York Health Economics Consortium

Economic Evaluation Case Study: PartoSure

1. BACKGROUND

Preterm birth (PTB) is defined as birth before 37 completed weeks of gestation. Infants born preterm are at increased risk of adverse neonatal outcomes, including bronchopulmonary dysplasia, intraventricular haemorrhage, retinopathy of prematurity, and neonatal sepsis. [1] In the UK, spontaneous preterm birth occurs in 7-12% of pregnancies before 37 weeks of gestation, and in about 4% of pregnancies before completion of the 34th week of gestation. [2]

For women presenting with symptoms of PTB, healthcare staff can offer interventions to reduce the risk of adverse outcomes. These interventions include administration of antenatal corticosteroids, which reduce neonatal morbidity and mortality, and tocolytics, which can delay the onset of labour by up to 48 hours. [3] Identification of the risk of PTB will result in a woman being admitted to hospital and, in cases that are identified in non-tertiary maternity units, the patient will have an in-utero transfer to a tertiary centre. However, identification of PTB risk is not precise. In one large RCT over 80% of women identified at risk of PTB had not delivered after seven days. [4]

Increased accuracy of tests for PTB is important, to ensure treatment is provided promptly where it is beneficial, and to prevent unnecessary interventions (with their associated costs) where PTB is less likely to occur. There are three tests currently available to assess the risk of PTB: a test for placental alpha microglobulin-1 (PAMG-1) (i.e. PartoSure); a test based on the phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) (ActimPartus); and a test based on fetal fibronectin (fFN) (Rapid fFN Q10), for which clinicians may use a cut-off for positive tests of 50 ng/ml or 200ng/ml. In the absence of eligibility for all tests, clinical evaluation only would be used to assess the risk of PTB within 7 days.

---

[1] Mangham L., et al. The Cost of Preterm Birth Throughout Childhood in England and Wales. *Pediatrics* 2009;123:e312–e327

[2] Deshpande SN, et al. Rapid fetal fibronectin testing to predict preterm birth in women with symptoms of premature labour: a systematic review and cost analysis. *Health Technology Assessment 2013* Vol 17 No 40. DOI: 10.3310/hta1740

[3] Ascarelli MH, Morrison JC. Use of fetal fibronectin in clinical practice. Obstet Gynecol Surv 1997;52 (suppl 4):S1–12.

[4] Kenyon, SL, et al. (2001). "Broad-spectrum antibiotics for spontaneous preterm labour: the ORACLE II randomised trial." *The Lancet* 357(9261): 989-994.

Table 1.1 shows the pooled positivity rate, the positive predictive value (PPV) and the negative predictive value (NPV) for each of these tests. [5,6,7,8,9]

Table 1.1 Positivity rate, PPV and NPV for each test

Test	Positivity*	PPV**	NPV***
PartoSure[5]	7.9%	76%	97%
Actim Partus[5]	29.7%	35%	99%
fFN 50ng/ml[5]	23.0%	34%	93%
fFN 200ng/ml[6-9]	17.7%	45%	96%

** Positivity rate: the rate at which a test turns positive.*
*** PPV (positive predictive value): the percentage of patients with a positive test who actually have the condition.*
**** NPV (negative predictive value): the percentage of patients with a negative test who do not have the condition.*

PartoSure can be used from 20+0 weeks to 36+6 weeks gestation. Contraindications are: advanced cervical dilatation (> 3cm); ruptured membranes; significant blood on the swab; within 6 hrs of vaginal disinfectant solutions or medicines.[10]

Actim Partus can be used from 22+0 weeks to 36+6 weeks gestation. Contraindications are: ruptured membranes; vaginal bleeding (moderate or heavy); presence of amniotic fluid.[11]

fFN can be used from 22+0 weeks to 35+6 weeks gestation. Contraindications are: advanced cervical dilatation (≥ 3cm); ruptured membranes; cervical cerclage; placental abruption; placenta previa (moderate) or vaginal bleeding (heavy). Inaccurate results may be likely following sexual intercourse, digital cervical exam or vaginal probe ultrasound and bacteria, bilirubin and semen.[9]

This case study reports a cost comparison analysis that calculates the economic impacts of using PartoSure compared to the other available tests for PTB. The results are based on an economic model prepared by York Health Economics Consortium (YHEC), which has been used to run two 'typical' scenarios for the use of PartoSure.

