations for delayed cord clamping	Thank you for your comment.
Royal College of Midwives	Small	21	12	This recommendation is unclear suggesting ' a large reduction' yet being 'inconclusive' and will confuse the discussion *to ' explain to the woman that …..* *there is some evidence that there may be a large reduction in perinatal mortality associated with caesarean section for preterm babies with breech presentation, but overall the evidence is inconclusive*	Thank you for your comment. The Committee considered a number of stakeholder comments regarding this recommendation. The Committee agreed with your comments that these statements may create confusion to women and there are now deleted.
Royal College of Nursing	General	General	General	This is to inform you that the Royal College of Nursing had no comments to submit to inform on the above guideline consultation at this time.	Thank you for your comment.
Royal College of Obstetricians and Gynaecologists	Full	General	General	Page 10 – 'Forthcoming' – I would leave this out as it won't be forthcoming when it is out.	Thank you for your comment. This has now been deleted.
Royal College of Obstetricians and Gynaecologists	Full	General	General	Thank you to the authors for proving this update on the management of preterm labour and birth. It provides guidance of the use of progesterone and cervical cerclage in the management of women at high risk of preterm labour.	Thank you for your comment.
Royal College of	Full	General	General	General comments about the flow charts were as	Thank you for your comment. The algorithms

Obstetricians and Gynaecologists				follows- The algorithms and flowcharts for management could be simplified and made more visually appealing, and easier to follow. Flow chart for the care pathway 4 is not clear. Yes and No 'bubbles' are too close and is confusing. All the other flow charts are too crowded and texts are overlapping with line. Suggest much clearer flow charts ideally one per page. 5th algorithm- care around the time of birth- Not sure that this diagram adds anything to the recommendations below and is not really going to be of particular value in clinical practice.	have been modified to improve the clarity of the flow charts following comments from stakeholders.
Royal College of Obstetricians and Gynaecologists	Full	7	122	Section 7 – there is no mention of maternal tachycardia – nor the frequency of visits or blood tests nor the timing of birth as per RCOG guideline.	Thank you for your comment. No evidence was identified regarding maternal tachycardia as a tool for diagnosis of intrauterine infection in women with P-PROM. Frequency of visits or bloods tests was outside the scope of this review question. However, the Committee discussed the evidence on outcomes measured at different timings since birth and decided that these were less useful because they did not reflect the real clinical scenario and hence no conclusions could be drawn.
Royal College of Obstetricians and Gynaecologists	Full	11.1.7	28	Point 38 is particularly relevant in serum monitoring of magnesium.	Thank you for your comment. Serum monitoring was not addressed by the Committee, but rather clinical symptoms of magnesium toxicity were

					discussed and formed the basis of the two following recommendations on monitoring for toxicity: For women on magnesium sulfate, monitor for clinical signs of magnesium toxicity at least every 4 hours by recording pulse, blood pressure, respiratory rate and deep tendon (for example, patellar) reflexes. If a woman has or develops oliguria or other signs of renal failure: • monitor more frequently for magnesium toxicity • think about reducing the dose of magnesium sulfate.
Royal College of Obstetricians and Gynaecologists	Full	14	2	Preventative care diagram - The initial care pathway algorithm is a little confusing as regards the management of women with a history of spontaneous preterm birth or midtrimester loss. The NO part of the flow chart seems to imply that regardless of history, a cervical length scan should be carried out. Is this the case or do the authors mean that women with an inadvertent finding on TVS of a cervix <25mm should have progesterones prescribed? Could the authors please clarify and make this flow chart easier to follow?	Thank you for your comment. The Committee reviewed the evidence and concluded that women with an inadvertent finding on transvaginal ultrasound of cervical length of less than 25 mm between 16+0 and 24+0 weeks, irrespective of history, should be offered progesterone. However, we appreciate that the algorithm may be confusing and he has been modified for greater clarity.
Royal College of Obstetricians and Gynaecologists	Full	14	2	Are the authors suggesting that women with a history of PPROM or cervical trauma should be offered cerclage only? Is progesterone not an option in these circumstances? Could the	Thank you for your comment. No evidence was identified to match the review protocol for the preventive role of progesterone in women with a history of P-PROM, history of mid-trimester loss,

