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

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1 Background

On the 6th December 2017, NICE relayed information to the ERG from Parsagen that the following were new full text articles were available:

- Bolotskikh et al. 2017 – published June 2017[1]
- Lofti et al. 2017 – published October 2017[2]
- Melchor et al. 2017 – published August 2017[3]
- Ravi et al. – unpublished [4]
- Renzo et al. 2017 – published September 2017[5]
- Wing et al. 2017 – published December 2017 (provided copy was an epub ahead of print)[6]

The ERG had already included Bolotskikh et al. 2017 in our report, since it was published prior to our search date (July 2017).[1] The Renzo et al. publication was of guidelines issued by the European Association of Perinatal Medicine and would be excluded from the test accuracy review.[5] The remaining four publications, Lofti et al, Melchor et al., Ravi et al. and Wing et al.[2-4, 6] provided relevant test accuracy data that would have been includable in the report had they been published prior to our search date. It was unreasonable given the timings for these studies to be fully incorporated into the ERG report, since this would have required a complete review update (new searches, screening, date extraction, quality appraisal etc.) and re-write of the whole DTA systematic review and new scenario analyses run in the cost effectiveness model. Therefore, in the report submitted to NICE on 10th January 2018, the ERG acknowledged their awareness of the studies.

On 1st February, NICE relayed information to the ERG from Parsagen that there were two new additional manuscripts in preparation, which were shared:

- Nikolova et al. [7]
- Melchor et al. [8]

The Melchor et al. [8] manuscript presents a systematic review and meta-analysis of the three index tests (Actim Partus, PartoSure and Fetal Fibronectin) and would not have been used within the ERG report. The Nikolova et al. [7] manuscript provided relevant test accuracy data that would have been includable in the report had it been published.

We therefore present a non-systematic update to the headline test accuracy results and a new scenario analysis for the economic model given the following five studies.

- Lofti et al. 2017 – published October 2017[2]

- Melchor et al. 2017 – published August 2017[3]
- Nikolova et al. [7]
- Ravi et al. – unpublished[4]
- Wing et al. 2017 – published December 2017 (provided copy was an epub ahead of print)[6]

We would like to highlight the following limitations:

- These studies have been provided to us by the company, we have not updated our search. Therefore, these results do not constitute results from a systematic review as there may be additional relevant studies (for any of the index tests) that have since been published that have not been highlighted to us. This incorporates signification study identification bias to these new results.
- Two of the publications are unpublished, and have not been through peer review.

2 Update to test accuracy review

2.1 Methods

Studies were identified following communication with NICE on behalf of Parsagen (PartoSure). Studies were independently checked for inclusion (as per the criteria in the report) by two reviewers.

Data were extracted and studies quality appraised by one reviewer and checked by a second. Any disagreement was resolved by discussion.

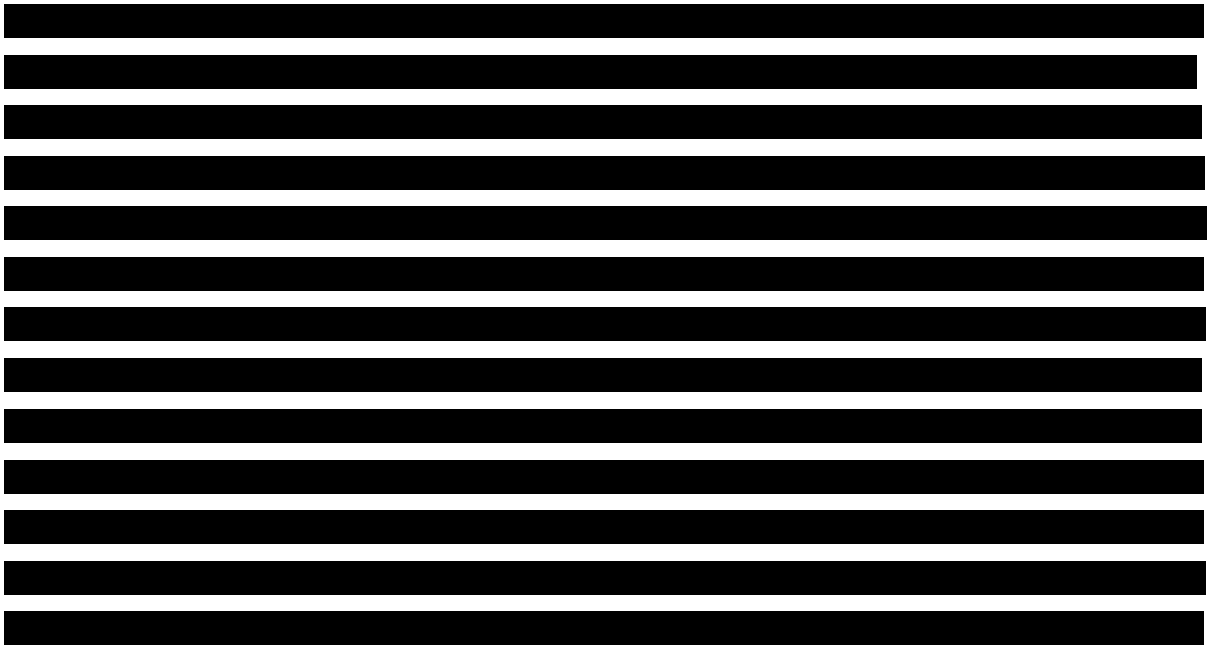
The following test accuracy results were calculated from the studies: sensitivity, specificity, positive and negative predictive value, positive and negative likelihood ratio, prevalence, concordance and diagnostic yield. Summary receiver operating characteristic (ROC) plots were generated to provide graphical depiction of the sensitivity and specificity data.

2.2 Results

From the 8 studies provided by Parsagen, five would have provided test accuracy data that would have been includable in the systematic review of diagnostic test accuracy (Lofti et al, Melchor et al., Ravi et al. and Wing et al. and Nikolova et al.).[2-4, 6, 7] Of the other three, one was already included in our report (Bolotskikh et al. 2017), one was a guidelines document and the other was a systematic review and meta-analysis (Melchor et al.).[1, 5, 8]

2.2.1 Study identification from relevant systematic reviews

As per the methods of our systematic review (section 2.1.1.1.1) we screened Melchor et al. for further includable studies.[8]



[redacted]

2.2.2 Additional studies

In total, Parsagen identified six new includable studies (Lofti et al, Melchor et al. 2017, Ravi et al.,Wing et al., Çekmez et al. 2017 and Fuchs et al. 2017).[2-4, 6, 11, 27] In addition, they provide a study with new data for Nikolova 2015(Nikolova et al.).[7, 10] We therefore update our results with these additional seven studies (and remove the old Nikolova 2015 data).[7, 10] All of these studies were published after the date of our search or provided as AIC by the company, and full update searches have not been conducted. Therefore these results to not form part of the systematic review process.

2.2.2.1 Description of the included studies

Characteristics of the new seven studies are summarised in Table 1. Two studies assess the diagnostic test accuracy of two different index tests in the same population; Ravi et al. (PartoSure and quantitative fFN) and Nikolova et al. (PartoSure and Actim Partus).[4, 7] The remaining five studies assess the diagnostic test accuracy of PartoSure only (four studies,

Melchor et al., 2017, Wing et al. 2017, Lofti et al. 2017 and Çekmez et al. 2017)[2, 3, 6, 11] and Actim Partus only (one study, Fuchs et al. 2017).[27]

2.2.2.1.1 Key differences

As with the previous review, these additional seven studies bring about the same issues with clinical and methodological heterogeneity, namely differences in:

- Inclusion/exclusion criteria
    - Gestational age
    - Risk status
    - Singleton/multiples
    - Dilation threshold
- Presentation of symptoms
- Prevalence rate
- Mode of delivery

2.2.2.1.2 Test administration

Actim Partus

There do not appear to be any obvious issues with how the samples were collected from the two new Actim Partus studies.[7, 27]

PartoSure

There do not appear to be any obvious issues with how the samples were collected from the six new PartoSure studies, other than Çekmez et al. 2017 inserted the swab into the vagina for 1 minute, rather than the 30 seconds advised.)[2-4, 6, 7, 11]

Quantitative fFN

There do not appear to be any obvious issues with how the samples were collected from the new quantitative fFN study.[4]

