NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

DIAGNOSTICS ASSESSMENT PROGRAMME

Diagnostics consultation document

Biomarker tests to help diagnose preterm labour in women with intact membranes

The National Institute for Health and Care Excellence (NICE) is producing guidance on using biomarker tests (Actim Partus, PartoSure and the Rapid fFN 10Q Cassette Kit) in the NHS in England. The diagnostics advisory committee has considered the evidence base and the views of clinical and patient experts.

This document has been prepared for public consultation. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the committee. NICE invites comments from registered stakeholders, healthcare professionals and the public. This document should be read along with the evidence base (the diagnostics assessment report and the diagnostics assessment report addendum).

The advisory committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound, and a suitable basis for guidance to the NHS?

Equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:

- could have a different effect on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology

Issue date: March 2018

- could have any adverse effect on people with a particular disability or disabilities.

Please provide any relevant information or data you have regarding such effects and how they could be avoided or reduced.

Note that this document is not NICE's final guidance on biomarker tests (Actim Partus, PartoSure and the Rapid fFN 10Q Cassette Kit). The recommendations in section 1 may change after consultation.

After consultation, the committee will meet again to consider the evidence, this document and comments from the consultation. After considering these comments, the committee will prepare its final recommendations, which will be the basis for NICE's guidance on the use of the technology in the NHS in England.

For further details, see the Diagnostics Assessment Programme manual.

Key dates:

Closing date for comments: 3 April 2018

Second diagnostics advisory committee meeting: 10 April 2018

1 Draft recommendations

1.1 There is currently insufficient evidence to recommend the routine adoption of the Rapid fFN (fetal fibronectin) 10Q Cassette Kit (at thresholds other than 50 ng/ml), Actim Partus and PartoSure biomarker tests to help diagnose preterm labour in women with intact membranes when transvaginal ultrasound measurement of cervical length is not available or not acceptable.

1.2 Further research is needed on the accuracy of the tests and their effect on clinical outcomes. Centres using the tests to help diagnose preterm labour in women with intact membranes are encouraged to take part in studies to address the research considerations (see sections 5.12 to 5.16). Data are needed on:

- the accuracy of the tests by gestational age
- how the tests affect clinical decision-making

- the effect of the tests on outcomes for mother and baby.

This guidance considers the use of fetal fibronectin at thresholds other than 50 ng/ml. Recommendations on qualitative fetal fibronectin with a fixed cut-off of 50 ng/ml are covered by NICE's guideline on preterm labour and birth, and are not affected by this guidance.

2 Clinical need and practice

The problem addressed

2.1 Biomarker tests (detecting placental alpha microglobulin-1 [PAMG-1] using PartoSure, phosphorylated insulin-like growth factor binding protein 1 [IGFBP-1] using Actim Partus and quantitative fetal fibronectin using the Rapid fFN 10Q Cassette Kit) are intended for use with other clinical information to assess the risk of preterm birth in women with symptoms of preterm labour who have intact amniotic membranes. These tests may be used instead of qualitative fetal fibronectin testing (using a threshold of 50 nanograms/millilitre [ng/ml]) or clinical assessment alone, when transvaginal ultrasound measurement of cervical length is not available or not acceptable. The results would help clinicians decide whether women can be sent home or need to be admitted to hospital for treatment to delay birth and improve neonatal outcomes.

2.2 The biomarker tests may result in more accurate diagnosis of preterm labour than tests currently used in NHS clinical practice. This could lead to improved health outcomes for women and their babies, and cost savings through reducing the length of hospital stay, reducing unnecessary hospital admissions, and minimising unnecessary transfers between hospitals. The tests may also

enable better resource planning based on the expected need for transfers between hospitals and neonatal intensive care.

2.3 The purpose of this assessment is to evaluate the clinical and cost effectiveness of biomarker tests (Actim Partus, PartoSure and quantitative fetal fibronectin using the Rapid fFN 10Q Cassette Kit) to help diagnose preterm labour in women with intact amniotic membranes when transvaginal ultrasound measurement of cervical length is not available or not acceptable.

The condition

Preterm labour and birth

2.4 Preterm labour is defined as regular contractions of the uterus resulting in changes in the cervix that start before 37 weeks of pregnancy. Preterm labour and birth is fairly common in the UK, with 8% of babies born before 37 weeks of pregnancy. However, less than 1% of babies are born between 22 and 28 weeks of pregnancy (Royal College of Obstetricians and Gynaecologists 2014).

2.5 The World Health Organization defines preterm birth based on gestational age:

- extremely preterm (less than 28 weeks of pregnancy)
- very preterm (28 to less than 32 weeks of pregnancy)
- moderate to late preterm (32 to less than 37 weeks of pregnancy).

2.6 Around 25% of preterm births are planned because of maternal factors such as pre-eclampsia, or fetal factors such as extreme growth restriction. But most preterm births occur because labour starts early naturally. Known risk factors for preterm labour include:

- previous preterm delivery
- twins or other multiple pregnancies
- genital tract infections
- preterm premature rupture of membranes
- problems with the uterus, cervix or placenta
- some chronic conditions, such as high blood pressure and diabetes
- smoking or drug use
- being underweight or overweight before pregnancy and
- stressful life events.

2.7 The Department of Health's toolkit for high quality neonatal services (2009) describes 3 types of hospital unit providing neonatal care for preterm babies:

- Special care units (level 1) provide special care for their local population, and may also provide some high dependency services.
- Local neonatal units (level 2) provide neonatal care for their local population, except for the sickest babies. Most babies over 27 weeks gestation will usually have full care, including short periods of intensive care, in their local neonatal unit.
- Neonatal intensive care units (level 3) are sited alongside specialist obstetric and fetomaternal medicine services. They provide the whole range of medical neonatal care for their local population, along with additional care for babies and their families referred from the neonatal network.

2.8 Clinical experts have noted that most babies born after 35 weeks of pregnancy will be looked after on postnatal wards with their mothers.

2.9 Preterm birth can potentially lead to short-term health problems in a newborn baby; for example, problems breathing and feeding, and higher risk of infection. The main concerns include:

- chronic lung disease at 36 weeks (corrected age)
- intraventricular haemorrhage
- necrotising enterocolitis
- retinopathy of prematurity.

2.10 Babies who are born early, particularly those born before 28 weeks of pregnancy, may have lifelong disabilities. These include physical disabilities, learning disabilities, behavioural problems, and visual and hearing problems.

The diagnostics and care pathways

Clinical assessment

2.11 NICE's guideline on preterm labour and birth states that women reporting symptoms of preterm labour who have intact membranes should have a clinical assessment.

2.12 If the clinical assessment suggests that the woman is in suspected preterm labour and she is 29 weeks plus 6 days pregnant or less, treatment for preterm labour is recommended.