				authors provide evidence for this?	history of cervical trauma (including surgery) or with a positive fetal fibronectin test. Therefore the Committee did not suggest the use of progesterone as a prophylactic measure for these subgroups.
Royal College of Obstetricians and Gynaecologists	Full	14	2	Midtrimester is 14 -28 weeks. Hence it would be best to state as pregnancy loss btw 16 and 34 weeks, to be factually correct.	Thank you for your comment. The care algorithm has been updated as suggested.
Royal College of Obstetricians and Gynaecologists	Full	14	3	diagnosis of PTL Table on diagnosis of PTL - It would sound more conventional to state 'woman presents with symptoms of PTL' than 'women presents symptoms of PTL' In the same table there is both singular and plural nouns as in 'women ' and 'woman'. Suggest stick to 'woman'.	Thank you for your comment. This has now been amended for consistency.
Royal College of Obstetricians and Gynaecologists	Full	14	3	If fetal fibronectin testing is positive, view the woman as being in diagnosed preterm labour and offer treatment as described in Chapters 10 – 12 Might be sensible to say "..view at high risk of preterm labour and consider treatment.." otherwise MgSO4 might be started just on the basis of a +FFN (Recommendation 35)	Thank you for your comment. The Committee reviewed the evidence on fetal fibronectin to diagnose preterm labour and the results were mixed in terms of its diagnostic accuracy. This test was found to be more useful to rule out preterm delivery and the Committee discussed that fetal fibronectin should be used for the PTLB diagnosis only if transvaginal ultrasound measurement of cervical length is indicated but is not available or not acceptable.
Royal College of Obstetricians and Gynaecologists	Full	14	3	I am a little unsure why we are not offering cervical length scanning for the prediction of PTL or fibronectin less than 30 weeks? This seems a	Thank you for your comment. The Committee carefully reviewed the clinical and cost effectiveness analysis of different diagnostic

				rather fundamental issue. If the cervical length is >15mm at 28 weeks – the woman is not in labour and yet the care pathway would have us admit her, give steroids and magnesium even though she is unlikely to deliver or are you saying we need to tocolyse and put in a cervical suture and then this is only up to 27+6 weeks. What happens to the women who are 28+0to 29+6 week? I think this need some clarification.	strategies for preterm labour. The results were based on the best available evidence which suggested that these tests have insufficient negative predictive value to be used when the adverse consequences of preterm birth are so high (gestational ages <30 weeks).
Royal College of Obstetricians and Gynaecologists	Full	14.1.7	30	Is it worth adding that "there is no evidence to support caesarean section over vaginal delivery at gestations less that 26 weeks'?"	Thank you for your comment. The Evidence to recommendations section of the Chapter 14 in the full guideline was amended to reflect the Committee's decision not to make any recommendations about the optimal mode of birth for women in pregnancy below 26 weeks.
Royal College of Obstetricians and Gynaecologists	Full	15	1	Diagnosis of PPROM The authors discuss the limited evidence at the present time to support the widespread use of IGFBP-1 or PAM1 (recommendations 6,7,8). These test are not widely available in clinical practice. It might therefore be more appropriate to remove this box from the flow chart Should be 'no pooling' not 'not pooling'	Thank you for your comment. The spelling error has now been corrected. Although the algorithm captures the main recommendations in this section and these tests were recommended by the Committee when there was no pooling of amniotic fluid, it was noted in the diagram that this is only to be "considered" reflecting the strength of this recommendation.
Royal College of Obstetricians and Gynaecologists	Full	15	1	Woman presents WITH symptoms of P-PROM	Thank you for your comment. This error has now been corrected.
Royal College of Obstetricians and	Full	15	2	care for suspected etc Offer steroids to all women up to 35+6 weeks –	Thank you for your comment. This recommendation has been amended to reflect the