Table 1 Study Characteristics

Study	Other tests used	N Included, (Recruited)	Country (number of centres)	Definition of Pre Term Labour Symptoms	Weeks gestation	Dilation threshold for exclusion	Other exclusion criteria
Quantitative fFN and PartoSure							
Ravi et al.[4]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Actim Partus and PartoSure							
Nikolova et al [7]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PartoSure							
Melchor et al. 2017[3]	QuikCheck fFN	367 (410)	Spain (1)	Symptoms of preterm labour	24+0-34+6	≥3cm	Vaginal bleeding, Placenta praevia, Cervical cerclage, Rupture of membranes, Multiple gestations, Iatrogenic delivery within 14 days of testing
Wing et al. 2017[6]	ELISA fFN [a]	701 (839)[b]	USA (15)	Uterine contractions, Intermittent lower abdominal pain, Dull backache, Pelvic pressure, Bleeding during second or third trimester, Menstrual-like or intestinal cramping, with or without diarrhoea	24+0-34+6	≥3cm	Previous tocolytic medication, Placenta praevia, Moderate-to-gross vaginal bleeding, Sexual intercourse within the past 24 hours, Cervical cerclage, Rupture of membranes, History non-consistent with idiopathic threatened preterm delivery such as trauma, Prior digital transvaginal ultrasonography, Examination immediately before specimen collection, Iatrogenic deliveries (defined as deliveries occurring as a result of one or more obstetric conditions or maternal conditions that do or do not coincide with spontaneous onset of preterm labour or pre-labour premature rupture of the membranes or fetal membrane prolapse.)
Lofti et al. 2017[2]	NA	148 (175)	United Arab Emirates (1)	Uterine contractions, Back pain, Intermittent lower abdominal pain, Pelvic pressure, Vaginal bleeding Cramping	24+0-36+6	>3cm	Suspected placental praevia, Digital exam prior to specimen collection, Previous tocolytic treatment, Rupture of membranes, Sexual intercourse within the past 24 hours, Participants under 18 years old were excluded, Active labour at enrolment (≥1 contraction per 10 minutes lasting more than 40 seconds, cervical effacement >80% and dilation 2-3cm),Iatrogenic deliveries (labour augmentation or caesarean delivery)
Çekmez et al. 2017[11]	Cervical Length and fFN[c]	72 (80)	Turkey	at least four contractions in 60 min based on external cardiotocography, effacement of >50%, and a cervical length of <30 mm on transvaginal ultrasound	24+0 – 34+0	<1 to ≥3cm	Ruptured membranes, active bleeding, multiple pregnancies, growth restriction, foetal anomalies, placental anomalies, history of coitus within 24 h, history of preterm birth, preeclampsia or signs of any infection,
Actim Partus							
Fuchs et al. 2017[27]	Cervical Length	180 (342)	France	regular uterine contractions, lasting >30 s and >3 times per 10 minutes, significant cervical changes during	24 – 34	>3cm	>18 years, multiple gestations, confirmed rupture of membranes, cervical length ≥25 mm at ultrasound, prolapse membranes, bulging in the vagina, cervical cerclage, vaginal bleeding, placenta previa, placental abruption, severe intrauterine growth restriction, fetal malformation and preeclampsia

	transvaginal sonographic examination		

Notes: a Unclear which test method used for fFN; “test specimen sent to certified laboratory” suggests ELISA technique; b Excluding participants with medically-indicated deliveries who were excluded from the final analysis; c. Unclear which test used for fFN, no manufacture detail reported.

2.2.2.2 Description of included participants

The characteristics of the study participants are reported in Table 2.

As with the previous review, these additional seven studies bring about the same issues relating to participant differences:

- Mean/median age of mother
- Mean/median weeks of gestation
- Mode of delivery
- Treatments given
- Whether the results of other tests impact the results

2.2.2.3 Quality Appraisal

We have not quality appraised the additional seven studies. Therefore we cannot comment on the risk of bias between studies.

Table 2 Participant Characteristics

		Participants *n*	Maternal Age mean ± SD	Gestational Age at Presentation (weeks) mean ± SD	Multiple Gestations *n* (%)	BMI kg/m^2 mean ± SD	Gravidity mean ± SD	Parity mean ± SD	Previous Preterm Delivery *n(%)*	Previous Miscarriage/ Stillbirth *n(%)*	Mode of delivery *n(%)*
Quantitative fFN and PartoSure											
Ravi et al. 2017[4]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Actim Partus and PartoSure											
Nikolova et al[7]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PartoSure											
Melchor et al. 2017[3]	PAMG-1	367	32.47 ± 5.89	30.52 ± 2.98	0 (0)	NR	NR	NR	NR	NR	Medically-indicated deliveries within 14 days from testing were excluded from the analysis
	QuikCheck fFN	378	32.60 ± 6.26	30.41 ± 2.88	0 (0)	NR	NR	NR	NR	NR	Medically-indicated deliveries within 14 days from testing were excluded from the analysis
Wing et al. 2017[6]		711[a]	28.3 ± 5.8 (17-44)	29.7 ± 3.0 (24.0–34.9)	66/711 (9.3%)	NR	NR	NR	152/709 (21.4)	NR	Medically-indicated deliveries due to obstetric/ maternal complications were later excluded from the analysis
Lofti et al. 2017[2]		148	NR	32 (24.2-36.0) [c]	0 (0)	NR	NR	NR	NR	NR	Iatrogenic deliveries (labour augmentation or caesarean delivery) excluded from final analysis
Cekmez et al.[11]		72	26 ± 2.6	32.4 ± 1.8	0 (0)	NR	1.15 ± 0.9	0.9 ± 0.2	NR	NR	NR
Actim Partus											
Fuchs et al. 2017[27]	*Fuchs et al. 2017*	180	28.8 ± 6.2	30.4 ±2.6	0 (0)	27.1 ± 4.4	NR	NR	NR	(26.6)	Medically-indicated preterm delivery was criteria for exclusions, however study reports “mode of delivery was caesarean for 15%.”

Notes: a Participant characteristics cohort includes women who were later excluded due to medically indicated deliveries; b average (range); c median (range)

2.2.3 Results of quantitative data synthesis (test accuracy data)

Table 3 reports the test accuracy data on the seven new studies. All studies reported test accuracy against the 7 day reference standard. None of the new studies reported test accuracy against the 48hr reference standard.

2.2.3.1 Studies evaluating more than one index test

When the additional studies are combined with those in the original ERG report, there are now four studies that report test accuracy data for more than one index test within the same population.

- APOSTEL-1: Actim Partus and Quantitative fFN (previously reported)
- Hadzi-Lega et al. 2017: PartoSure and Actim Partus (previously reported)
- Nikolova et al.: Actim Partus and Quantitative fFN (new study)
- Ravi et al.: PartoSure and Quantitative fFN (new study)

Taken directly from section 2.2.6.1.1. of the ERG report:

> *Two studies (APOSTEL-1 and Hadzi-Lega 2017) reported test accuracy data on two index tests.[9, 20, 44] Both studies only used the 7 day (and not the 48hr) delivery reference standard. Prevalence of preterm birth within 7 days was 19.7% (95% CI 15.7, 24.3) in the APOSTEL-1 study and 10.5% (95% CI 4.0, 21.5) in the Hadzi-Lega 2017 study.*
>
> *The APOSTEL-1 study reports test accuracy from 350 women for both Actim Partus and quantitative fFN.[20, 44] The sensitivity and specificity for Actim Partus, against delivery within 7 days, were 78.3% (95% CI 66.7, 87.3) and 89.3% (95% CI 85.1, 92.7) respectively. As would be expected, in the quantitative fFN results from the APOSTEL-1 study, lowering the threshold for a positive test result increased sensitivity and decreased specificity whereas elevating the threshold for a positive test result increased specificity and decreased sensitivity. The quantitative fFN sensitivity and specificity values that were most similar to Actim Partus values for the APOSTEL-1 study were those provided at a threshold of 200 ng/ml, where sensitivity was 71.0% (95% CI 58.8-83.1) and specificity 83.6% (95% CI 78.8, 87.8). With regard to the quantitative fFN data from APOSTEL-1, the threshold with the highest PPV was 500ng/ml (70.7%; 95%CI 54.5, 83.9) and the lowest was at 10ng/ml (28.9%; 95% CI 23.2, 35.3). For Actim Partus the PPV of delivery within 7 days was 64.3% (95% CI 53.1, 74.4). For quantitative fFN, the highest NPV was at a threshold*

> *of 10ng/ml (97.5%; 95% CI 93.0, 99.5) and the lowest at a threshold of 500ng/ml (87.1%; 82.8, 90.6). For Actim Partus, NVP was 94.4% (95% CI 90.9, 96.8).*
>
> *The other study providing data on more than one index test in the same sample was Hadzi-Lega (2017), where test accuracy data from 57 women were reported for both Actim Partus and PartoSure [9] The sensitivity of both Actim Partus and PartoSure for delivery within 7 days was 83.3% (95% CI 35.9, 99.6) whilst specificity was higher for PartoSure 90.2% (95% CI 78.6-96.7) compared to Actim Partus 76.5% (95% CI 62.5, 87.2). In addition, PPV, LR+ and concordance were higher for PartoSure than for Actim Partus, although the wide confidence intervals, particularly for PPV, are notable. LR- and NVP were similar for both tests and diagnostic yield was higher for Actim Partus than PartoSure.*

The two new studies (Nikolova et al. and Ravi et al.) both reported test accuracy data on two index tests against the 7 day reference standard. Prevalence of preterm birth within 7 days was [redacted] in the Nikolova et al. study and [redacted] in the Ravi et al. study.