[5] Melchor JC, Khalil A, Wing D et al. Prediction of preterm delivery in symptomatic women using placental alphamicroglobulin-1, fetal fibronectin and phosphorylated insulin-like growth factorbinding protein-1 tests: systematic review and meta-analysis stratified by risk. *Ultrasound Obstet Gynecol*. 2018 Jun 19. doi: 10.1002/uog.19119.
[6] Bruijn M, Vis J, Wilms F, et al. Quantitative fetal fibronectin testing in combination with cervical length measurement in the prediction of spontaneous preterm delivery in symptomatic women. BJOG: *An International Journal of Obstetrics & Gynaecology.* 2016;123:1965-1971.
[7] Ravi M, Beljorie M, El Masry K. Evaluation of the quantitative fetal fibronectin test and **PAMG-1**test for the prediction of spontaneous preterm birth in patients with signs and symptoms suggestive of preterm labor. *J Matern Fetal Neonatal Med.* 2018 May 28:1-6. doi: 10.1080/14767058.2018.1476485
[8] Abbott, D. S., et al. "Evaluation of a quantitative fetal fibronectin test for spontaneous preterm birth in symptomatic women." *American journal of obstetrics and gynecology*. 2013; 208(2): 122 e121-126.
[9] Hologic. *Rapid fFN 10Q Cassette Kit: Instructions for use* 2016.
[10] Parsagen Diagnostics Inc. *PartoSure, Assess the risk of preterm birth: Instructions for use* 2015.
[11] Alere. *Alere Actim Partus Test: Instructions for use* 2015.

2. TEST COSTS

The cost of each test for risk of PTB is composed of the cost of the test itself and the cost of the midwife time used in performing the test. The costs in each case are shown in table 2.1.

Table 2.1 Costs of available tests for risk of PTB

Test	Cost of test (exc VAT)*	Cost of midwife time**	Total cost per test
PartoSure	£32.00	£43.33	£75.33
Actim Partus	£15.00	£43.33	£58.33
fFN 50ng/ml	£35.00	£65.00	£100.00
fFN 200ng/ml	£35.00	£65.00	£100.00

** Average market values at the time of writing.*
*** Personal Social Services Research Unit. Unit Costs of Health and Social Care 2017. University of Kent, Canterbury.*

3. TREATMENT COSTS

A patient who is identified as having a risk of PTB may receive some or all of the following four interventions: administration of antenatal corticosteroids (ACS); administration of tocolysis (Toc), hospital admission; admission and in-utero transfer. Table 3.1 shows the treatment costs for patients who have a positive PTB test result.

Table 3.1: Impacts, metrics and proxy values for PartoSure

Impact	Metric	Proxy value
More appropriate use of ACS	Treatment of patient with identified risk of PTB with antenatal corticosteroids	£5.00[a]
More appropriate use of Toc nefidipine	Treatment of patient with identified risk of PTB with nefidipine tocolysis	£1.00[b]
More appropriate use of Toc atosiban	Treatment of patient with identified risk of PTB with atosiban tocolysis	£362.00[a]
More appropriate use of hospital admission	Patient with identified risk of PTB is admitted to hospital as an inpatient	£1,325.00[a]
More appropriate use of in-utero transfer	Where the patient is initially seen in a non-tertiary hospital, they will be transferred to a tertiary hospital	£965.00[c]

[a] Parisaei M, Currie J, O'Gorman N, Morris S, David AL. Implementation of foetal fibronectin testing: Admissions, maternal interventions and costs at 1year. Journal of Obstetrics and Gynaecology. 2016;36(7):888-92.
[b] Preterm labour and birth. NICE Guideline [NG25]. 20 November 2015. Available from: nice.org.uk/guidance/ng25.
[c] Gale C, Morris I. The UK National Neonatal Research Database: using neonatal data for research, quality improvement and more. Archives of disease in childhood - Education & practice edition. 2016;101(4):216-8. For midwife time: Personal Social Services Research Unit. Unit Costs of Health and Social Care 2017. University of Kent, Canterbury.

4. ECONOMIC ANALYSIS

The information above enables a cost comparison to be made, based on the costs of using PartoSure relative to the alternative tests for PTB. YHEC has developed an economic model which calculates the costs and allows different input values to be entered, so that different scenarios can be compared by the user of the model. This section reports the results of two scenarios. They are based on the following assumptions:

- Any patient that receives ACS and/or Toc would be admitted as a hospital inpatient.
- Any non-tertiary hospital would transfer a patient via in-utero transfer to a tertiary hospital if the mother is suspected of PTB before 28 weeks' gestation.
- Hospitals will use Nifedipine rather than the more expensive Atosiban for tocolysis.
- In line with results of a compliance evaluation, 67% of patients with positive biomarker results are treated with ACS and 6% of those with negative results are treated. [12]
- From the same study, 14% of women with positive test results are treated with tocolytics and 2% of those testing negative are treated.