2.13 Clinical experts have noted that, in practice, not all women in suspected preterm labour who are 29 weeks plus 6 days pregnant or less have treatment. They have stated that these women often have diagnostic testing because there are insufficient resources available to admit or transfer all women, there is concern about the effect of unnecessary treatment and women may prefer to avoid hospital admission and transfer when possible.

Transvaginal ultrasound measurement of cervical length

2.14 If the clinical assessment suggests that the woman is in suspected preterm labour and she is 30 weeks plus 0 days pregnant or more, transvaginal ultrasound measurement of cervical length should be considered to determine the likelihood of birth within 48 hours. If cervical length is more than 15 mm, it is unlikely that the woman is in preterm labour. If cervical length is 15 mm or less, preterm labour should be diagnosed and treatment offered.

2.15 NICE's guideline on preterm labour and birth notes that ultrasound scans should be done by healthcare professionals with training in, and experience of, transvaginal ultrasound measurement of cervical length. The guideline committee also noted that transvaginal ultrasound scanning is not routinely available across the NHS because equipment or expertise is limited, and that investment in technology and training may be needed for its universal implementation in the NHS. These limitations also increase the likelihood that biomarker testing will be carried out.

Fetal fibronectin testing

2.16 If transvaginal ultrasound measurement of cervical length is indicated but is not available or not acceptable, fetal fibronectin testing should be considered to determine the likelihood of birth within 48 hours for women who are 30 weeks plus 0 days pregnant or more. If the fetal fibronectin test result is negative (concentration 50 ng/ml or less) it is unlikely that the woman is in preterm labour. If the fetal fibronectin test result is positive (concentration more than 50 ng/ml), preterm labour should be diagnosed and treatment offered. NICE's guideline on preterm labour and birth notes that if a swab for fetal fibronectin testing is anticipated, it should be taken before any digital vaginal examination.

2.17 If a woman in suspected preterm labour who is 30 weeks plus 0 days pregnant or more does not have transvaginal ultrasound measurement of cervical length or fetal fibronectin testing to exclude preterm labour, treatment should be offered consistent with her being in diagnosed preterm labour.

2.18 A women in suspected preterm labour, but with a negative diagnostic test result suggesting that preterm labour is unlikely, may go home or may continue to be monitored and have treatment in hospital. If the woman goes home she is advised to return to hospital if symptoms suggesting preterm labour persist or recur.

2.19 NICE's guideline on preterm labour and birth notes that transvaginal ultrasound measurement of cervical length and fetal fibronectin testing should not be used in combination to diagnose preterm labour.

2.20 The European Association of Perinatal Medicine's recommendations on preterm labour and birth management state that 2 methods can be used to improve the accuracy of the diagnosis of preterm labour in women with symptoms:

- transvaginal ultrasound cervical length measurement
- measurement of biochemical markers in cervical-vaginal secretions (fetal fibronectin or PAMG-1 or IGFBP-1).

3 The diagnostic tests

Three interventions and 2 comparators were included in this assessment.

The interventions

Actim Partus

3.1 Actim Partus is a CE-marked qualitative immunochromatographic point-of-care test designed to detect phosphorylated IGFBP-1

(insulin-like growth factor binding protein-1) in cervical secretions during pregnancy. Phosphorylated IGFBP-1 is a protein made by the cells lining the uterus. When delivery is imminent, small amounts of phosphorylated IGFBP-1 leak into the cervix.

3.2 The Actim Partus test kit contains a sterile polyester swab for specimen collection, a tube of specimen extraction buffer and a dipstick in a sealed foil pouch. No other instrumentation or consumables are needed. The sample is collected from the cervical os during a sterile speculum examination. The results are available in 5 minutes or less. Two lines indicate a positive result; 1 line is a negative result that indicates the woman will not deliver within 7 to 14 days; if no lines appear the test is invalid.

3.3 The dipstick contains 2 monoclonal antibodies to human IGFBP-1. One is bound to blue latex particles (the detecting label). The other is immobilised on a carrier membrane to catch the complex of antigen and latex-labelled antibody and indicate a positive result. If phosphorylated IGFBP-1 is present in the sample it binds to the antibody labelled with latex particles. The particles flow to the results area of the dipstick, and if phosphorylated IGFBP-1 is bound to them, they bind to the catching antibody. A test line will appear if the concentration of phosphorylated IGFBP-1 in the sample exceeds the detection limit of the test. A control line confirms correct performance of the test.

3.4 Actim Partus is for use in pregnant women with signs and symptoms of preterm labour and intact amniotic membranes, after 22 weeks plus 0 days of pregnancy. The test can be used if vaginal infections, vaginal medications and semen are present, but active vaginal bleeding may cause a false positive result. The test has a limit of detection of 10 ng/ml and a measuring range of 10 to 8,000 ng/ml.

PartoSure

3.5 PartoSure is a CE-marked qualitative lateral flow, immunochromatographic point-of-care test designed to detect placental alpha microglobulin-1 (PAMG-1) in vaginal secretions during pregnancy. PAMG-1 is a protein released from the lining of the uterus into the amniotic cavity throughout pregnancy. It is found in very high concentrations in amniotic fluid and in very low concentrations in normal vaginal discharge. Studies have demonstrated a strong correlation between the presence of PAMG-1 in cervicovaginal discharge and imminent delivery.

3.6 The PartoSure test kit contains a test strip, a vaginal swab and a plastic vial containing a solvent solution. No other instrumentation or consumables are needed. The sample may be collected with or without a speculum. The results are available in 5 minutes or less. Two lines indicate a positive result and a high risk of delivery within 7 days; 1 line indicates a negative result and a low risk of delivery within 7 to 14 days; no lines indicate an invalid result.

3.7 The test strip has a reactive area containing monoclonal anti-PAMG-1 antibodies bound to a gold particle (the detecting label). The sample flows through the reactive area and if PAMG-1 is present it binds to the anti-PAMG-1 antibodies, forming an antigen-antibody complex. This complex then flows to the test region of the strip where it is immobilised by a second anti-PAMG-1 antibody. A test line appears if the concentration of PAMG-1 in the sample exceeds the detection limit of the test. Unbound antigen-antibody complexes continue to flow along the test strip and are immobilised by a second antibody, leading to the appearance of the internal control line.

3.8 PartoSure is for use in pregnant women with signs and symptoms of preterm labour, intact amniotic membranes and minimal cervical

dilatation (3 cm or less), between 20 weeks plus 0 days and 36 weeks plus 6 days of pregnancy. The test can be used if vaginal infections, urine, semen and trace amounts of blood are present, but should not be used if there is significant discharge of blood. It can also be used shortly after a vaginal examination. The test has a limit of detection of 1 ng/ml and a measuring range of 1 to 40,000 ng/ml.