Nikolova et al. report test accuracy from [redacted] women for both PartoSure and Actim Partus (Table 3). The sensitivity for PartoSure was [redacted] whilst for Actim Partus, it was [redacted] The specificity for PartoSure was [redacted] whilst for Actim Partus, it was [redacted] In addition, LR+, LR-, PPV, and concordance were [redacted] NPV was [redacted]. Specific values are given in **Error! Reference source not found.**

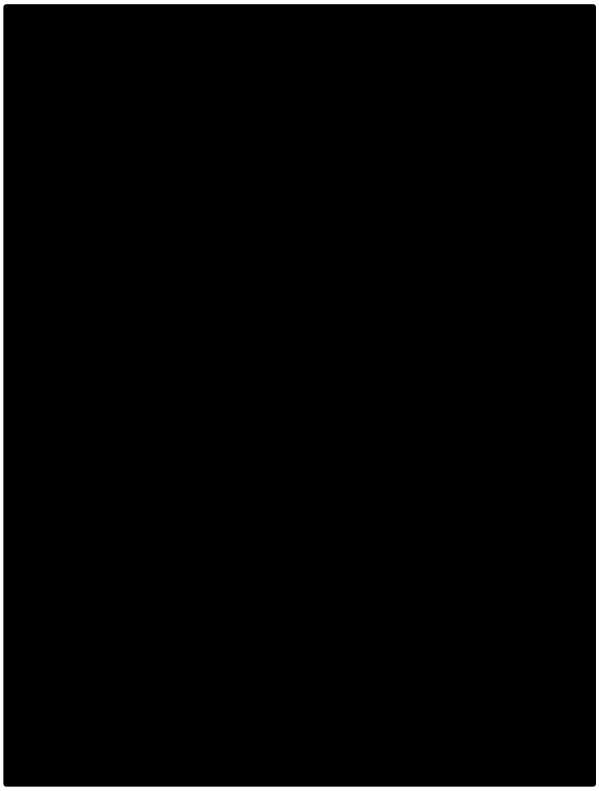
The study by Ravi et al. reports test accuracy from [redacted] women for both PartoSure and Quantitative fFN. The sensitivity and specificity for PartoSure, were [redacted] and [redacted] in the quantitative fFN results from Ravi et al, lowering the threshold for a positive test result [redacted] whereas elevating the threshold for a positive test result [redacted] (see Table 3). The quantitative fFN sensitivity and specificity values [redacted] where sensitivity was [redacted] and specificity [redacted] The LR+, PPV, NPV and concordance were all [redacted] Specific values are given in Table 3.Actim Partus

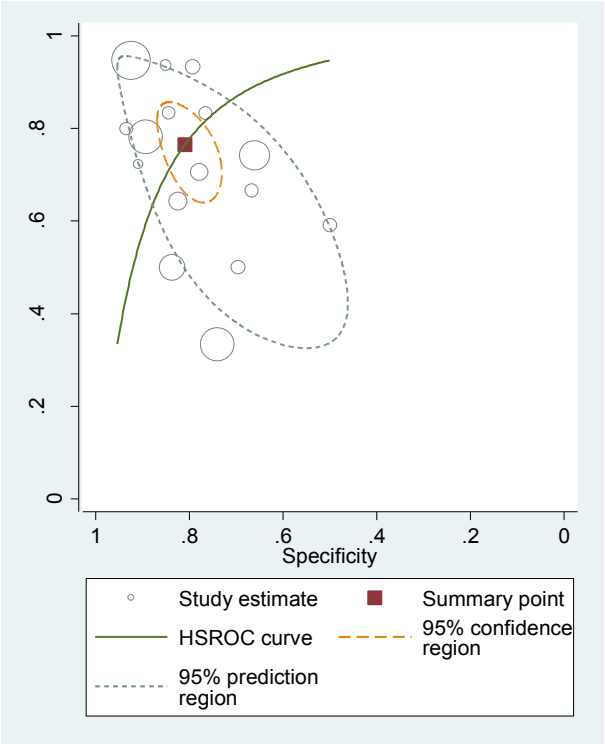
In total (original report and new studies), there were 18 studies that provided test accuracy results against the 7 day reference standard for Actim Partus (previously 16 studies).

Across these studies, sensitivity ranged from 28.6% (95% CI 8.39, 58.1) in Fuchs et al. 2017 to 94.7% (95% CI 89.9, 97.7) in Tripathi (2016). Specificity of Actim Partus ranged from 50.0% (95% CI 24.7-75.3) in Goyal (2016) to 93.5% (95% CI 82.1-98.6) in Azlin (2010).

A summary ROC plot for all 18 studies and the ROC plot from the original 16 studies assessing Actim Partus against the 7-day delivery reference standard are provided in Figure 1. Pooled analyses were performed for these data and provided a pooled sensitivity of 74.3% (95%CI 64.2, 82.3). The new pooled results (n=18 studies) present a lower pooled sensitivity than that of the original n=16 studies which was 77% (95% CI 68, 83). Conversely, the new pooled specificity (n=18 studies) is ever so slight higher at 81.2% (95%CI 76.2, 85.4) compared to the original (n=16 studies) at 81% (95%CI 76, 85).

Figure 1 New ROC curve for Actim Partus on the left and old ROC curve on the right





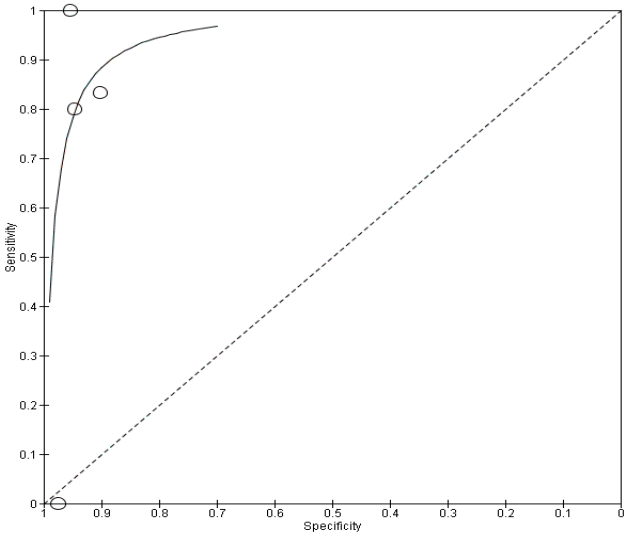
2.2.3.2 PartoSure

In total (original report and new studies), there were 10 studies that provided test accuracy results against the 7 day reference standard for PartoSure (previously four studies). Since it is unclear whether the patients from Nikolova et al. 2015 overlap with the patients from Nikolova et al. (since some of the centres and dates of data collection overlap), the update analysis does not include the results from Nikolova et al 2015 and has been replaced by the more recent and larger sample of Nikolova et al. Therefore, we present data on nine PartoSure studies, three from the original report and six new studies.

These nine studies had wide ranging sensitivity, from 0% (95% CI 0.0, 97.5) in Werlen (2015) to 100% (95% CI 73.5-100.0) in Bolotskikh (2017), whereas specificity was more similar across studies, ranging from 90.2 (95% CI 78.6, 96.7) in Hadzi-Lega (2017) to 98.6% (95% CI 94.9, 99.8) in Lofti (2017). The low sensitivity, from Werlen (2015), was due to the fact that in the sample of 41 participants, only one tested (falsely) positive using the PartoSure test. Discounting this study, the sensitivity range would be 33.3% (95% CI 7.5, 70.1) in Wing (2017) to 100% (95% CI 73.5-100.0) in Bolotskikh (2017).