Gynaecologists				this is different to RCOG as we say up to 34+6 and then 35+6 if suspicions of FGR – but I presume our guideline will be archived	evidence base for women from 26+1 weeks to 34+6 weeks and a new recommendation has been added for women from 35 to 36+6 weeks.
Royal College of Obstetricians and Gynaecologists	Full	16	1	Recommendation 48,49 - Could the authors provide evidence to support the extrapolation of the NICE guidelines on Intrapartum Care, which applies to low risk women, in this high risk group?	Thank you for your comment. The Committee discussed extensively this section. They believed that although electronic fetal monitoring guidelines for term fetuses (see the NICE guideline on intrapartum care) cannot be always applied during labour to preterm babies, they can be considered as relevant after 32 weeks, as physiological maturity of the cardiovascular and neurological systems from this gestational age is comparable to that of term babies. Thus, from 32 weeks, baseline fetal heart rate and variability should be similar to that in term fetuses and accelerations with an amplitude of more than 15 beats from the baseline should be present as an indicator of fetal well-being. Decelerations can be interpreted as for the term fetus. The Committee discussed that theoretically, compared to term fetuses, preterm fetuses tend to have lower reserves and may deteriorate more quickly than term fetuses. Thus earlier and/or more prompt intervention may be required compared to term fetuses. With regards to monitoring by IA, the Committee agreed that in the absence of any evidence to the contrary, this should be carried out in accordance with the guidelines on monitoring the term fetus. The Committee felt that women's views should be taken into account when the decision of fetal monitoring is made and that it was important to

					provide ongoing information and support for mothers when using either CTG or IA.
Royal College of Obstetricians and Gynaecologists	Full	16	11	Recommendation 50 - Could the authors provide evidence for discussion regarding the benefits and risks for application of a FSE at gestations <34 weeks? The supporting text in section 13 discusses theoretical risks only. '*The Committee felt that the attachment of an electrode to the preterm fetus's soft scalp could theoretically cause trauma as well as local or more widespread infection in the fetus. There was no evidence that met the protocol which could demonstrate whether FSE usage was of benefit or harm to preterm babies, but there was consensus in the Committee (based on their knowledge of preterm fetal anatomy) that attaching a scalp electrode had the potential to cause complications.*	Thank you for your comment. There was no relevant evidence to include this review with respect to using FSE at <34 weeks' gestation. The Committee also noted that it is not current practice to routinely use FSE in preterm fetuses less than 34 weeks. The Committee did discuss non-routine circumstances where use of FSE at <34 weeks' gestation may be indicated eg to avoid potentially unnecessary caesarean section and made recommendations for these exceptional circumstances based on their expert opinion and consideration of the health economics as is stated in the Evidence to recommendations section 13.4.4.
Royal College of Obstetricians and Gynaecologists	Full	16	14	Recommendation 34 - The evidence statements (concerning the use of repeated doses of corticosteroids) conclude that there is currently limited evidence in terms of improvement in fetal and neonatal morbidity. There appeared to be a small reduction in immediate need for mechanical ventilation in the repeat steroid group but an increased incidence of chronic lung disease in the survivors. The authors noted that a number of studies were concluded prematurely due to concerns about harm associated with repeat doses. From the limited long term	Thank you for your comment. The Committee agrees that there was insufficient evidence of benefit to support a recommendation that courses of steroids should be repeated routinely, but that this should not rule out the judicious use of repeat courses of corticosteroids in circumstances where clinical judgement suggested that it might be beneficial given the lack of clear evidence that such practice would cause harm. The Committee noted that, based on their clinical experience, these decisions should be based upon gestation, likelihood of imminent birth, and time period since