4.1 Scenario 1

The characteristics used for Scenario 1 are:

- The hospital is a tertiary centre, so in-utero transfers are not required.
- 500 patients present with symptoms of PTB per annum (out of 5,000 births).
- PartoSure is compared with fFN 50ng/ml and Actim Partus.
- The level of risk of PTB is intermediate, based on the risk stratification outlined in the recent meta-analyses. [6]
- 100% of patients are eligible for a PartoSure test and 90% are eligible for the comparator tests, due to contraindications.

The results of this scenario are in Table 4.1.

Table 4.1: Cost comparisons for Scenario 1

Cost breakdown	PartoSure	Actim Partus	Difference: Actim Partus-PartoSure	fFN 50ng/ml	Difference: fFN 50ng/ml-PartoSure
Cost of test (incl. staff time)	£37,665	£26,249	£11,417	£45,000	-£7,335
Cost of treating those eligible for the biomarker test	£89,232	£202,804	-£113,571	£165,156	-£75,924
Cost of treating those not eligible for biomarker test	£0	£66,250	-£66,250	£66,250	-£66,250
Grand total	**£126,897**	**£295,302**	**-£168,405**	**£276,406**	**-£149,509**

These results show that in a tertiary hospital with 500 patients presenting with symptoms of PTB per year, PartoSure is cost saving when compared to both Actim Partus and fFN 50ng/ml tests, with savings of £168,405 and £149,509 respectively.

[12] Tekesin I et al. Assessment of rapid fetal fibronectin in predicting preterm delivery. *Obstet Gynecol* 2005; **105** : 280-4.

4.2 Scenario 2

The characteristics used Scenario 2 are:

- The hospital is a non-tertiary centre, so in-utero transfers are required.
- 300 patients present with symptoms of PTB per annum (out of 3,000 births).
- PartoSure is compared with fFN 50ng/ml and Actim Partus.
- The level of risk of PTB is intermediate, based on the risk stratification outlined in the recent meta-analyses. [6]
- 100% of patients are eligible for a PartoSure test and 90% are eligible for the comparator tests, due to contraindications.

The results of this scenario are in Table 4.2.

Table 4.2: Cost comparisons for Scenario 2

Cost breakdown	PartoSure	Actim Partus	Difference: Actim Partus-PartoSure	fFN 50ng/ml	Difference: fFN 50ng/ml-PartoSure
Cost of test (incl. staff time)	£22,599	£15,749	£6,850	£27,000	-£4,401
Cost of treating those eligible for the biomarker test	£60,419	£137,324	-£76,905	£111,831	-£51,412
Cost of treating those not eligible for biomarker test	£0	£44,874	-£44,874	£44,874	-£44,874
Grand total	£83,018	£197,948	-£114,929	£183,706	-£100,687

These results show that in a non-tertiary hospital with 300 patients presenting with symptoms of PTB per year, PartoSure is cost saving when compared to both Actim Partus and fFN 50ng/ml tests, with savings of £114,929 and £100,687 respectively.

An example decision tree is provided at Appendix 1, to illustrate the calculations used for the results above. This uses the results for PartoSure under Scenario 1.

4.1 Other benefits of PartoSure as a test for PTB

There are a number of other benefits of PartoSure, leading to an increase in the number of cases in which it can be used, as compared to the other tests, as follows:

- PartoSure is the only test for which the specimen can be collected without a speculum examination, which midwives may not be able to perform, depending on hospital policy.
- Vaginal examination shortly before specimen collection does not lead to false positive PartoSure test results,[13,14] unlike fFN 50ng/ml.

[13] Werlen S, Raia T, Di Bartolomeo A, Chauleur C. [Preterm labor: Reproducibility of detection test of PAMG-1before and after digital examination, and transvaginal ultrasound cervical length]. *Gynecol Obstet Fertil*. 2015 Oct;43(10):640-5. doi: 10.1016/j.gyobfe.2015.07.002. Epub 2015 Jul 30. French.