A summary ROC plot for the nine studies and the ROC plot from the original four studies assessing PartoSure Partus against the 7-day delivery reference standard is provided in Figure 2. Pooled analyses were performed for these data and provided a pooled sensitivity of 68.5% (95%CI 51.2, 81.9) and the pooled specificity was 96.6% (95%CI 95.1, 97.6). The new pooled results (n=7 studies) have a much lower sensitivity and slightly higher specificity than the original pooled results (n=4 studies) which were 83% (95% CI 61, 94) and 95% (95%CI 89, 98) respectively.

Figure 2 New ROC curve for PartoSure on the left and old ROC curve on the right



2.2.3.3 Quantitative fFN

In total (original report and new studies), there were three studies that provided test accuracy results against the 7 day reference standard for quantitative fFN (previously two studies).

Results against the 7 day delivery reference standard for the three quantitative fFN studies (EUIFS, APOSTEL-1 and Ravi et al), at the three thresholds (10ng/ml, 200ng/ml and 500ng/ml). EUIFS presented with slightly lower (within 2%) sensitivity values compared to APOSTEL-1 at both the 10 and 200ng/ml threshold (at the 10ng/ml threshold sensitivity was 93.8% (82.8, 98.7) for EUIFS and 95.7% (95%CI 87.8, 99.1) for APOSTEL-1 and at the 200ng/ml threshold, sensitivity was 70.8% (55.9, 83.0) for EUIFS and 71.0% (95%CI 58.8, 81.3) for APOSTEL-1). At the 500ng/ml threshold the sensitivity was much lower (29.2%; 95% CI 17.0, 44.1 in EUIFS vs 42%; 95% CI 30.2, 54.4) in APOSTEL-1. The new study by Ravi et al. reports much lower sensitivities than both these studies, at the threshold of 10ng/ml the sensitivity was [redacted] at the threshold of 200ng/ml the sensitivity was [redacted] and at the threshold of 500ng/ml the sensitivity was [redacted] It is likely that the differences in sensitivities are largely attributed to sample size, APOSTEL and EUIFS had 350 and 455 participants respectively, whilst Ravi et al. had [redacted]

Similarly, specificity values were slightly lower (within 5%) in EUIFS compared with APOSTEL-1 at both the 200ng/ml and 500ng/ml thresholds, (at the 200ng/ml threshold specificity was 78.6% (95%CI 74.3, 82.5) for EUIFS and 83.6% (78.8, 87.8) for APOSTEL-1 and at the 500ng/ml threshold, specificity was 94.3% (95%CI 91.6, 96.4) for EUIFS and 95.7% (92.7, 97.8) for APOSTEL-1). Whereas at the 10ng/ml threshold the specificity was much lower (32.2%; 95% CI 27.7, 37.0 in EUIFS vs 42.3%; 95% CI 36.5, 48.4 in APOSTEL-1). The new study by Ravi et al. reports [redacted], at the threshold of 10ng/ml the specificity was [redacted] at the threshold of 200ng/ml the specificity was [redacted] and at the threshold of 500ng/ml the specificity was [redacted] It is likely that the differences in specificities are again largely attributed to sample size, APOSTEL and EUIFS had 350 and 455 participants respectively, whilst Ravi et al. had [redacted]

Table 3 Test accuracy results [% (95%CI)]

Study		Sensitivity	Specificity	LR+	LR-	PPV	NPV	Prevalence	Concordance	Yield
Quantitative fFN and PartoSure										
Ravi et al. [4]										
Actim Partus and PartoSure										
Nikolova et al [7]										
PartoSure										
Melchor et al. 2017[3]	PartoSure	50.0; 21.1-78.9	96.9; 94.5-98.4	16.14; 7.17-36.33	0.52; 0.29-0.91	35.3; 14.2-61.7	98.3; 96.3-99.4	3.3; 1.7-5.6	0.95; 0.93-0.97	0.05; 0.03-0.07
	fFN @50	30.0; 6.7-65.2	90.5; 87.0-93.3	3.15; 1.16-8.56	0.77; 0.51-1.16	7.9; 1.7-21.4	97.9; 95.8-99.2	2.6; 1.3-4.8	0.89; 0.85-0.92	0.10; 0.07-0.14
Wing et al. 2017[6]	PartoSure	33.3; 7.5-70.1	98.1; 96.8-99.0	17.74; 6.09-51.70	0.68; 0.43-1.08	18.8; 4.0-45.6	99.1; 98.1-99.7	1.3; 0.6-2.4	0.97; 0.96-0.98	0.02; 0.01-0.04
	fFN @50	77.8; 40.0-97.2	85.4; 82.6-88.0	5.33; 3.60-7.89	0.26; 0.08-0.88	6.5; 2.6-12.9	99.7; 98.8-100.0	1.3; 0.6-2.4	0.85; 0.82-0.88	0.15; 0.13-0.18
Lofti et al. 2017[2]	PartoSure	66.7; 29.9-92.5	98.6; 94.9-99.8	46.33; 10.85-197.80	0.34; 0.13-0.85	75.0; 34.9-96.8	97.9; 93.9-99.6	6.1; 2.8-11.2	0.97; 0.92-0.99	0.05; 0.02-0.10
Cekmez et al. 2017[11a]	PartoSure	73.3; 44.9- 92.2	93; 83-98.1	10.4; 3.87-28.2	0.29; 0.12-0.67	73.3; 44.9-92.2	93; 83-98.1	21; 12-32	0.89; 0.79-0.95	0.21; 0.12-0.32
	fFN @ 50	93.3; 68.1-99.8	91.2; 80.7-97.1	10.6; 4.56-24.8	0.07;0.01-0.49	73.7; 48.8-90.0	98.1; 89.9-100	21; 12-32	0.92; 0.83-0.97	0.26; 0.17-0.38
Actim Partus										
Fuchs et al. 2017[27]	Actim Partus	28.6; 8.39-58.1	89.8; 84.1-93.9	2.79; 1.09-7.16	0.80; 0.57-1.11	19; 5.45, 41.9	93.7; 88.7-96.9	7.8; 4.3-12.7	0.85; 0.79-0.90	0.12; 0.07-0.17

Notes: a, data take from text and not table within paper as they do not match

Table 4 Summary of new and old test accuracy data (range and pooled data)

Analysis	Studies	Sensitivity % (95%CI)	Specificity % (95%CI)
Pooled			
Old PartoSure	N= 4 from previous review[1, 9, 10, 43]	83 (61, 94)	95 (89, 98)
Updated PartoSure	***N= 3 from previous review (without Nikolova 2015) [9, 43] ADDED: Nikolova et al , Ravi et al. , Melchor et al. 2017, Lofti et al. 2017, Wing et al. 2017 and Cekmez et al. 2017[2-4, 6, 7, 11]***	***68.5 (51.2, 81.9)***	***96.6 (95.1, 97.6)***
Old Actim Partus	N= 16 from previous review [9, 17-26, 38-42]	77 (68, 83)	81 (76, 85)
Updated Actim Partus,	***N= 16 from previous review [9, 17-26, 38-42] ADDED: Nikolova et al. and Fuchs et al. 2017[7, 27]***	***74.3 (64.2, 82.3)***	***81.2 (76.2, 85.4)***
Range			
Old PartoSure	N= 4 from previous review[1, 9, 10, 43]	0 (0.0, 97.5) - 100.0 (73.5, 100.0)	90.2(78.6, 96.7) - 97.5(96.8, 99.9)
Updated PartoSure	***N= 3 from previous review (without Nikolova 2015) [1 9, 43] ADDED: Nikolova et al , Ravi et al. , Melchor et al. 2017, Lofti et al. 2017, Wing et al. 2017 and Cekmez et al. 2017[2-4, 6, 7, 11]***	***0 (0.0, 97.5) - 100.0 (73.5, 100.0)***	***90.2(78.6, 96.7) - 98.6 (94.9, 99.8)***
Old Actim Partus	N= 16 from previous review[9, 17-26, 38-42]	33.3 (4.3, 77.7) - 94.7 (89.9, 97.7)	50.0 (24.7, 75.3) - 93.5 (82.1, 98.6)
Updated Actim Partus,	***N= 16 from previous review [9, 17-26, 38-42] ADDED: Nikolova et al. and Fuchs et al. 2017[7, 27]***	***28.6 (8.39, 58.1) - 94.7 (89.9, 97.7)***	***50.0 (24.7, 75.3) - 93.5 (82.1, 98.6)***
Old fFN at 10ng/ml	N= 2 from previous review[20, 44, 45]	93.8 (82.8, 98.7) - 95.7 (87.8, 99.1)	32.2 (27.7, 37.0) - 42.3 (36.5, 48.4)
Updated fFN at 10ng/ml	***N= 2 from previous review[20, 44, 45] ADDED: Ravi et al. [4]***	[redacted]	[redacted]
Old fFN at 200ng/ml	N= 2 from previous review[20, 44, 45]	70.8 (55.9, 83.0) - 71.0 (58.8, 81.3)	78.6 (74.3, 82.5) - 83.6 (78.8, 87.8)
Updated fFN at 200ng/ml	***N= 2 from previous review [20, 44, 45] ADDED*: Ravi et al. [4]***	[redacted]	[redacted]
Old fFN at 500ng/ml	N= 2 from previous review[20, 44, 45]	29.2 (17.0, 44.1) - 42.0 (30.2, 54.5)	94.3 (91.6, 96.4) - 95.7 (92.7, 97.8)
Updated fFN at 500ng/ml	***N= 2 from previous review [20, 44, 45] ADDED: Ravi et al. [4]***	[redacted]	[redacted]
Supplementary data from included studies			
Old fFN at 50ng/ml	N= 8 from previous review[10, 20, 21, 24, 26, 39, 41, 44, 45]	23.8 (17.3, 31.4) - 91.3 (82.0, 96.7)	62.2 (57.3,66.9) - 99.1 (97.3,99.8)
Updated fFN at 50ng/ml	***N= 8 from previous review[10, 20, 21, 24, 26, 39, 41, 44, 45] ADDED: Ravi et al. , Melchor et al. 2017 Wing et al. 2017 and Cekmez et al. 2017[3, 4, 6, 11]***	***23.8 (17.3, 31.4) - 93.3 (68.1, 99.8)***	***62.2 (57.3,66.9) - 99.1 (97.3,99.8)***