Rapid fFN 10Q Cassette Kit

3.9 The Rapid fFN 10Q Cassette is a CE-marked test for use in the PeriLynx System or the Rapid fFN 10Q System. It is designed for the quantitative detection of fetal fibronectin in cervicovaginal secretions to assess the risk of preterm delivery within 7 to 14 days. Fetal fibronectin is an adhesive glycoprotein that holds the membranes of the uterus to the fetal membranes. After 35 weeks of pregnancy, it begins to break down naturally, and is detectable in vaginal secretions. Fetal fibronectin detected between 22 and 35 weeks of pregnancy is an indicator of preterm birth risk.

3.10 NICE's guideline on preterm labour and birth recommends fetal fibronectin testing to determine the likelihood of birth within 48 hours for women who are 30 weeks plus 0 days pregnant or more, if transvaginal ultrasound measurement of cervical length is indicated but is not available or not acceptable. The guideline recommends a threshold of 50 ng/ml to interpret the test results. However, clinical experts have noted that a quantitative fetal fibronectin test would enable other thresholds to be used.

3.11 The Rapid fFN 10Q Cassette test can be done near the woman. In addition to the test kit an analyser, printer, Rapid fFN Control Kit, QCette (quality control device) and pipette are needed. The sample is collected from the posterior fornix of the vagina during a speculum examination. It is incubated in the analyser for 7 minutes

and then analysed, which takes 2 to 3 minutes. The analyser reports fetal fibronectin concentrations ranging from 0 to 500 ng/ml; concentrations greater than 500 ng/ml are displayed as 'greater than 500 ng/ml'. The instructions for use do not give any thresholds, therefore laboratories would need to set and validate their own thresholds. Internal controls are done automatically with every test.

3.12 The Rapid fFN 10Q Cassette is for use in pregnant women with signs and symptoms of early preterm labour, intact amniotic membranes, and minimal cervical dilatation (less than 3 cm), between 22 weeks plus 0 days and 35 weeks plus 6 days of pregnancy. Assay interference from blood, bacteria, bilirubin and semen has not been ruled out. However, a negative test result (less than 10 ng/ml) in the presence of blood or semen is valid. Also, the fetal fibronectin concentration may be influenced by cervical disruption caused by, but not limited to, sex, digital cervical examination, or vaginal probe ultrasound.

The comparators

Fetal fibronectin

3.13 Fetal fibronectin testing, at a threshold of 50 ng/ml, is recommended in NICE's guideline on preterm labour and birth (see sections 2.16 to 2.19 of this document).

3.14 The fetal fibronectin test is available as a quantitative enzyme-linked immunosorbent assay (ELISA), and as a qualitative membrane immunosorbent assay. Examples include:

- Fetal Fibronectin Enzyme Immunoassay; a quantitative assay with a recommended threshold of 50 ng/ml (Hologic)

- Rapid fFN for the TLilQ System; a qualitative immunochromatographic assay with a limit of detection of 50 ng/ml (Hologic)
- QuikCheck Fetal Fibronectin Test; a qualitative test with a limit of detection of 50 ng/ml (Hologic).

Clinical assessment

3.15 Clinical assessment is described in NICE's guideline on preterm labour and birth and in sections 2.11 to 2.13 of this document.

4 Evidence

The diagnostics advisory committee (section 7) considered evidence on the biomarker tests (PartoSure, Actim Partus and Rapid fFN 10Q Cassette Kit) for diagnosing preterm labour from several sources. Full details of all the evidence are in the committee papers.

Clinical effectiveness

4.1 The external assessment group (EAG) did 2 systematic reviews of the clinical effectiveness evidence for Actim Partus, PartoSure and quantitative fetal fibronectin using the Rapid fFN 10Q Cassette Kit; 1 for diagnostic accuracy and 1 for clinical outcomes.

4.2 The EAG also did a non-systematic update of their report to include 7 new studies submitted for PartoSure with stakeholder comments on the diagnostics assessment report.

4.3 For the diagnostic accuracy review, studies were included if:

- they recruited women with signs and symptoms of preterm labour who were not in established labour and who had intact amniotic membranes
- the population was described as preterm

- twin or multiple pregnancies made up 20% or less of the total population recruited
- at least 1 index test was reported and at least 1 of the following reference standards or comparators was included:
  - preterm delivery within 48 hours
  - preterm delivery within 7 days
  - clinical assessment of symptoms
  - fetal fibronectin at a threshold of 50 ng/ml.
- they were prospective or retrospective diagnostic accuracy studies with random or consecutively recruited women; both single- and two-gate[1] designs were eligible.

4.4 All studies included in the diagnostic accuracy review were appraised using the QUADAS-2 tool. In total, 20 studies met the inclusion criteria for the diagnostic accuracy review.

4.5 The EAG also searched for studies in which clinical outcomes were reported, but did not identify any studies. The inclusion criteria were restricted to controlled studies only because the EAG considered that uncontrolled study designs are likely to be susceptible to bias.

Study characteristics

4.6 Of the 20 diagnostic accuracy studies, data for more than 1 index test were reported in 2 studies (Hadzi-Lega et al. 2017, APOSTEL-1 2016), 16 studies assessed Actim Partus, 4 assessed PartoSure and 2 assessed fetal fibronectin at thresholds other than 50 ng/ml (APOSTEL-1, EUIFS 2016). All 20 studies assessed the index tests against a reference standard of preterm delivery within 7 days, and 7 studies also assessed the index tests against a reference standard of preterm delivery within 48 hours.

[1] A single-gate study recruits patients whose disease status is unknown before testing (a consecutive series) whereas a two-gate study recruits patients with the target condition and patients who do not have the target condition (a case-control study).

4.7 The characteristics of women in the study varied and this introduced heterogeneity:

- Mean maternal age was 25 to 31 years.
- The proportion of multiple gestations was 0% to 20%.
- The mean number of previous term pregnancies was 0.4 to 2.9 per person.
- The proportion of previous preterm deliveries was 0% to 30%.
- The proportion of previous miscarriages was 4% to 27%.
- The prevalence of preterm birth within 7 days was 1.7% to 73.3%.
- The prevalence of preterm birth within 48 hours was 2.4% to 58.3%.
- Gestational age was 20 weeks to 37 weeks.

4.8 The reporting of whether delivery was spontaneous or as a result of medical intervention varied between studies. Only 11 studies provided details on delivery; in 4 the authors stated that they excluded women from test accuracy calculations if birth occurred because of medical intervention before the 7-day or 48-hour reference standard.