				evidence available it would appear that repeated doses of corticosteroids offer no benefit. The recommendations here therefore should recommend that repeat doses of steroids should not be given. There are no data to support the 'taking into account' the other factors listed. The suggestion that steroids did 'show benefit in terms of respiratory outcomes when the original course was given at 24 weeks and the repeat was given at 34 weeks', is based upon data from one study – it is not clear from the discussion provided in section 10 which one this is. For clinicians this is confusing and unless there is good evidence to support repeat steroid in the absence of harm this recommendation should be modified.	the last course of steroids.
Royal College of Obstetricians and Gynaecologists	Full	16	2	care around the time of birth Consider LSCS as mode of delivery for preterm breech? I would remove this as it will be used by people as evidence to perform LSCS – the new RCOG guideline is likely to recommend that breech delivery is safe in selected groups	Thank you for your comment. This diagram has been removed from the algorithm as it was very lengthy and lacked clarity. However, the Committee decided that the recommendation was still valid as they were aware that in current clinical practice the selection of the mode of birth for preterm babies is often extrapolated from full-term babies. For example if the baby has a breech presentation then CS would be the most favoured mode of birth.
Royal College of Obstetricians and Gynaecologists	Full	17	3	Recommendation 5 - Could the authors please clarify what is meant by cervical trauma. This isn't clear in the recommendation nor in the supporting text in section 4.3	Thank you for your comment. Cervical trauma is further defined in the scope under groups that will be covered. However, we appreciate that this definition may be benefited from more information and this has been updated in the glossary of the

					full guideline. We defined pregnant women with cervical trauma those who are considered to be at risk of preterm labour and birth because they have a history of cervical trauma (including surgery – for example, previous cone biopsy [cold knife or 29 laser], large loop excision of the transformation zone [LLETZ – any number] and radical 30 diathermy).
Royal College of Obstetricians and Gynaecologists	Full	17	10	Recommendations 6 and 7 - As above re additional biochemical tests. The authors state in page 23 that there is limited evidence about the accuracy of these diagnostic tests and the GRADE evidence in section 6 suggests that the studies included were of low quality. These tests are not widely available in clinical practice. In view of this we think that the authors should consider removing this recommendation. Furthermore the recommendation in section 7 suggests that if these tests are positive, they don't really add to the diagnosis and the women's clinical condition, medical and pregnancy history and gestational age should be taken into account. From a clinical point of view therefore there seems to be of no value in doing these tests.	Thank you for your comment. The Committee recognised that the included studies provided low to very low quality evidence that showed that the 2 tests (placenta alpha-microglobulin-1 and insulin-like growth factor binding protein-1) were useful for correct identification of P-PROM, though the Committee's confidence in the results was limited. However, the Committee recognised that failure to identify those women with P-PROM correctly can result in either failure to implement helpful prophylactic measures or delay in discharge from hospital or inappropriate intervention such as hospitalisation, induction of labour for elective preterm birth and inappropriate use of antibiotics. Therefore, the Committee decided that the role of these tests (placenta alpha-microglobulin-1 and insulin-like growth factor binding protein-1) is supplementary on diagnosis of P-PROM along woman's clinical condition, medical and pregnancy history and gestational age.
Royal College of Obstetricians and	Full	17	4	Recommendation 4 - Could the authors please clarify under what circumstances this might	Thank you for your comment. Screening for cervical length was outside the scope of this

Gynaecologists				apply. The implication from the way that this is written is that all women should have a cervical length scan done to see if they have a short cervix. Additionally patients reading this recommendation may feel that they would like a scan done just in case their cervix is shortened due to fear of preterm birth as they perceive that a potential treatment is available. Does the evidence support cervical progesterone in women who are found 'by chance' to have a short cervix on scan in the absence of any relevant history? The RCOG (CTG no. 60), ACOG and SOGC all currently suggest 'that cerclage is not indicated in singleton pregnancies in women *without* a history of preterm birth or spontaneous loss who have an incidentally identified short cervix of ≤25 mm.' Do the authors have evidence to support the use of cerclage when the cervix is found (by chance) to be shortened in low risk women?	guideline. This recommendation was based on the reviewed evidence which concluded that vaginal progesterone was beneficial in reducing preterm birth (compared to no progesterone) in women identified with a short cervix of less than 25mm on ultrasound scan but who did not necessarily have a previous history of spontaneous preterm delivery. Please see section 4.2 in the full guideline for full description of the reviewed evidence.
Royal College of Obstetricians and Gynaecologists	Full	16.4.2.5.1	General	Capitalise authors names please throughout this section (eg page 363 line 32; page 364 line 28).	Thank you for your comment. These have now been corrected, as suggested.
Royal College of Obstetricians and Gynaecologists	Full	18	15	Recommendation 18 - It would be helpful for clinicians to have further guidance re the consideration of rescue cerclage in the guideline when the cervix is dilated re the extent of cervical dilatation when this can be considered. Again RCOG GTC no. 60 and SOGC discuss the	Thank you for your comment. The recommendation has been amended to reflect that the extent of cervical dilatation should be taken into consideration along with the gestational age when the decision to consider rescue cerclage is made.