3 Update to economic model

Below we present results based on additional diagnostic accuracy data provided by Parsagen from the following studies

- Wing et al. 2017[6]
- Nikolova et al. [7]
- Ravi et al. 2017[4]

This is only a subset of the studies provided by the company, and we limited our additional analyses to them on the basis that i) they compared at least one index test with another index test or fFN 50ng/ml, and ii) they compared tests on the same patient sample. In this regard we did not consider the study by Melchor et al. 2017 that the company provided, because it was a before-and-after study that compared an index test, PartoSure, with a historical control, fFN 50 ng/ml. [3]

In addition, we present a scenario analysis to reflect local practice based on treatment guidelines put in practice at the Royal Devon and Exeter maternity hospital. The company had suggested in comment to the Diagnostic Assessment Report that a scenario reflecting the local practice in the 2017 treatment guidelines at Guy and St Thomas' hospital should be considered. In particular, it was suggested that such guidelines advised that hospital admission should occur at or above fFN 50ng/ml threshold, whereas antenatal steroids be given at or above the fFN 200ng/ml. After communication with our clinical expert at that hospital, it was revealed that the hospital admission at 50ng/ml should be considered but is at the discretion of the attending obstetrician and that in any case such guidelines are not being followed since the decision to admit is being based on the quantitative preterm birth risk prediction which includes fFN and other factors, not fFN concentration alone.

3.1 Women presenting at 30 weeks' gestation (at a Level 2 hospital)

We present the Wing et al. 2017 and [redacted] studies alongside our initial base case results for women presenting at 30 weeks (Table 5, Table 6,Table 7), 26 weeks (Table 8) and 33 weeks (Table 11).[6, 7] In these tables, the incremental costs, incremental QALYs and incremental cost-effectiveness ratios of PartoSure relative to fFN50ng/ml for Nikolova et al. 2018 are derived indirectly from the comparison of costs and QALY differences of PartoSure in Nikolova et al. 2018 and fFN50 ng/ml in APOSTEL-1, relative to the common comparator of Actim Partus.[7, 20] We separately presents the results for Ravi et al. 2017 (

Table 13).[4]

Other studies submitted by the company were not considered because they evaluated competing tests in different patient samples ([redacted]), or synthesised different sets of studies across tests (Melchor et al).[3, 8]

As presented in Table 5, the discounted costs per woman of PartoSure that correspond to the accuracy results published by Wing and colleagues (£5,224)[6] are higher than our original results based on Hadzi-Lega et al.[9] (£4,895), which in turn are[redacted]Nikolova's test accuracy results[redacted][7] The respective discounted QALYs are 21.999, 22.010, and[redacted]. [6, 7, 9] In comparison with fFN 50ng/ml, PartoSure saves costs and loses QALYs [redacted] but, contrary to results based on Hadzi-Lega's test accuracy data, PartoSure produces less cost savings per QALY lost than Actim Partus in the APOSTEL-1 population when we use the test accuracy data of Wing et al, 2017 (£22,349 vs. £56,033) or Nikolova et al.[redacted][6, 7, 9, 20]

Actim Partus appears to dominate PartoSure as it results in more QALYs and lower costs from an indirect comparison of APOSTEL-1 and Wing et al. 2017 data (Table 5).[6, 20] However, using diagnostic accuracy data from direct head-to-head comparisons of the two index tests produces higher total costs for the same amount of QALYs (Hadzi-Lega et al. 2017) or an incremental cost per QALY gained of £49,664 (Nikolova et al) (Table 8) with Actim Partus relative to PartoSure. [7, 9]

Detailed results are presented in

Table 7 and, for the evaluation of the Actim Partus vs. PartoSure based on the head-to-head study of Nikolova et al., Table 8. [7]

Table 5 Summary of ICERs for the base case (women presenting at 30 weeks at level II hospital)

			Versus treat all			Versus fFN 50 ng/ml		
Test	**Total cost**	**Total QALYs**	**Incremental costs**	**Incremental QALYs**	**ICER (per QALY)**	**Incremental costs**	**Incremental QALYs**	**ICER (per QALY)**
Actim Partus[a20]	£5,055	22.010	-£1,116	-0.010	£108,323*	-£346	-0.006	£56,033*
PartoSure (Hadzi-Lega)[b9]	£4,895 †	22.010 †	-£1,276	-0.010	£123,858*	-£506	-0.006	£81,925*
PartoSure (Wing)[c6]	£5,224 ‡	21.999 ‡	-£946	-0.012	£78,717*	-£177	-0.008	£22,349*
PartoSure (Nikolova)[d7]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treat all	£6,171	22.020	£0	0	-	£770	0.004	£186,757
fFN 10 ng/ml[a20]	£5,690	22.018	-£481	-0.002	£233,245*	£289	0.002	£140,270
fFN 50 ng/ml[a20]	£5,401	22.016	-£770	-0.004	£186,757*	£0	0	-
fFN 200 ng/ml[a20]	£5,159	22.006	-£1,012	-0.014	£73,676*	-£242	-0.010	£25,213*
fFN 500 ng/ml[a20]	£5,004	21.992	-£1,167	-0.027	£42,474*	-£398	-0.023	£17,013*

Key: fFN - fetal fibronectin; ICER - incremental cost effectiveness ratio; QALY - quality adjusted life years; a Bruijn et al.[20, 44]; b Hadzi-Lega et al.47, indirect comparison with Bruijn et al. used as the reference study; c Wing et al., indirect comparison with Bruijn et al. used as the reference study; d Nikolova et al., indirect comparison with Bruijn et al. used as the reference study; * ICER represents a reduction in both costs and QALYs (the south-west quadrant in the cost-effectiveness plane); † Inferred total cost and QALYs for PartoSure obtained by applying relative differences vs Actim Partus, found using Hadzi-Lega et al. and Bruijn et al.; ‡ Inferred total cost and QALYs for PartoSure obtained by applying relative differences vs fFN 50, found using Wing et al. and Bruijn et al.; § Inferred total cost and QALYs for PartoSure obtained by applying relative differences vs Actim Partus, found using Nikolova et al. and Bruijn et al.

Table 6 Fully incremental analysis of ICERs for the base case

			Versus next option in the QALY ranking		
Test	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER vs next strategy (£)**
Treat-all (test none)	£6,171	22.020	£481	0.002	£233,245
fFN 10 ng/ml[a20]	£5,690	22.018	£289	0.002	£140,270
fFN 50 ng/ml[a20]	£5,401	22.016	£346	0.006	£56,033
Actim Partus[a20]	£5,055	22.010	£160	0.000	£49,664
fFN 200 ng/ml[a20]	£5,159	22.006	£375	0.002	Extended dominated §§
PartoSure (Nikolova)[d7]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
fFN 500 ng/ml[a20]	£5,004	21.992	-	-	-

Notes: Options have been ranked from most to least effective (in terms of QALYs). ICERs are relative to the next most effective option (i.e. the test in the row immediately below).