Diagnostic accuracy

Delivery within 7 days: Actim Partus

4.9 In the 16 studies that included data for Actim Partus, the prevalence of birth within 7 days of testing was 1.7% to 73.3%. Across the studies sensitivity estimates were 33.3% to 94.7%. The 3 studies (Cooper 2012, Danti 2011, Riboni 2011) with the lowest sensitivity estimates also had a lower prevalence of preterm birth (1.7% to 6.7%) than the other studies (9.8% to 73.3%). Specificity was 50.0% to 93.5%. The EAG did not identify any major differences in methods or participant characteristics in the 3 studies

with the lowest specificity estimates. The pooled analysis of these 16 studies estimated a sensitivity of 77% (95% confidence interval [CI] 68% to 83%) and a specificity of 81% (95% CI 76% to 85%).

4.10 There were 6 studies that tested each sample with both Actim Partus and fetal fibronectin at a threshold of 50 ng/ml. Using delivery within 7 days as the reference standard, sensitivity for Actim Partus was lower than for fetal fibronectin in 1 study (APOSTEL-1 2016), higher in 2 studies (Ting 2017, Tripathi 2016) and the same for both tests in the remaining 3 studies (Cooper 2012, Eroglu 2007, Riboni 2011). Specificity was higher for Actim Partus than for fetal fibronectin in 4 of the 6 studies, and lower in the 2 remaining studies (Cooper, Tripathi). Cooper only reported test accuracy results for a proportion of the total Actim Partus group (58 fewer women had results for the qualitative fFN test).

4.11 In response to stakeholder comments on the diagnostics assessment report the EAG updated the diagnostic accuracy estimates for Actim Partus to include 18 studies identified by a company. The updated pooled sensitivity decreased compared with the original review; from 77% (95% CI 68% to 83%) to 74.3% (95% CI 64.2% to 82.3%) and specificity increased slightly from 81% (95% CI 76% to 85%) to 81.2% (95% CI 76.2% to 85.4%).

Delivery within 7 days: PartoSure

4.12 In the 4 studies that included diagnostic accuracy for PartoSure, the prevalence of birth within 7 days of testing was 2.4% to 17.2%. Specificity was similar across studies, 90.2% to 97.5%, but sensitivity was 0% to 100%. Werlen et al. (2015) reported 0% sensitivity because only 1 of 41 women tested positive and this was a false positive. The pooled analysis of the 4 studies estimated a sensitivity of 83% (95% CI 61% to 94%) and a specificity of 95% (95% CI 89% to 98%).

4.13 Nikolova et al. (2015) assessed fetal fibronectin at a threshold of 50 ng/ml and PartoSure in the same samples (66 of the total 203 women). Against the 7-day reference standard, sensitivity for PartoSure was 80% (95% CI 63.1 to 91.6) and for fetal fibronectin it was 50% (95% CI 21.1% to 79.0%). Specificity for PartoSure was 94.6% (95% CI 90.1% to 97.5%) and for fetal fibronectin it was 72.2% (95% CI 58.4% to 83.5%).

4.14 In response to stakeholder comments on the diagnostics assessment report the EAG updated the diagnostic accuracy estimates for PartoSure to include 9 studies identified by a company. The updated pooled sensitivity decreased compared with the original review; from 83% (95% CI 61% to 94%) to 68.5% (95% CI 51.2% to 81.9%) and pooled specificity slightly increased from 95% (95% CI 89% to 98%) to 96.6% (95% CI 95.1% to 97.6%).

Quantitative fetal fibronectin

4.15 There were 2 studies (APOSTEL-1 2016, EUIFS 2016) that included diagnostic accuracy for quantitative fetal fibronectin. The prevalence of preterm birth within 7 days was 10.5% (EUIFS) to 19.7% (APOSTEL-1). In both studies sensitivity decreased as the threshold increased and specificity increased as the threshold increased.

4.16 The EAG reviewed 1 unpublished study (Ravi et al.) that included evidence for quantitative fetal fibronectin, submitted with stakeholder comments on the diagnostics assessment report. This presented sensitivity values lower than APOSTEL-1 and EUIFS, but higher specificity values. The details of the study cannot be reported here because they are confidential.

Delivery within 48 hours: Actim Partus

4.17 There were 6 studies that assessed the diagnostic accuracy of Actim Partus. The prevalence of delivery within 48 hours of testing was 5.3% to 58.3%. Sensitivity was 65.7% to 100.0% and specificity was 56.0% to 82.4%. The pooled analysis of the 6 studies estimated a sensitivity of 87% (95% CI 74% to 94%) and a specificity of 73% (95% CI 62% to 82%).

Delivery within 48 hours: PartoSure

4.18 Only 1 study (Werlen et al. 2015) assessed the diagnostic accuracy of PartoSure against the 48-hour reference standard. The prevalence of preterm birth was 2.4%. Sensitivity was 0% (95% CI 0% to 97.5%) and specificity was 97.5% (95% CI 86.8% to 99.9%). Sensitivity was 0% because only 1 of 41 women tested positive and this was a false positive.

Accuracy of comparator (fetal fibronectin with a threshold 50 ng/ml)

4.19 The EAG identified studies in the diagnostic accuracy systematic review that included data for fetal fibronectin at a threshold of 50 ng/ml. The generalisability of these data was assessed by comparing them with results from 3 recently published systematic reviews of fetal fibronectin.

4.20 Of the 20 studies included in the diagnostic accuracy review, 8 included accuracy data for quantitative fetal fibronectin at 50 ng/ml. Of these, 2 studies (APOSTEL-1 2016, EUIFS 2016) used a quantitative fetal fibronectin test, 3 used the QuikCheck qualitative fetal fibronectin test (Eroglu 2007, Nikolova 2015, Tripathi 2016), 1 used an ELISA-based laboratory test (Riboni 2011), and in the remaining 2 studies (Cooper 2012, Ting 2007) it was not clear which fetal fibronectin test was used.

4.21 For the 8 studies looking at the diagnostic accuracy of fetal fibronectin at a threshold of 50 ng/ml against a 7-day reference standard, sensitivity was 23.8% to 91.3% and specificity was 62.2% to 99.1%. These results were similar to those from the 3 existing literature reviews.

Diagnostic accuracy data informing the economic model

4.22 The EAG concluded that there was too much heterogeneity in the pooled results to use them for indirect comparisons between tests in the economic modelling. It decided to prioritise studies that reported results for more than 1 test in the same population. Therefore, 2 studies (APOSTEL-1 2016, Hadzi-Lega et al. 2017) were used in the base case for the economic model.