				use of a cut off of 4 cm.	
Royal College of Obstetricians and Gynaecologists	Full	20	10	Recommendation 30 - The recommendation for not waiting for more than 3 minutes to clamp the cord is presumably based on the available data. There do not appear to be any documented studies presented here that have allowed the cord to be clamped after 3 minutes. What advice therefore should be given to the woman who wishes to wait more that 3 minutes and how should these babies be monitored? The need for further studies in this area is discussed in the RCOG scientific impact paper on delayed cord clamping 2015.	Thank you for your comment. The Committee noted the limited evidence in the area which was of low to very low quality and hence they did not feel confident to make strong recommendations for practice regarding the timing of cord clamping. They noted there is some evidence in favour of delayed cord clamping and no evidence of harm is associated with it. This recommendation was driven by both the reviewed evidence and the Committee's expert opinion. The Committee noted that there may be individual circumstances such as gestational age and maternal reasons for separation between the woman and baby straight after birth that might make a difference to the care strategy. The Committee felt this decision would need to be made on an individual case-by-case basis following the clinician's judgement on the balance between benefits and harms.
Royal College of Obstetricians and Gynaecologists	Full	20	18	What about prophylactic antibiotics? Cochrane Database Syst Rev. 2007 Jan 24;(1):CD000262. Antibiotics for treating bacterial vaginosis in pregnancy.	Thank you for your comment. This area was outside the scope of the guideline.
Royal College of Obstetricians and Gynaecologists	Full	20	30	Point 37 - is it worth considering magnesium levels?	Thank you for your comment. Serum monitoring was not addressed by the Committee, but rather clinical symptoms of magnesium toxicity were discussed and formed the basis of the two following recommendations on monitoring for toxicity:

					For women on magnesium sulfate, monitor for clinical signs of magnesium toxicity at least every 4 hours by recording pulse, blood pressure, respiratory rate and deep tendon (for example, patellar) reflexes. If a woman has or develops oliguria or other signs of renal failure: • monitor more frequently for magnesium toxicity • think about reducing the dose of magnesium sulfate.
Royal College of Obstetricians and Gynaecologists	Full	22	39	Recommendation 58 (Third point) - The evidence suggests a 'reduction in perinatal death in babies with breech presentation was RR 0.28 (0.05 to 1.49)'. The authors acknowledge the wide confidence intervals here. Therefore the current evidence cannot support the statement the 'there may be a large reduction in perinatal mortality associated with caesarean section ' for the preterm breech baby. I think the wording of this recommendation needs to be altered with more stress on the inconclusive nature of the evidence.	Thank you for your comment. The Committee considered a number of stakeholder comments regarding this recommendation. The wording of the recommendation has been amended to reflect the uncertainty around this effect estimate and the limited data availability in this area.
Royal College of Obstetricians and Gynaecologists	Full	25	22	Point 7. As the recommendation is already to 'consider milking the cord' and wait at least 30 seconds ' as in pg 16, does this still qualify for a research recommendation?	Thank you for your comment. The evidence base for this recommendation was not strong therefore the Committee decided to make a research recommendation to assess whether a clear benefit for babies' neurodevelopmental outcomes can be demonstrated when different cord clamping methods are compared.