Key: fFN - fetal fibronectin; ICER - incremental cost effectiveness ratio; QALY - quality adjusted life years; a Bruijn et al.[20, 44]; b Hadzi-Lega et al.47, indirect comparison with Bruijn et al. used as the reference

study; c Wing et al., indirect comparison with Bruijn et al. used as the reference study; d Nikolova et al., indirect comparison with Bruijn et al. used as the reference study; * ICER represents a reduction in both costs and QALYs (the south-west quadrant in the cost-effectiveness plane); † Inferred total cost and QALYs for PartoSure obtained by applying relative differences vs Actim Partus, found using Hadzi-Lega et al. and Bruijn et al.; ‡ Inferred total cost and QALYs for PartoSure obtained by applying relative differences vs fFN 50, found using Wing et al. and Bruijn et al.; § Inferred total cost and QALYs for PartoSure obtained by applying relative differences vs Actim Partus, found using Nikolova et al. and Bruijn et al. [redacted]

Table 7 Breakdown of base case results (discounted costs and QALYs)

		Bruijn, 2016: APOSTEL-1 [a 20]						Hadzi-Lega [b 9]	Wing [c 6]	Nikolova [d 7]
		Treat all	**fFN 10 ng/ml**	**fFN 50 ng/ml**	**fFN 200 ng/ml**	**fFN 500 ng/ml**	**Actim Partus**	**PartoSure**	**PartoSure**	**PartoSure**
Discounted Costs	Diagnosis	£0	£66	£66	£66	£66	£35	£52	£52	
	Treatment	£5	£3	£2	£1	£0	£1	£0	£1	
	Hospital admission	£1,325	£781	£493	£250	£95	£177	£1	£329	
	In-utero transfer	£0	£0	£0	£0	£0	£0	£0	£0	
	Neonatal RDS	£4,006	£4,008	£4,010	£4,018	£4,030	£4,015	£4,015	£4,017	
	Neonatal IVH	£788	£788	£789	£791	£793	£790	£789	£790	
	Survival due to ANS[1]	£47	£45	£43	£33	£20	£36	£36	£35	
	Total	£6,171	£5,690	£5,401	£5,159	£5,004	£5,055	£4,895	£5,224	
	Incremental Costs (vs. fFN 50ng/ml)	£770	£289	-	-£242	-£397	-£346	-£506	-£177	
Discounted QALYs	Baseline without morbidity	21.999	21.999	21.999	21.999	21.999	21.999	21.999	21.999	
	New-born morbidity – RDS	-0.023	-0.023	-0.023	-0.024	-0.024	-0.023	-0.023	-0.023	
	New-born morbidity – IVH	0.000	0.000	-0.001	-0.001	-0.001	-0.001	-0.001	-0.001	
	Survival due to ANS	0.044	0.042	0.040	0.031	0.019	0.034	0.034	0.033	
	Total	22.020	22.018	22.016	22.006	21.992	22.010	22.010	22.008	
	Incremental QALYs (vs. fFN 50ng/ml)	0.004	0.002	-	-0.010	-0.023	-0.006	-0.006	-0.008	
	ICER (vs. fFN 50ng/ml)	£186,757	£140,270	**-**	£25,213*	£17,013*	£56,033*	£81,925*	£22,349*	

Notes: [1] These are the neonatal hospital costs associated with those infants saved by steroid treatment;

Key: AE, adverse events; fFN - fetal fibronectin; ICER - incremental cost effectiveness ratio; QALY - quality adjusted life years; [a] Bruijn et al.[20, 44]; [b] Hadzi-Lega et al.[47], indirect comparison with Bruijn et al. used as the reference study, using the relative differences in the values for PartoSure vs Actim Partus; [c] Wing et al., indirect comparison with Bruijn et al. used as the reference study, using the relative differences in the values for PartoSure vs fFN 50; d Nikolova et al., indirect comparison with Bruijn et al. used as the reference study, using the relative differences in the values for PartoSure vs Actim Partus; * ICER represents a reduction in both costs and QALYs (the south-west quadrant in the cost-effectiveness plane)

Table 8 Results for PartoSure and no-testing vs Actim Partus using data from Nikolova 2018; presenting at 30 weeks gestation (level 2 hospital)

		Nikolova 2018 [7]		
		Treat all	PartoSure	Actim Partus
Discounted Costs	Diagnosis	[redacted]	[redacted]	[redacted]
	Medication	[redacted]	[redacted]	[redacted]
	Admission	[redacted]	[redacted]	[redacted]
	Transfer	[redacted]	[redacted]	[redacted]
	RDS	[redacted]	[redacted]	[redacted]
	IVH	[redacted]	[redacted]	[redacted]
	Neonatal death	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]
	Incremental costs vs. Actim Partus	[redacted]	[redacted]	[redacted]
Discounted QALYs	Baseline w/o morbidity	[redacted]	[redacted]	[redacted]
	RDS	[redacted]	[redacted]	[redacted]
	IVH	[redacted]	[redacted]	[redacted]
	Newborn mortality	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]
	Incremental QALYs vs. Actim Partus	[redacted]	[redacted]	[redacted]
ICER vs Actim Partus		[redacted]	[redacted]	[redacted]

Key: fFN, fetal fibronectin; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year; * ICER represents a reduction in both costs and QALYs (the south-west quadrant in the cost-effectiveness plane);

3.2 Women presenting at 26 weeks' gestation (at a Level 2 hospital)

Although the same pattern of results is found for this group of women as women presenting at older gestational ages, there is one salient difference. Based on the accuracy results reported by Wing et al. 2017, PartoSure is expected to produce much lower savings per QALY lost in women presenting at 26 weeks than in women presenting at 30 weeks (or indeed than in women presenting at 33 weeks; see below) relative to fFN 50ng/ml: £14,167 (Table 9) vs. £22,349 (Table 5). [6]

The indirect comparisons of fFN 50ng/ml with PartoSure based on data from Nikolova et al 2018 and Wing et al. 2017 suggest that PartoSure results in [redacted] Actim Partus (Table 9), but evaluating the head-to-head comparison of these index tests in the former study results in [redacted] relative to Actim Partus.[6, 7]

Table 9 Summary of ICERs for women presenting at 26 weeks' gestation (level 2 hospital)

			Versus treat all			Versus fFN 50 ng/ml		
Test	**Total cost**	**Total QALYs**	**Incremental costs**	**Incremental QALYs**	**ICER (per QALY)**	**Incremental costs**	**Incremental QALYs**	**ICER (per QALY)**
Actim Partus[a]	£17,745	21.619	-£2,261	-0.031	£72,871*	-£660	-0.019	£35,441*
PartoSure (Hadzi-Lega)[b]	£17,409 †	21.619 †	-£2,2598	-0.031	£83,721*	-£997	-0.019	£53,524*
PartoSure (Wing)[c]	£18,068 ‡	21.614 ‡	-£1,938	-0.036	£53,544*	-£337	-0.024	£14,167*
PartoSure (Nikolova)[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treat all	£20,007	21.650	£0	0	-	£1,601	0.012	£129,017
fFN 10 ng/ml[a]	£18,982	21.643	-£1,025	-0.006	£165,111*	£577	0.006	£92,923
fFN 50 ng/ml[a]	£18,405	21.637	-£1,601	-0.012	£129,017*	£0	0	-
fFN 200 ng/ml[a]	£17,924	21.608	-£2,083	-0.041	£50,338*	-£481	-0.029	£16,618*
fFN 500 ng/ml[a]	£17,619	21.567	-£2,388	-0.083	£28,856*	-£786	-0.070	£11,180*

Key: fFN - fetal fibronectin; ICER - incremental cost effectiveness ratio; QALY - quality adjusted life years; [a] Bruijn et al.[20, 44]; [b] Hadzi-Lega et al.[47], indirect comparison with Bruijn et al. used as the reference study; [c] Wing et al., indirect comparison with Bruijn et al. used as the reference study; [d] Nikolova et al., indirect comparison with Bruijn et al. used as the reference study; * ICER represents a reduction in both costs and QALYs (the south-west quadrant in the cost-effectiveness plane); † Inferred total cost and QALYs for PartoSure obtained by applying relative differences vs Actim Partus, found using Hadzi-Lega et al. and Bruijn et al.; ‡ Inferred total cost and QALYs for PartoSure obtained by applying relative differences vs fFN 50, found using Wing et al. and Bruijn et al.; § Inferred total cost and QALYs for PartoSure obtained by applying relative differences vs Actim Partus, found using Nikolova et al. and Bruijn et al.