Cost effectiveness

Review of economic evidence

4.23 The EAG did a systematic search to identify studies that investigated the cost effectiveness of Actim Partus, PartoSure and quantitative fetal fibronectin. One study (Gibson et al. 2013) assessed the effect of a fetal fibronectin test (at thresholds of 10, 50, 200 and 500 ng/ml) on the use of antenatal corticosteroids. There were a further 3 observational cost–minimisation studies that reported costs and resource use data, but these were published over 10 years ago and it was not certain whether the protocols used in the studies reflect current clinical practice.

4.24 The EAG also identified 6 economic models. A cost–minimisation modelling approach was used in 2 studies. Chuck and Nguyen (2015) looked at the cost of adopting fetal fibronectin in Alberta, Canada and estimated that introducing the test between 2008 and 2013 increased costs by US$4 million. Conversely, the Deshpande et al. (2013) study was done in the UK and found that the rapid

fetal fibronectin test saved the NHS £23.88 per patient compared with clinical examination alone.

4.25 Cost-effectiveness modelling was used in 3 studies (Boyd et al. 2011, Mozurkewich et al. 2000 and van Baaren et al. 2017) and in NICE's guideline on preterm labour and birth. The NICE guideline model was hypothetical and assessed what the specificity and sensitivity of the tests (cervical length measurement by ultrasound, Actim Partus and fetal fibronectin) would need to be for them to be considered cost effective compared with a no-test, treat-all strategy. It accounted for the effect of test accuracy on cost effectiveness at different gestational ages and found that testing was not cost effective below 30 weeks of pregnancy. The main assumptions in the NICE guideline model were:

- the choice of diagnostic strategy had no significant effect on the mother's health outcomes
- clinicians did not deviate from the diagnostic protocol
- neonatal morbidity outcomes were based on respiratory distress syndrome and intraventricular haemorrhage
- the lifetime quality of life and costs are the same for both full-term and preterm infants.

Modelling approach

4.26 The EAG developed a de novo economic model to evaluate the cost effectiveness of quantitative fetal fibronectin using the Rapid fFN 10Q Cassette Kit at thresholds other than 50 ng/ml, Actim Partus and PartoSure compared with fetal fibronectin at 50 ng/ml. The model was based on the NICE guideline model, but several parameters used to populate the model were updated. The base case took the perspective of the NHS and personal social services and had a lifetime time horizon (100 years). A discount rate of 3.5% was applied to both costs and effects.

4.27 The population was women with intact membranes presenting with symptoms of threatened preterm labour between 24 and 36 weeks' of pregnancy. It was assumed that, before entering the model, a clinical assessment had been done that could not rule out preterm labour.

Model structure

4.28 A decision tree structure that included a diagnostic phase followed by treatment and long-term outcomes was used. The model started with an assessment of preterm labour, and then modelled the decision of whether to admit to hospital or discharge home, and whether to offer corticosteroids. It evaluated:

- the interventions (Actim Partus, PartoSure, and quantitative fetal fibronectin at thresholds of 10, 200 and 500 ng/ml)
- a no-test, treat-all strategy, which assumes that all women entering the model are admitted to hospital
- the comparator (fetal fibronectin at a threshold of 50 ng/ml).

Longer-term costs and quality-adjusted life years (QALYs) were then calculated for each branch of the decision tree.

Model inputs

4.29 The model was populated with data from the diagnostic accuracy review, published literature and expert opinion. Estimates of diagnostic accuracy for fetal fibronectin and Actim Partus were taken from APOSTEL-1, which included a direct comparison of the 2 tests. None of the studies directly compared PartoSure with fetal fibronectin, so diagnostic accuracy was estimated using data from APOSTEL-1 and Hadzi-Lega et al. Scenario analyses were done using data from alternative sources: Cooper et al. 2012, Abbott et al. 2013 and an EAG meta-analysis. The diagnostic accuracy estimates are in table 1.

Table 1 Diagnostic accuracy values used in the economic model

Study	Diagnostic test (threshold)	Sensitivity %	Specificity %
Bruijn et al. 2016 (APOSTEL-1), n=350 (base case)	fFN (10 ng/ml)	0.957	0.423
	fFN (50 ng/ml)	0.913	0.648
	fFN (200 ng/ml)	0.710	0.836
	fFN (500 ng/ml)	0.420	0.957
	Actim Partus	0.783	0.893
Hadzi-Lega et al. 2017 n=57 (base case)	PartoSure	0.833	0.902
	Actim Partus	0.833	0.765
Cooper et al. 2012 n=349 (scenario)	Actim Partus	0.333	0.741
	fFN (50 ng/ml)	0.333	0.898
Abbott et al. 2013 n=299 (scenario)	fFN (10 ng/ml)	0.778	0.576
	fFN (50 ng/ml)	0.778	0.790
	fFN (200 ng/ml)	0.778	0.931
	fFN (500 ng/ml)	0.556	0.972
EAG meta-analysis n=963 (scenario)	Actim Partus	0.832	0.879
	fFN (50 ng/ml)	0.683	0.872
Abbreviations: fFN, fetal fibronectin; ng/ml, nanograms per millilitre			

Costs

4.30 The following costs, from companies, published literature and routine sources of NHS costs, were used in the model:

- fetal fibronectin test: £66 (includes 15 minutes of midwife time)
- Actim Partus test: £35 (includes 10 minutes of midwife time)
- PartoSure test: £52 (includes 10 minutes of midwife time)
- maternal steroid injection: £5
- tocolytics (atosiban plus infusion equipment): £362
- inpatient hospital stay: £1,325
- in utero transfer: £965
- long-term healthcare costs of intraventricular haemorrhage: £114,648
- neonatal hospital costs for respiratory distress syndrome: £5,587
- neonatal hospital costs: infant dies before discharge: £22,834.

Health-related quality of life and QALY decrements

4.31 Health-related quality-of-life estimates were included for neonates in the base case, and a scenario analysis also included maternal health-related quality-of-life estimates. A utility for severe persistent asthma was applied to 56% of children with respiratory distress syndrome based on clinical expert opinion. Utilities used in the model are shown in table 2.

Table 2 Utilities used in the economic model

Variable	Patient	Source	Utility
'Severe' RDS (severe persistent asthma used as proxy)	Child	Carroll and Downs 2009	0.85
IVH grades 3 to 4 (moderate cerebral palsy used as proxy)	Child	Carroll and Downs via Bastek et al. 2012	0.76
Death	Child	Vandenbussche et al. 1999	0
Preterm survivor	Child	Cooke 2004	0.879
Mother with previous adverse child outcome	Mother	Couto et al. 2009	0.644
Mother with no adverse child outcome	Mother	Couto et al. 2009	0.834
Abbreviations: IVH, intraventricular haemorrhage; RDS, respiratory distress syndrome			

Base-case results

4.32 The following assumptions were applied in the base-case analysis:

- The population entered the model after a clinical examination which did not rule out preterm labour.
- QALY outcomes were the same for false positives (who did not deliver before the reference standard), true negatives and false negatives.
- All treatment decisions were driven by the test result, and clinical judgement did not override this.
- Diagnostic accuracy was equivalent across all gestational ages.