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Royal College of Radiologists	Full	General	General	The Royal College of Radiologists (RCR) finds this guideline to be appropriate and evidence based. The issue that might affect radiologists is the use of transvaginal ultrasound to measure cervical length as a predictor of preterm delivery. The RCR thinks that the evidence has been extensively and appropriately reviewed and we have no issue with the recommendations regarding ultrasound. It clearly states the role of transvaginal ultrasound and expresses the need for this to be performed by appropriately trained and experienced personnel. The RCR supports the guideline with no issues.	Thank you for your comment. The issue of radiologists training will be sent to our Implementation Team for review.
Royal Devon and Exeter Hospital	Full	134	13	Will this guideline supersede the RCOG green top guideline on Preterm rupture of membranes, as they currently contradict each other. This would be confusing for clinicians. They advise not to perform CRP and FBC as surveillance as the detection of intrauterine infection is low	Thank you for your comment. The Committee recommend that clinicians use both a combination of clinical assessment and tests (C reactive protein, white blood cell count and measurement of fetal heart rate using cardiotocography) to diagnose intrauterine infection in women with P-PROM. The RCOG green- top guideline (No 44) discusses about the role of weekly performing CRP and FBC in isolation to detect intrauterine infection and this decision stands outside the remit of this guideline. In addition, updated evidence on the use of these tests was included in our evidence review compared to the evidence underpinned the RCOG guideline.
Royal Devon and Exeter Hospital	Full	141	34	I personally feel that the advice to perform a rescue cerclage up to 27+6/40 is inappropraite particularly if a woman has already received a	Thank you for your comment. The Committee based the upper limit of gestational age for this recommendation on the evidence reviewed.

				full course of antenatal steroids. A cervical suture placed in a women with a dilated cervix and bulging membranes is more likely to cause spontaneous rupture of membranes and possible complications including infection and cord prolapse.	However, the Committee acknowledged that the decision for rescue cerclage must be made only after a full discussion between the consultant obstetrician and the woman taking the woman's gestation and her own stated wishes into account.
Royal Devon and Exeter Hospital	Full	170	26	I completely disagree with the advice to treat all women who present with possible symptoms of threatened preterm labour at <30/40. The evidence given is that it is as cost effective. Many women present with symptoms and currently have a fetal fibrinectin test and are dischraged home if negative. I work in a level 2 district general hospital in the South West which is over 45 miles from the level 3 unit. Women who are <27/40 require intrauterine transfers out of the unit which has a cost implication with ambulance services and loss of midwifery staff (during transfer). I can not see that this is taken into account in the cost analysis. Also, often neonatal units are full and if this advice was followed there would be a significant increase in the need for IU transfers between units in our network which is spread over a large geographic area. We currently only transfer out if a quantative ffn level is >200. In addition, we currently use atosiban as our tocolytic and hence having to treat all these potential women with atosiban, magnesium and steroids would be a massive cost to our trust	Thank you for your comment. In recognition that some units may face additional costs associated with treatment - such as transfers out of unit - we have undertaken a sensitivity analysis to assess the impact that this would have on the cost-effectiveness thresholds for diagnostic accuracy at different gestational ages. The GDG did not feel that their recommendations needed to be amended as a result of this sensitivity analysis. We recognise that the recommendations to treat all women in suspected preterm labour below a gestational age of 30 weeks will increase costs but our analysis suggested that this additional cost is justified by the additional benefits. Our guidance does not recommend that women be treated with atosiban unless calcium channel blockers are contraindicated

				when very few of them will be in labour. Admitting all these potential women may be cost effective in your analysis, but it will increase antenatal work load of staff and those units who have only a few antenatal beds may struggle with capacity and may need to close their units. I feel this is a significant backwards step to the way we worked 15 years ago and further reflection need to be done as to why this is advised	
Royal Devon and Exeter Hospital	Full	170	29	As a unit who has used fetal fibrinectin for many years, I am concerned regarding the advice that cervical length is the first line screening tool. This would have a significant impact on many units: Cervical length scanning takes training and practice, a unit will need and USS machine with a transvaginal probe and the ability to print or store images for confirmation and audit. Trainees will required additional scanning competencies and although I am the labour ward lead Consultant I am not competent in cervical length scanning. Of the 8 Obstetricians who work in my unit, only 1 regularly scans cervical lengths. Fetal fibrinectin is a simple test which can be performed by junior doctors and midwives.	Thank you for your comment. These recommendations refer to diagnostic tools for preterm labour whereas screening for cervical length during pregnancy was outside the scope of this guideline. The Committee appreciates that this may involve change in practice however the evidence showed that a short cervical length (<15mm) appears to be the most reliable tool to diagnose women with preterm delivery at 48 hours. In terms of the other issues related to training for cervical length scanning and resource implications, these have been passed to the NICE implementation team to inform their support activities for this guideline.