[14] Di Fabrizio L, Giardina I, Cetin I, Di Tommaso M, Ciavattini A, Locci M, Facchinetti F, Zonca M, Di Renzo GC. [New methods for prediction of preterm birth: the PAMG-1 Test]. *Minerva Ginecol.* 2018 May 31. doi: 10.23736/S0026-4784.18.04243-0. [Epub ahead of print] Italian.

- PartoSure has a wider gestational age limit (20 weeks and 0 days to 36 weeks and 6 days) compared to fFN (24 weeks and 0 days to 35 weeks and 6 days).
- PartoSure can be used in patients with a cervical dilatation of 3cm, whereas fFN 50ng/ml is intended for use in patients with a cervical dilatation of <3cm.
- Semen does not lead to false positive PartoSure test results, which it can with fFN 50ng/ml.

4.2 Sensitivity Analysis

The scenarios above are based on the assumption that 100% of patients are eligible for a PartoSure test and 90% are eligible for the comparator tests. To assess the robustness of the results, the scenarios have been re-calculated using different levels of eligibility for PartoSure and the comparator tests.

Firstly, the calculations have been done assuming 90% of patients are eligible for a PartoSure test and 90% are eligible for the comparator tests. Secondly the calculations were repeated, assuming 95% of patients are eligible for a PartoSure test and 80% are eligible for the comparator tests. The results are shown in Table 4.3 below.

Table 4.3 Results of sensitivity analyses

	Total cost of PartoSure	**Total cost of Actim Partus**	**Total cost of fFN 50ng/ml**
Sensitivity analysis 1: 90% eligible for PartoSure; 90% eligible for comparators			
Scenario 1	£180,458	£295,302	£276,406
Scenario 2	£119,590	£197,948	£183,706
Sensitivity analysis 2: 95% eligible for PartoSure; 80% eligible for comparators			
Scenario 1	£153,678	£336,102	£319,306
Scenario 2	£101,304	£225,814	£213,154

These sensitivity analyses show that PartoSure continues to have a lower total cost than Actim Partus and fFN 50ng/ml when the proportions of patients eligible for the tests are varied.

5. CONCLUSION

This economic analysis indicates that use of PartoSure to test for risk of PTB has a lower total cost than use of Actim Partus and fFN 50ng/ml. This is true in both tertiary and non-tertiary hospitals. These savings arise due to the avoided cost of treatments associated with the risk of PTB, particularly the cost of hospital admission and in-utero transfer. This also brings benefits to patients, who may avoid unnecessary admission and treatment with tocolytic drugs.

The sensitivity analyses indicate that the results are robust under different levels of eligibility for the use of the different tests. The range of conditions under which PartoSure can be used suggests that it can be more widely used than the alternatives. It also has higher positive predictive value and similar negative predictive value.

To improve the accuracy of the fetal fibronectin test, quantification of the biomarker is available. In recent studies [6-9] an increase in the fFN quantification provides an improved predictive value but with a reduction in negative predictive value. This additional option has led to some users admitting patients with a >50ng/ml reading but administering therapeutics when a reading exceeds 200ng/ml. Subsequently, (false) admission rates remain the same as the 50ng/ml option, but the use of therapeutics differs with the 200ng/ml option.