- The prevalence of preterm birth within 7 days of testing was 3%, and the preterm birth rate was 12.1%.
- Antenatal corticosteroids were only effective within 7 days of delivery; infants born more than 7 days after treatment did not benefit.
- In utero transfers were only available for women presenting to a level 1 or 2 hospital at less than 28 weeks of pregnancy.
- Tocolysis was used for all in utero transfers at less than 28 weeks of pregnancy.
- Only intraventricular haemorrhage resulted in longer-term costs.
- Neonates who survived beyond 1 year had a long-term quality of life equivalent to the average for preterm survivors.

4.33 The base-case results were given for groups of women presenting at 33, 30 and 26 weeks of pregnancy. Results were also stratified according to the level of neonatal care available at the place of birth.

4.34 Base-case results for women presenting at 30 weeks of pregnancy at a level 2 hospital are shown in table 3. Most tests were cheaper and less effective than fetal fibronectin 50 ng/ml, apart from a treat-all strategy and fetal fibronectin at 10 ng/ml, which resulted in very small QALY gains and additional cost. Many of the tests were cheaper and less effective than the comparator; this means that the results are in the south-west quadrant of the cost-effectiveness plane.

Table 3 Base-case results for women presenting at 30 weeks of pregnancy at a level 2 hospital

			Versus fFN 50 ng/ml
Test	**Total costs (£)**	**Total QALYs**	**ICER (£ per QALY)**
PartoSure	4,895	22.010	81,925*
fFN 500 ng/ml	5,004	21.992	17,013*
Actim Partus	5,055	22.010	56,033*
fFN 200 ng/ml	5,159	22.006	25,213*
fFN 50 ng/ml	5,401	22.016	–
fFN 10 ng/ml	5,690	22.018	140,270
Treat all	6,171	22.020	186,757

* ICER represents cost saved per QALY lost, it is in the south-west quadrant of the cost-effectiveness plane

Abbreviations: fFN, fetal fibronectin; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; ng/ml, nanograms per millilitre

4.35 The incremental cost-effectiveness ratios (ICERs) for women in a level 2 hospital at 26 weeks of pregnancy reduced compared with the base-case results. This reduction applied to tests that were cheaper and less effective than the comparator (which became less cost effective) and to tests that cost more and were more effective than the comparator (which became more cost effective).

4.36 The ICERs for women in a level 2 hospital at 33 weeks of pregnancy increased compared with the base-case results. This increase applied to tests that were cheaper and less effective than the comparator (which became more cost effective) and to tests that cost more and were more effective than the comparator (which became less cost effective).

4.37 The EAG updated the results of the analyses using data from 2 additional studies (Nikolova et al. and Wing et al.) that were highlighted in stakeholder comments on the diagnostics assessment report. For PartoSure compared with fetal fibronectin at 50 ng/ml the addition of accuracy data from these studies

resulted in a greater QALY loss than was seen in the EAG's base case. However, using the accuracy estimates from Nikolova et al. resulted in greater cost savings and using the accuracy estimates from Wing et al. resulted in lower cost savings.

Alternative scenario analyses

4.38 The effect of changing assumptions about the accuracy of the tests was explored in 2 scenario analyses. Alternative diagnostic accuracy data from Cooper et al. (2016) were used to calculate ICERs for Actim Partus compared with fetal fibronectin at a threshold of 50 ng/ml. In this analysis Actim Partus was dominated by fetal fibronectin (that is, fetal fibronectin was more effective and less expensive). Also, alternative diagnostic accuracy data were obtained for fetal fibronectin at thresholds of 10, 200 and 500 ng/ml compared with fetal fibronectin at a threshold of 50 ng/ml from an unpublished study by Abbott et al. The results of this analysis are academic in confidence.

4.39 The scenario analysis with the greatest effect on the ICERs was limiting the time horizon of the analysis to the first year after birth. The ICERs became less favourable for all interventions and increased by more than 20 times the base-case value.

4.40 Assuming that antenatal steroids have partial benefits if given more than 7 days before birth also had a considerable effect on all the ICERs. This produced more favourable ICERs for PartoSure, the treat-all strategy and fetal fibronectin at a threshold of 10 ng/ml. However, it produced less favourable ICERs for Actim Partus and fetal fibronectin at thresholds of 200 ng/ml and 500 ng/ml.

Sensitivity analyses

4.41 Deterministic sensitivity analyses were done by varying the base-case parameters by 20%. These analyses found that the ICERs

were most sensitive to changes in health-related quality of life of preterm survivors. Other parameters affecting the ICERs were cost of hospital admission, prevalence of preterm birth within 7 days, effectiveness of steroid treatment and baseline mortality risk.

4.42 The EAG also ran probabilistic sensitivity analyses and presented the results as cost-effectiveness acceptability curves. Probabilistic ICERs were not presented.

5 Committee discussion

Care pathway

5.1 The committee discussed current practice for diagnosing and managing preterm labour in women with intact membranes. The clinical experts explained that the incidence of birth before 37 weeks of pregnancy in the UK was around 8% and an estimated 50,000 to 60,000 babies are born preterm each year. Women with suspected preterm labour have a clinical assessment and a fetal fibronectin (fFN) test is commonly used to help determine whether labour is established. Although NICE's guideline on preterm labour and birth recommends transvaginal ultrasound as the preferred diagnostic option, this is not available everywhere. Also, it needs healthcare professionals with appropriate training to perform and interpret the scan. The committee noted that the NICE guideline recommends that all women who present at less than 30 weeks of pregnancy have treatment based on clinical assessment alone, but heard that in practice many of these women also have a fFN test, or another test. The committee concluded that for women who present at 30 weeks or above, the most appropriate comparator was fFN at a threshold of 50 ng/ml. For women who present at less than 30 weeks, a treat-all management pathway and fFN testing should be considered to reflect variation in current practice.

Patient experience

5.2 The committee discussed the effect that suspected preterm labour can have on pregnant women and their partners. The patient experts explained that preterm labour is associated with substantial anxiety, particularly when a diagnosis is difficult to confirm. For example, women who have a false positive result might be transferred to a higher level hospital unnecessarily. The committee noted that understanding whether preterm labour is established is of considerable importance to pregnant women. It heard about the importance of communicating the risks and benefits associated with the different diagnostic options so that women are able to understand the test results. The possibility of false negative results should also be explained and women given reassurance that they can return to hospital if they feel that their symptoms have not resolved despite a negative test result.