				Quantative levels give more information and all the units in our network use this. The machine prints out a result sticker to aid audit and documentation.	
Royal Devon and Exeter Hospital	Full	196	4	I am concerned that yet again the gestation up to which we give steroids has changed. This guideline contradicts the RCOG guideline who advises steroids up to 34+6/40.	Thank you for your comment. The Committee decided upon a strong recommendation of the use of maternal corticosteroids for women from 26 to 33+6 weeks based on the clinical and cost effectiveness analyses. The Committee concluded that some of these benefits would be seen in babies born at lower and higher gestational ages, but that the evidence was less robust at these gestations. The extrapolation of findings to the groups outside the gestational age range of 26-34 weeks was more complex in terms of clinical effectiveness, which warranted less strong recommendations at gestations below 26 weeks and above 34 weeks. The different methodology followed by the two guidelines for example only RCTs were included in this NICE guideline whereas the RCOG guideline included both RCT and observational data may explain the difference in the upper limit of gestational age in the recommendation on maternal corticosteroids.
Royal Devon and Exeter Hospital	Full	261	35	I am confused that the guideline states consider tocolysis up to 34/40 but steroids up to 35+6/40. Tocolysis is usually only used to enable a woman to receive steroids or transfer out to another unit. Please can the gestations (which ever you choose) be the same to reduce confusion.	Thank you for your comment. The consideration of different interventions (tocolysis, corticosteroids, magnesium sulfate) for different gestational ages is driven by both the clinical and cost effectiveness analysis. The strong recommendations of 'offering tocolysis or maternal corticosteroids' align on the same

				Nifedipine is advised as the first line tocolytic - although I dispute this as it is not licensed and I am likely to continue to use atosiban. One of the many confusions is the doing regimen for nifedipine and hence please can this be added to the guidance to assist trusts.	gestational ages (between 26^{+0} and 33^{+6} weeks of pregnancy) for women who have intact membranes and are in suspected or diagnosed preterm labour. The only difference applies to the higher gestational ages (between 34^{+0} and 35^{+6} weeks) that maternal corticosteroids can be considered for women who are in suspected, diagnosed or established preterm labour, are having a planned preterm birth or have P PROM. A network meta-analysis was used to estimate treatment effectiveness of a number of tocolytics and this evidence was also incorporated into an assessment of cost effectiveness. This assessment suggested that calcium channel blockers would generate more benefit than oxytocin receptor blockers and that this would be achieved at a lower cost. The clinical evidence that drove this result was the NMA data on IVH in particular although calcium channel blockers were also ranked as a better treatment for neonatal mortality and RDS. The Committee decided that in terms of the calcium channel blockers, nifedipine should be preferred over nicardipine given the side profile of nicardipine. The recommendations on calcium channel blokcers were amended to include only nifedipine.Information on the recommended dosage of nifedipine was added as a footnote in the relevant recommendations. Recommended dosages are not usually included in the NICE recommendations. The guideline

					assumes that prescribers will use a medicine's summary of product characteristics to inform decisions made with individual patients. However, we appreciate that given that nifedipine has an unlicensed indication, guidance on the most optimal dose of this treatment has been included as a footnote in the recommendations and in the Evidence to recommendations section (Chapter 10) in the full guideline.
Royal Devon and Exeter Hospital	Full	292	27	What evidence do you have that a FSE causes trauma - neonates have venflons and CFAM monitoring placed in their scalps often after birth	Thank you for your comment. There was agreement among the clinicians in the Committee that this is a possible adverse event associated with fetal scalp electrodes.
Royal Devon and Exeter Hospital	Full	303	30	Please do not put in that preterm breech baby's should be delivered by LSCS. The evidence is poor and the caesarean section rates are increasing enough as it is. Just leave it out and leave it to the doctors discretion.	Thank you for your comment. The Committee was aware that in current clinical practice the selection of the mode of birth for preterm babies is often extrapolated from full-term babies as described in the NICE Guideline for Caesarean section (CS). For example if the baby has a breech presentation then CS would be the most favoured mode of birth. No evidence was found in this review to suggest that following current practice for term babies (e.g. delivery by CS for breech presentation) would be harmful to the baby.
Royal Devon and Exeter Hospital	Short	11	3	Contrary to your NICE medical technology guideline - Vision Amniotic Leak Detector to assess unexplained vaginal wetness in pregnancy. You have not included this in your guidance at all - I presume therefore that you	Thank you for your comments. We searched for the evidence on the diagnostic use of panty-liner with polymer-embedded strip for the diagnosis of P-PROM and we did not identify any study to match with our review protocol. The three studies

				have decided that they are not effective. I have never used them and do not plan to bring them into my practice anyway	that were included in NICE MTG15 (https://www.nice.org.uk/guidance/mtg15/chapter/3-Clinical-evidence) were excluded mainly because they referred to older gestational ages (more than 37 weeks) or they included results on different gestational ages without a subgroup analysis on women below 37 weeks (please refer to Appendix G.3 for further details). This research recommendation has now been withdrawn from the final version of full and NICE guideline.
Royal Devon and Exeter Hospital	Short	16	27	Use of magnesium until 34/40 - as previously suggested it would be less confusing to clinicians if the gestation of when steroids, tocolysis and magnesium could be the same.	Thank you for your comment. The upper limit of use of magnesium sulfate and tocolysis is the same. However, the Committee carefully considered the evidence around these interventions and concluded that different interventions need to be considered for different gestational ages.
University of Perugia	Short	11	12	Recent research found that 55% of patients with a cervical length measurement between 15 and 20 mm, and 21% of patients with cervical length between 20 and 25 mm, delivered within 7 days of presenting with signs or symptoms of threatened preterm labour. Therefore, a cut-off of 25 mm may be an optimal cut-off for the treatment pathway outlined in this section. We propose that the recommended cut-off be reconsidered to 25 mm.	Thank you for your comment. The Committee considered in detail the cut off point of 25 cm which was based on the reviewed evidence. The reasons are detailed in the Evidence to recommendations section.
University of Perugia	Short	15	18	Recent research compared the placental alpha microglobulin-1 (PAMG-1) test to the detection of fetal fibronectin	Thank you for your comment. Placental alpha microglobulin-1 (PAMG-1) testing was not included the protocol for this review out of the

				(fFN) and cervical length measurement using a cut-off of <25 mm in a large, multi-national cohort (n=203). Of note, it was found that while all tests had high Negative Predictive Values (96% vs. 87% vs 89%, PAMG-1, fFN, and cervical length, respectively), the PAMG-1 test was found to have a statistically superior Positive Predictive Value (PPV) compared to the others (76% vs. 29% vs 30%, PAMG-1, fFN, and cervical length, respectively). A test that offers fewer false positives would ultimately reduce unnecessary admissions and administration of potentially harmful therapeutics to patients. We propose that where fFN is recommended, the option for the PAMG-1 test is also indicated.	review scope and the related evidence has not been reviewed.
University of Perugia	Short	15	4	Recent research compared the placental alpha microglobulin-1 (PAMG-1) test to the detection of fetal fibronectin (fFN) and cervical length measurement using a cut-off of <25 mm in a large, multi-national cohort (n=203). Of note, it was found that while all tests had high Negative Predictive Values (96% vs. 87% vs 89%, PAMG-1, fFN, and cervical length, respectively), the PAMG-1 test was found to have a statistically superior Positive Predictive Value (PPV) compared to the others (76% vs. 29% vs 30%,	Thank you for your comment. The Committee considered in detail the cut off point of 25 cm which was based on the reviewed evidence. The reasons are detailed in the Evidence to recommendations section.

				PAMG-1, fFN, and cervical length, respectively). A test that offers fewer false positives would ultimately reduce unnecessary admissions and administration of potentially harmful therapeutics to patients. We propose that where fFN is recommended, the option for the PAMG-1 test is also indicated.	

Registered stakeholders: http://www.nice.org.uk/guidance/indevelopment/gid-cgwave0660/documents