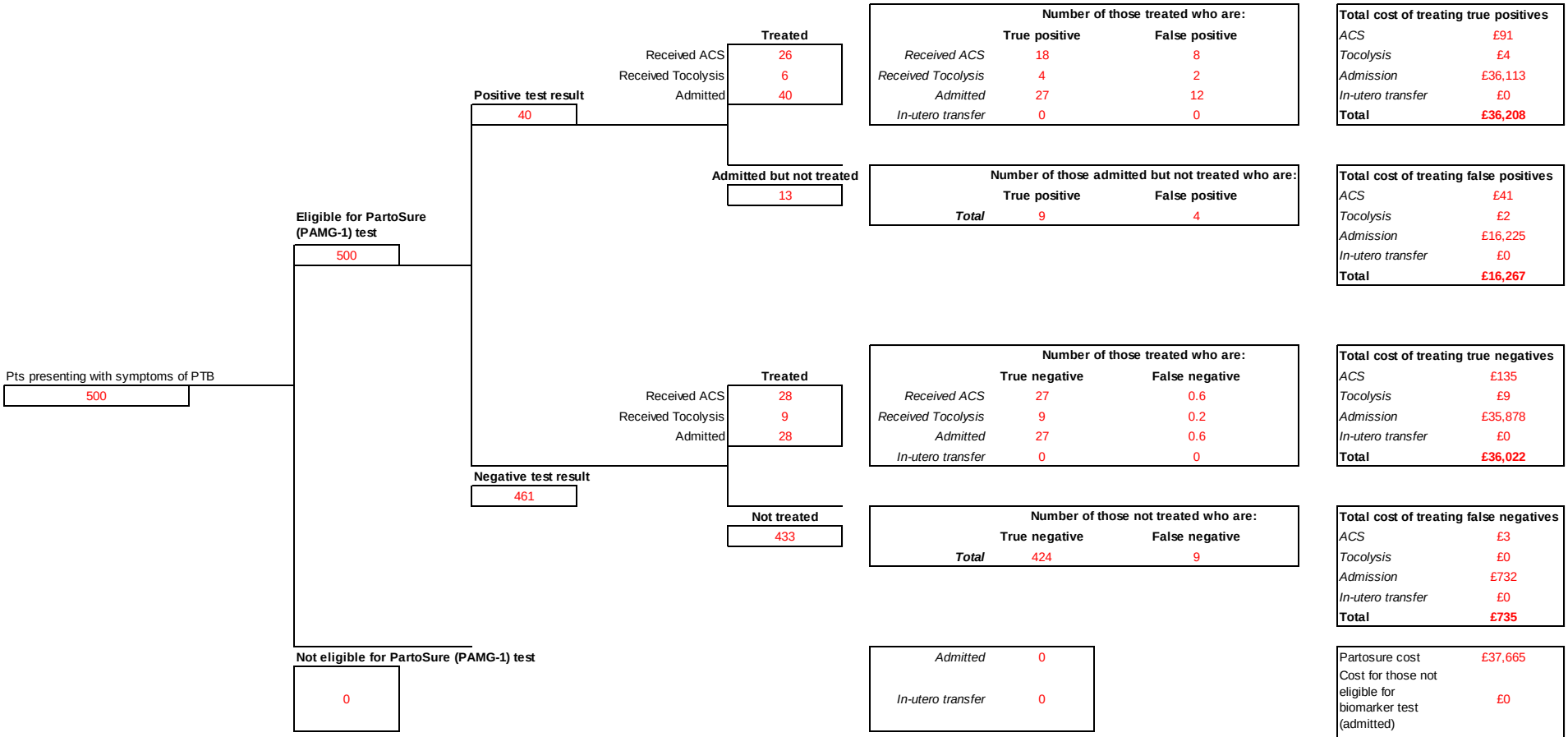
Users of the economic model underpinning this case study may explore the impact of different scenarios to reflect their local circumstances. Parameters in the model which may be varied include:

- Number of patients with symptoms of PTB per year.
- Type of maternity hospital.
- Level of risk of preterm birth.
- Choice of comparator test.
- Proportions of patients eligible for use of the biomarker tests being compared.
- Choice of tocolytic drug used.
- Costs of the test and staff time required to perform the test.

This analysis was developed in July 2018 and was based on the information and evidence available at the time. The analysis makes use of certain assumptions, which are explained in Section 4.

York Health Economics Consortium
July 2018

Appendix 1. Example decision tree using Scenario 1, results for PartoSure



Number of those treated who are:	True positive	False positive
Received ACS	18	8
Received Tocolysis	4	2
Admitted	27	12
In-utero transfer	0	0

Total cost of treating true positives	
ACS	£91
Tocolysis	£4
Admission	£36,113
In-utero transfer	£0
Total	**£36,208**

Number of those admitted but not treated who are:	True positive	False positive
Total	9	4

Total cost of treating false positives	
ACS	£41
Tocolysis	£2
Admission	£16,225
In-utero transfer	£0
Total	**£16,267**

Number of those treated who are:	True negative	False negative
Received ACS	27	0.6
Received Tocolysis	9	0.2
Admitted	27	0.6
In-utero transfer	0	0

Total cost of treating true negatives	
ACS	£135
Tocolysis	£9
Admission	£35,878
In-utero transfer	£0
Total	**£36,022**

Number of those not treated who are:	True negative	False negative
Total	424	9

Total cost of treating false negatives	
ACS	£3
Tocolysis	£0
Admission	£732
In-utero transfer	£0
Total	**£735**

Admitted	0
In-utero transfer	0

Partosure cost	£37,665
Cost for those not eligible for biomarker test (admitted)	£0
Cost for those not eligible for biomarker test (in-utero transfer)	£0

Grand total	**£126,897**