Clinical effectiveness

Diagnostic accuracy

5.3 The committee discussed the studies included in the diagnostic accuracy review. It noted that 16 studies were available for Actim Partus, 2 studies were available for fFN using thresholds of 10 ng/ml, 200 ng/ml and 500 ng/ml and 4 studies were available for PartoSure. It acknowledged that 7 studies had been submitted by 1 company after the diagnostics assessment report had been completed. The variation in estimates of diagnostic accuracy from the additional studies was similar to that seen in the studies assessed by the external assessment group (EAG), and so added further uncertainty to the results.

5.4 The committee noted that the studies included in the review were done outside of the UK. It understood that the management of preterm labour was likely to vary from country to country and that

this had the potential to affect test accuracy. The EAG was unable to explore the likely effect of this variation because many studies did not provide details on how preterm labour was managed, particularly whether the delivery was spontaneous or induced for medical reasons. This variable had a direct effect on how the reference standards of birth within 48 hours or 7 days of testing were interpreted, and on determining true and false positive index test results. The committee concluded that because of shortcomings in how the results of the included studies were reported, it was not able to judge whether the results were generalisable to the NHS.

5.5 The committee considered the results of the EAG's diagnostic accuracy meta-analyses, and noted that the accuracy estimates differed substantially between studies. The studies included in the review recruited a wide range of women and the EAG raised concerns that there was substantial heterogeneity in a number of important patient characteristics, including gestational age, multiple pregnancy and history of preterm birth. The EAG explained that it did not consider the pooled diagnostic accuracy results to be reliable, because variables that may affect test accuracy such as the use of tocolytics, mode of delivery and gestational age were not reported in many of the studies. Therefore the EAG had not been able to explore which variables were driving the differences in test accuracy estimates between studies. More detailed reporting of the results would be needed for the EAG to have confidence in the pooled diagnostic accuracy results. The EAG further cautioned that the confidence intervals around the pooled estimates were unlikely to sufficiently characterise the uncertainty in the included studies. The committee concluded that there was substantial uncertainty in the pooled results. It also considered that there was a need for

further robust diagnostic accuracy studies which aim to address the methodological limitations identified by the EAG (see section 5.12).

5.6 The committee questioned whether gestational age was likely to affect the accuracy of the tests. It noted that the EAG had not been able to do subgroup analyses by gestational age because insufficient data were available. The clinical experts explained that it was plausible that test accuracy could vary by gestational age, because the causes of preterm labour might be different at certain gestational ages. Although the biomarkers detected by each of the tests are thought to be associated with a common preterm labour biochemical signal, their expression may differ depending on the cause of preterm labour. For example, the biomarkers may perform differently in women with preterm labour caused by placental bleeding compared with preterm labour caused by ascending infection. The committee concluded that further evidence is needed on the effect of gestational age on test accuracy (see section 5.14).

5.7 The committee discussed how the test results would be used to guide clinical management. The EAG explained that it had not found any studies which reported the effect of the tests on decision-making, but noted that its search had been restricted to controlled study designs only. The clinical experts explained that biomarker test results are used as an aid to decision-making and are not intended to provide a final decision on the treatment pathway for a woman with symptoms of preterm labour. The importance given to biomarker test results varies in practice depending on the presenting symptoms and clinical history. The clinical experts noted that negative results are often interpreted with caution. They highlighted a study (Dutta et al. 2011) which looked at clinicians' compliance with test results and found that 20% to 30% of women with negative test results had corticosteroid treatment as if they were in preterm labour. The committee considered that it was

uncertain how differences in test accuracy might translate to differences in patient outcomes in practice, particularly quality of life for the mother and child, and concluded that further research was needed to collect these data (see section 5.15 and 5.16).

Cost effectiveness

5.8 The committee noted that because the EAG considered the results of the meta-analyses to be unreliable, the EAG preferred to use data from studies comparing at least 2 of the biomarker tests in the same population to assess their relative accuracy in the economic model. The committee understood that this approach was taken to minimise bias in the accuracy estimates, which might arise because of differences in study design. It noted that no studies assessed all 3 biomarker tests in the same population. The EAG used diagnostic accuracy results from 2 studies (APOSTEL-1 and Hadzi-Lega et al. 2017) in the base-case analysis, although this was subsequently revised to include additional studies for PartoSure. The clinical experts noted that the studies were unlikely to be representative of women in NHS clinical practice. In APOSTEL-1 there was a high proportion of women who would be considered high risk, with 23% of women having previous preterm delivery. The clinical experts explained that this would be lower in practice. Also, Hadzi-Lega et al. included a small number of women (n=57) and was carried out in Macedonia, where the care pathway was likely to vary considerably compared with NHS clinical practice. The committee concluded that the women in the studies included in the model (APOSTEL-1 and Hadzi-Lega et al.) did not represent those seen in NHS clinical practice.

5.9 The committee was aware that the EAG's de novo model comprised a decision tree, which took account of both the neonatal care options available at a hospital (levels 1 to 3) and gestational

age. The EAG explained that all tests included in the model were compared with no treatment. The committee questioned the quality-adjusted life year (QALY) payoffs that had been attached to each of the test outcomes. The EAG explained that because of a lack of clinical outcome data, equal QALYS had been assumed for true negative, false positive and false negative results. The patient and clinical experts noted that this approach did not adequately capture the outcomes that could arise from testing. False positive results may be associated with substantial anxiety and may also result in unnecessary treatment, particularly because the model assumed that clinical judgement did not influence the interpretation of test results. Also, although in practice women with false negative results are likely to return with ongoing symptoms, the patient experts said that sometimes these results give women false reassurance and they may not return to hospital in time for effective treatment. This could severely affect the longer-term health of the child born preterm. Therefore the committee considered that the costs and longer-term health outcomes of the child were unlikely to have been adequately captured for false negative results. It concluded that, to capture the full effect of testing, future models should incorporate the effect of changes in both sensitivity and specificity.

5.10 The committee considered whether the economic model adequately captured the costs relating to adverse events and long-term health outcomes of the mother and child. The clinical experts explained that the cost of intraventricular haemorrhage in the economic model was likely to be an underestimate, at an average cost of £114,648 per child, and noted that it had been estimated using costing data for cerebral palsy. They also explained that they would expect the lifetime healthcare costs to be at least 10 times higher than those in the model, particularly for neonates who were extremely preterm and more likely to have a more severe form of

intraventricular haemorrhage (grades 3 to 4). Also the committee noted that the model did not account for costs relating to necrotising enterocolitis, which can be significant, and it excluded costs of neonatal and maternal sepsis. The EAG explained that not all costs for long-term health events could be included because there were no data about this. The committee concluded that the model was likely to considerably underestimate the longer-term costs of preterm birth.