Table 10 Results for PartoSure and no-testing vs Actim Partus using data from Nikolova 2018; presenting at 26 weeks gestation (level 2 hospital)

		Nikolova 2018 [7]		
		Treat all	PartoSure	Actim Partus
Discounted Costs	Diagnosis	[redacted]	[redacted]	[redacted]
	Medication	[redacted]	[redacted]	[redacted]
	Admission	[redacted]	[redacted]	[redacted]
	Transfer	[redacted]	[redacted]	[redacted]
	RDS	[redacted]	[redacted]	[redacted]
	IVH	[redacted]	[redacted]	[redacted]
	Neonatal death	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]
	Incremental costs vs. Actim Partus	[redacted]	[redacted]	[redacted]
Discounted QALYs	Baseline w/o morbidity	[redacted]	[redacted]	[redacted]
	RDS	[redacted]	[redacted]	[redacted]
	IVH	[redacted]	[redacted]	[redacted]
	Newborn mortality	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]
	Incremental QALYs vs. Actim Partus	[redacted]	[redacted]	[redacted]

ICER vs Actim Partus	[redacted]	[redacted]	[redacted]

Key: fFN, fetal fibronectin; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year; * ICER represents a reduction in both costs and QALYs (the south-west quadrant in the cost-effectiveness plane);

3.3 Women presenting at 33 weeks' gestation (at a Level 2 hospital)

As for the other gestational ages considered, indirect comparisons of fFN 50ng/ml with PartoSure based on data from Nikolova et al 2018 and Wing et al. 2017 suggest that PartoSure results in [redacted] However, evaluating the head-to-head comparison of these index tests in the former study produces [redacted]

Table 11 Summary of ICERs for women presenting at 33 weeks' gestation (level 2 hospital)

			Versus treat all			Versus fFN 50 ng/ml		
Test	**Total cost**	**Total QALYs**	**Incremental costs**	**Incremental QALYs**	**ICER (per QALY)**	**Incremental costs**	**Incremental QALYs**	**ICER (per QALY)**
Actim Partus[a20]	£2,716	22.096	-£1,117	-0.006	£187,479*	-£347	-0.004	£97,075*
PartoSure (Hadzi-Lega)[b 9]	£2,556 †	22.096 †	-£1,111	-0.005	£243,269*	-£507	-0.004	£141,844*
PartoSure (Wing)[c6]	£2,886 ‡	22.095 ‡	-£947	-0.007	£136,297*	-£177	-0.005	£38,835*
PartoSure (Nikolova)[d7]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treat all	£3,833	22.102	£0	0	-	£770	0.002	£323,098
fFN 10 ng/ml[a 20]	£3,352	22.101	-£481	-0.001	£403,469*	£289	0.001	£242,722
fFN 50 ng/ml[a20]	£3,063	22.100	-£770	-0.002	£323,093*	£0	0	-
fFN 200 ng/ml[a20]	£2,820	22.094	-£1,013	-0.008	£127,575*	-£244	-0.006	£43,787*
fFN 500 ng/ml[a20]	£2,663	22.086	-£1,170	-0.016	£73,650*	-£400	-0.014	£29,609*

Key: fFN - fetal fibronectin; ICER - incremental cost effectiveness ratio; QALY - quality adjusted life years; [a] Bruijn et al.[20, 44]; [b] Hadzi-Lega et al.[47], indirect comparison with Bruijn et al. used as the reference study; [c] Wing et al., indirect comparison with Bruijn et al. used as the reference study; [d] Nikolova et al., indirect comparison with Bruijn et al. used as the reference study; * ICER represents a reduction in both costs and QALYs (the south-west quadrant in the cost-effectiveness plane); † Inferred total cost and QALYs for PartoSure obtained by applying relative differences vs Actim Partus, found using Hadzi-Lega et al. and Bruijn et al.; ‡ Inferred total cost and QALYs for PartoSure obtained by applying relative differences vs fFN 50, found using Wing et al. and Bruijn et al.; § Inferred total cost and QALYs for PartoSure obtained by applying relative differences vs Actim Partus, found using Nikolova et al. and Bruijn et al.

Table 12 Results for PartoSure and no-testing vs Actim Partus using data from Nikolova 2018; presenting at 33 weeks gestation (level 2 hospital)

		Nikolova 2018 [7]		
		Treat all	PartoSure	Actim Partus
Discounted Costs	Diagnosis	[redacted]	[redacted]	[redacted]
	Medication	[redacted]	[redacted]	[redacted]
	Admission	[redacted]	[redacted]	[redacted]
	Transfer	[redacted]	[redacted]	[redacted]
	RDS	[redacted]	[redacted]	[redacted]
	IVH	[redacted]	[redacted]	[redacted]
	Neonatal death	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]
	Incremental costs vs. Actim Partus	[redacted]	[redacted]	[redacted]
Discounted QALYs	Baseline w/o morbidity	[redacted]	[redacted]	[redacted]
	RDS	[redacted]	[redacted]	[redacted]
	IVH	[redacted]	[redacted]	[redacted]
	Newborn mortality	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]
	Incremental QALYs vs. Actim Partus	[redacted]	[redacted]	[redacted]
ICER vs Actim Partus		[redacted]	[redacted]	[redacted]

Key: fFN, fetal fibronectin; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year; * ICER represents a reduction in both costs and QALYs (the south-west quadrant in the cost-effectiveness plane);

3.4 PartoSure vs. qfFN using data from a direct comparison (Ravi et al. 2017)

According to the accuracy results from Ravi and colleagues, PartoSure would [redacted]

[redacted][4] Moreover, PartoSure would either [redacted]

Table 13 Results for fFN (various thresholds), PartoSure and no-testing vs fFN 50 ng/ml using data from Ravi 2017; presenting at 30 weeks gestation (level 2 hospital)

		Ravi 2017[4]					
		[redacted]					
Discounted Costs	Diagnosis	[redacted]					
	Medication	[redacted]					
	Admission	[redacted]					
	Transfer	[redacted]					
	RDS	[redacted]					
	IVH	[redacted]					
	Neonatal death	[redacted]					
	Total	[redacted]					
	Incremental costs vs. fFN 50 ng/ml	[redacted]					
Discounted QALYs	Baseline w/o morbidity	[redacted]					
	RDS	[redacted]					
	IVH	[redacted]					
	Newborn mortality	[redacted]					
	Total	[redacted]					
	Incremental QALYs fFN 50 ng/ml	[redacted]					
ICER vs fFN 50 ng/ml		[redacted]					

Key: fFN, fetal fibronectin; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year; * ICER represents a reduction in both costs and QALYs (the south-west quadrant in the cost-effectiveness plane);

Table 14 Results for fFN (various thresholds), PartoSure and no-testing vs fFN 50 ng/ml using data from Ravi 2017; presenting at 26 weeks gestation (level 2 hospital)

		Ravi 2017 [4]					
		Treat all	fFN 10	fFN 200	fFN 500	PartoSure	fFN 50
		[redacted]					
Discounted Costs	Diagnosis	[redacted]					
	Medication	[redacted]					
	Admission	[redacted]					
	Transfer	[redacted]					
	RDS	[redacted]					
	IVH	[redacted]					
	Neonatal death	[redacted]					
	Total	[redacted]					
	Incremental costs vs. fFN 50 ng/ml	[redacted]					
Discounted QALYs	Baseline w/o morbidity	[redacted]					
	RDS	[redacted]					
	IVH	[redacted]					
	Newborn mortality	[redacted]					

	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental QALYs fFN 50 ng/ml	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER vs fFN 50 ng/ml		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: fFN, fetal fibronectin; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year; * ICER represents a reduction in both costs and QALYs (the south-west quadrant in the cost-effectiveness plane);

Table 15 Results for fFN (various thresholds), PartoSure and no-testing vs fFN 50 ng/ml using data from Ravi 2017; presenting at 33 weeks gestation (level 2 hospital)

		Ravi 2017 [4]					
		Treat all	fFN 10	fFN 200	fFN 500	PartoSure	fFN 50
Discounted Costs	Diagnosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Medication	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Admission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Transfer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	IVH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Neonatal death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental costs vs. fFN 50 ng/ml	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discounted QALYs	Baseline w/o morbidity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	IVH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Newborn mortality	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental QALYs fFN 50 ng/ml	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ICER vs fFN 50 ng/ml		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Key: fFN, fetal fibronectin; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year; * ICER represents a reduction in both costs and QALYs (the south-west quadrant in the cost-effectiveness plane);

3.5 Scenario: different fFN thresholds for ANS and hospital admission; presentation at 33 weeks' gestation (at a Level 2 hospital)

In order to reflect local variation in practice, e.g. at a level 2 hospital in Exeter, we present the scenario where admission occurs only at fFN concentration levels of 200ng/ml or above; for the fFN 500 ng/ml test option, admission occurs at the threshold of 500ng/ml, as in the base case analysis. For women presenting at 33 weeks gestation, the fFN 10ng/ml option now has a cost of £465 per QALY gained relative to fFN 50ng/ml, while Actim Partus saves £16,828 and PartoSure saves £22,349 - £42,721 per QALY lost, relative to fFN 50ng/ml (Table 16). Detailed results are presented in Table 17.

Table 16 Summary of ICERs for women presenting at 33 weeks' gestation (level 2 hospital) using the Royal Devon and Exeter fFN admission threshold procedure

			Versus treat all			Versus fFN 50 ng/ml		
Test	**Total cost**	**Total QALYs**	**Incremental costs**	**Incremental QALYs**	**ICER (per QALY)**	**Incremental costs**	**Incremental QALYs**	**ICER (per QALY)**
Actim Partus[a20]	£5,055	22.010	-£1,116	-0.010	£108,323*	-£104	-0.006	£16,828*
PartoSure (Hadzi-Lega)[b 9]	£4,895 †	22.010 †	-£1,276	-0.010	£123,858*	-£264	-0.006	£42,721*
PartoSure (Wing)[c6]	£5,224 ‡	21.999 ‡	-£946	-0.012	£78,717*	-£177	-0.008	£22,349*
PartoSure (Nikolova)[d7]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treat all	£6,171	22.020	£0	0	-	£1,012	0.004	£245,564
fFN 10 ng/ml[a20]	£5,160	22.018	-£1,012	-0.002	£490,664*	£1	0.002	£465
fFN 50 ng/ml[a20]	£5,159	22.016	-£1,012	-0.004	£245,564*	£0	0	-
fFN 200 ng/ml[a20]	£5,159	22.006	-£1,012	-0.014	£73,676*	£0	-0.010	£10*
fFN 500 ng/ml[a20]	£5,004	21.992	-£1,167	-0.027	£42,474*	-£155	-0.023	£6,635*

Key: fFN - fetal fibronectin; ICER - incremental cost effectiveness ratio; QALY - quality adjusted life years; a Bruijn et al.[20, 44]; b Hadzi-Lega et al.47, indirect comparison with Bruijn et al. used as the reference study; c Wing et al., indirect comparison with Bruijn et al. used as the reference study; d Nikolova et al., indirect comparison with Bruijn et al. used as the reference study; * ICER represents a reduction in both costs and QALYs (the south-west quadrant in the cost-effectiveness plane); † Inferred total cost and QALYs for PartoSure obtained by applying relative differences vs Actim Partus, found using Hadzi-Lega et al. and Bruijn et al.; ‡ Inferred total cost and QALYs for PartoSure obtained by applying relative differences vs fFN 50, found using Wing et al. and Bruijn et al.; § Inferred total cost and QALYs for PartoSure obtained by applying relative differences vs Actim Partus, found using Nikolova et al. and Bruijn et al.

Table 17 Breakdown of results (discounted costs and QALYs) for women presenting at 33 weeks' gestation (level 2 hospital) using the Royal Devon and Exeter fFN admission threshold procedure

					Bruijn, 2016: APOSTEL-1 [a20]			Hadzi-Lega [b 9]	Wing [c6]	Nikolova [d7]
		Treat all	**fFN 10 ng/ml**	**fFN 50 ng/ml**	**fFN 200 ng/ml**	**fFN 500 ng/ml**	**Actim Partus**	**PartoSure**	**PartoSure**	**PartoSure**
Discounted Costs	Diagnosis	£0	£66	£66	£66	£66	£35	£52	£52	
	Treatment	£5	£3	£2	£1	£0	£1	£0	£1	
	Hospital admission	£1,325	£250	£250	£250	£95	£177	£1	£87	
	In-utero transfer	£0	£0	£0	£0	£0	£0	£0	£0	
	Neonatal RDS	£4,006	£4,008	£4,010	£4,018	£4,030	£4,015	£4,015	£4,017	
	Neonatal IVH	£788	£788	£789	£791	£793	£790	£790	£790	
	Survival due to ANS[1]	£47	£45	£43	£33	£20	£36	£36	£35	
	Total	£6,171	£5,160	£5,159	£5,159	£5,004	£5,055	£4,895	£4,982	
	Incremental Costs (vs. fFN 50ng/ml)	£1,012	£1	-	£0	-£155	-£104	-£264	-£177	
Discounted QALYs	Baseline without morbidity	21.999	21.999	21.999	21.999	21.999	21.999	21.999	21.999	
	New-born morbidity – RDS	-0.023	-0.023	-0.023	-0.024	-0.024	-0.023	-0.023	-0.023	
	New-born morbidity – IVH	0.000	0.000	-0.001	-0.001	-0.001	-0.001	-0.001	-0.001	
	Survival due to ANS	0.044	0.042	0.040	0.031	0.019	0.034	0.034	0.033	
	Total	22.020	22.018	22.016	22.006	21.992	22.010	22.010	22.008	
	Incremental QALYs (vs. fFN 50ng/ml)	0.004	0.002	-	-0.010	-0.023	-0.006	-0.006	-0.008	
	ICER (vs. fFN 50ng/ml)	£245,564	£465		£10*	£6,635*	£16,828*	£42,721*	£22,349*	

Notes: 1 These are the neonatal hospital costs associated with those infants saved by steroid treatment;

Key: AE, adverse events; fFN - fetal fibronectin; ICER - incremental cost effectiveness ratio; QALY - quality adjusted life years; a Bruijn et al.[20, 44]; b Hadzi-Lega et al.47, indirect comparison with Bruijn et al. used as the reference study, using the relative differences in the values for PartoSure vs Actim Partus; c Wing et al., indirect comparison with Bruijn et al. used as the reference study, using the relative differences in the values for PartoSure vs fFN 50; d Nikolova et al., indirect comparison with Bruijn et al. used as the reference study, using the relative differences in the values for PartoSure vs Actim Partus; * ICER represents a reduction in both costs and QALYs (the south-west quadrant in the cost-effectiveness plane)

3.6 Summary

We have presented results based on new data provided by the company. Direct new evidence on the relative test accuracy against fFN 50ng/ml provided for patients in the US, Wing et al. 2017, results in PartoSure saving costs to the NHS but producing lower health outcomes, i.e. QALYs, in women presenting at 30 weeks to a level 2 hospital; its expected cost saving per QALY lost is £22,349. [6] This amount increases to a cost saving per QALY lost of £38,835 in women presenting at 33 weeks, but is reduced to £14,167 in women presenting at age 26 weeks. [6] With its rate of spontaneous preterm birth of 1.28%, the study by Wing had as major strength its large sample size (n=701), and the limitation that it used a laboratory-based fFN test, which is no longer in use. [6] Evidence from the study by Ravi (Ravi et al. 2017) provides better results on PartoSure than these, but the sample was small [redacted]A third study was provided within 3 days of our deadline to respond to comments from stakeholders to our Diagnostic Assessment Report. This study directly compared Actim Partus with PartoSure in women living in one of three centres, from Macedonia, Russia and Finland (Nikolova et al. 2018).[redacted]These results provide evidence that PartoSure may be[redacted]relativ e to Actim Partus in women presenting at 30, 26 and 33 weeks' gestation, respectively.[7]

Given the limited time allowed to process the new data provided by Parsagen, the results presented above must be considered with caution since a) the studies considered are likely to suffer from selection bias as they are not the result of a systematic search and review of the clinical literature, b) we had no time not assess the degree of sampling uncertainty in these new results, c) new evidence is forthcoming in larger samples including the QUIDS and QUIDS2 studies. The results of this assessment should be updated on these three aspects before conclusions on cost-effectiveness of biochemical tests for preterm labour in symptomatic women may be drawn.

4 Discussion

It is worth noting, that Parsagen in their consultation comments to the ERG comment heavily about the omission of Lofti et al, Melchor et al, Ravi et al and Wing et al.[2-4, 6] However, in the unpublished systematic review and meta-analysis they also provided (Melchor et al.) there is a further study – Cekmez et al. 2017 – also published after our search date, that Parsagen have not highlighted.[11] Secondly from the same systematic review, a new Actim Partus study was identified – Fuchs et al. 2017.[27] Both these points demonstrate the huge bias of all the data presented in this addendum, since the inclusion of studies here are following the notification of one test developer and their systematic review.

Given the time-scale set out by NICE, we would also like to remind the reader that this addendum has been put together rapidly and the usual attention to detail and second checking for errors has not been possible.

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