5.11 The committee discussed the economic model's results. It recalled its previous considerations of the limitations in the clinical data available for the biomarker tests. These included the lack of studies on clinical outcomes, poor reporting of studies, the heterogeneity and lack of head-to-head studies comparing all 3 tests (see sections 5.3 to 5.7). This led to many simplifying assumptions in the economic model, which the committee did not consider to be clinically plausible. It noted that probabilistic ICERs had not been presented, and that the fully incremental analyses appeared to contain errors. It therefore considered the available pairwise deterministic ICERs, but noted that probabilistic ICERs would have been preferred. Many of the deterministic ICERs for the tests compared with fetal fibronectin at a threshold of 50 ng/ml were in the south-west quadrant of the cost-effectiveness plane, that is, the index tests were cheaper and less effective than the comparator. The committee noted that the QALY loss in most comparisons was relatively small (−0.006). However, because of the limitations in the clinical data and the implementation of the model (see sections 5.8 and 5.9) it was not possible to determine the magnitude or direction of the health-related outcomes that might occur in practice. Also, it noted that the model's predicted cost savings may not be realised in practice (see section 5.10). The committee agreed that the degree of uncertainty in the current clinical evidence was too high

for it to be able to use the ICERs for decision-making. It considered that the scope of any further revisions to the assumptions in the modelling would be limited without more robust clinical data. The committee concluded that without robust diagnostic accuracy and clinical outcome data, it was not able to recommend Actim Partus, quantitative fFN testing using the Rapid fFN 10Q Cassette Kit at thresholds other than 50 ng/ml and PartoSure for use in the NHS to diagnose preterm labour in women with intact membranes.

Research considerations

5.12 The clinical experts explained that there are 2 ongoing studies looking at the use of biomarker tests for preterm labour in the NHS; QUIDs II and PETRA. QUIDs II plans to recruit over 2,000 women and includes Actim Partus, PartoSure and quantitative fFN testing. It is scheduled to complete by September 2018. PETRA plans to recruit over 1,000 women and includes quantitative fFN testing. It is scheduled to report by the end of 2018. The committee considered that the results of these studies could provide diagnostic accuracy data that are generalisable to NHS practice and additional data on patient-reported outcomes. Also, it noted that QUIDs II would provide comparative accuracy data for all 3 interventions from the same population, which should overcome some of the bias introduced to the analyses by indirect comparisons.

5.13 The committee questioned how reproducible the test results were in clinical practice. The companies explained that each test has a recommended sample collection protocol which should be followed, although the clinical experts commented that it was uncertain how strictly these were followed in practice. The EAG noted that the reproducibility of PartoSure in practice had been explored (Werlen et al. 2015), but that equivalent data were not available for Actim Partus or quantitative fFN testing. The committee encouraged the

companies to do similar studies to show the reproducibility of Actim Partus and quantitative fFN testing using the Rapid fFN 10Q Cassette Kit.

5.14 The committee noted the need for further diagnostic accuracy studies to assess whether the accuracy of Actim Partus, PartoSure and quantitative fetal fibronectin using the Rapid fFN 10Q Cassette Kit differs by gestational age (see section 5.6).

5.15 The committee noted that there were no data on how the test results affect clinical decision-making. It considered that further studies should be done to address this uncertainty (see section 5.7). This could be incorporated into a clinical outcome study, or could be done as a standalone study with clinical experts being asked to provide a management plan for a clinical scenario both with and without knowledge of the biomarker test result.

5.16 The committee noted that further studies should be done to assess the effect of Actim Partus, PartoSure and quantitative fetal fibronectin testing using the Rapid fFN 10Q Cassette Kit on maternal and neonatal outcomes, including quality of life (see section 5.7). When possible, these studies should also collect data on resource use associated with preterm birth.

6 Review

NICE reviews the evidence 3 years after publication to ensure that any relevant new evidence is identified. However, NICE may review and update the guidance at any time if significant new evidence becomes available.

Mark Kroese
Chair, Diagnostics Advisory Committee
March, 2018

7 Diagnostics advisory committee members and NICE project team

Diagnostics advisory committee

The diagnostics advisory committee is an independent committee consisting of 22 standing members and additional specialist members. A list of the committee members who participated in this assessment appears below.

Standing committee members

Dr Mark Kroese

Chair, Diagnostics Advisory Committee

Mr John Bagshaw

In-vitro Diagnostics Consultant

Professor Enitan Carrol

Chair in Paediatric Infection, University of Liverpool

Dr Owen Driskell

Lead for Laboratory Medicine, National Institute for Health Research Clinical Research Network West Midlands

Dr Steve Edwards

Head of Health Technology Assessment, BMJ Evidence Centre

Dr Simon Fleming

Consultant in Clinical Biochemistry and Metabolic Medicine, Royal Cornwall Hospital

Dr James Gray

Consultant Microbiologist, Birmingham Children's Hospital

Dr Shelley Rahman Haley

Consultant Cardiologist, Royal Brompton and Harefield NHS Foundation Trust

Professor Steve Halligan

Professor of Radiology, University College London

Mr John Hitchman

Lay member

Mr Patrick McGinley

Head of Costing and Service Line Reporting, Maidstone and Tunbridge Wells NHS Trust

Dr Michael Messenger

Deputy Director and Scientific Manager NIHR Diagnostic Evidence Co-operative, Leeds

Mrs Alexandria Moseley

Lay member

Dr Peter Naylor

GP, Wirral

Dr Dermot Neely

Consultant in Clinical Biochemistry and Metabolic Medicine, Newcastle upon Tyne NHS Trust

Professor Matt Stevenson

Professor of Health Technology Assessment, School of Health and Related Research, University of Sheffield

Professor Anthony Wierzbicki

Consultant in Metabolic Medicine/Chemical Pathology, St Thomas Hospital

Specialist committee members

Miss Ciara Curran

Lay specialist committee member

Dr Ruth Gottstein

Consultant Neonatologist, Manchester University NHS Foundation Trust

Sister Marianne Rowntree

Ward Manager, Plymouth Hospitals NHS Trust

Mr Nigel Simpson

Senior Lecturer and Honorary Consultant, University of Leeds

Mrs Alison Stanley

Lay specialist committee member

Dr Meekai To

Consultant in Fetal Medicine and Obstetrics, King's College Hospital NHS Foundation Trust

Mr David Wells

Director of Operations, King's College, Guy's and St Thomas' Hospitals

NICE project team

Each diagnostics assessment is assigned to a team consisting of a technical analyst (who acts as the topic lead), a technical adviser and a project manager.

Jessica Maloney

Topic Lead

Rebecca Albrow

Technical Adviser

Donna Barnes

Project Manager

ISBN: