NICE National Institute for Health and Care Excellence

Diagnostics Assessment Programme

PLGF-based testing to help diagnose suspected preterm pre-eclampsia (update of DG23)

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Contents:

Economic analyses in the Diagnostics Assessment Report (DAR), and addendum and erratum to this document, are replaced by the NICE Decision Support Unit (DSU) report. The parts of these documents that are superseded by the DSU's report are indicated with a watermark. Further detail on the reasons for this can be found in the diagnostics consultation document.

Any information supplied to NICE which has been marked as confidential has been redacted. All personal information has also been redacted.

At the first committee meeting for this topic the committee was concerned about the external assessment group's (EAG's) model and approach to modelling. Further detail can be found in the diagnostic consultation document.

The committee concluded that more work on the model was needed to address these concerns before any recommendations could be made. As a result of these concerns, NICE commissioned the DSU to carry out further modelling work. For the second committee meeting, the DSU provided an updated model and analyses.

Economic analyses in the EAG's diagnostics assessment report (DAR) are therefore replaced by the DSU's report. Details in the DAR which are superseded by the DSU's report are indicated with a watermark.

CONFIDENTIAL UNTIL PUBLISHED

Technology Assessment Report commissioned by the NIHR Evidence Synthesis Programme on behalf of the National Institute for Health and Care Excellence (NICE)

Placental growth factor (PlGF)-based testing to help diagnose suspected pre-eclampsia (update of DG23)

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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Date completed **11th May 2021**

Word count: 83,492 (including appendices)

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 132386 and will be published in full in *Health Technology Assessment* (http://www.journalslibrary.nihr.ac.uk/hta).

Declared competing interests of authors

None

All authors have completed the unified competing interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare 1) no financial support for the submitted work from anyone other than their employer; 2) no financial relationships with commercial entities that might have an interest in the submitted work; 3) no spouses, partners, or children with relationships with commercial entities that might have an interest in the submitted work; and 4) no non-financial interests that may be relevant to the submitted work.

Acknowledgements

We are grateful to the following for providing expert methodological/clinical advice and comments on the draft report:

- Dr Jeremy Jones, Principal Research Fellow in Health Economics, University of Southampton, UK.
- Professor Sam Oddie, Consultant Neonatologist, Bradford Teaching Hospitals NHS Foundation Trust, UK.
- Professor Steve Robson, Professor of Fetal Medicine, Institute of Cellular Medicine, Newcastle University, UK.
- Dr David Williams, Consultant Obstetric Physician, Institute for Women's Health, University College London Hospital, UK.
- Suzanne Thomas, Midwifery lead for the Manchester Placenta Clinic and St Mary's Rainbow Clinic, UK.
- Rowan Grigg, Education Officer, Action on Pre Eclampsia (APEC), UK.

Additionally, we thank the Specialist Committee Members of the NICE Diagnostics Advisory Committee for providing comments on a draft of this report.

We would also like to thank Dr Jaime Peters, Senior Research Fellow, Exeter Medical School and Professor Chris Hyde, Professor of Public Health and Clinical Epidemiology, University of Exeter for expert advice on diagnostic assessment, and Professor Joanne Lord, SHTAC, for reviewing and commenting on a draft of this report.

Rider on responsibility for the report

The views and opinions expressed in this report are those of the authors and do not necessarily reflect those of NIHR, NHS or the Department of Health. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Frampton, G; Pickett, K; Tikhonova I; Souto Ribeiro, I; Woods, L; Cooper, K; Hazell, L; Scott, D; and Shepherd, J. Placental growth factor (PlGF)-based testing to help diagnose suspected pre-eclampsia (update of DG23). Southampton Health Technology Assessments Centre (SHTAC), 2021.

Contribution of authors

Geoff Frampton carried out the systematic review of test accuracy and clinical effectiveness, drafted the report, managed the project, and is the project guarantor; Karen Pickett carried out the systematic review of test accuracy and clinical effectiveness, and drafted the report; Irina Tikhonova developed the independent economic model and drafted the report; Inês Souto Ribeiro carried out the review of economic evaluations, developed the independent economic model, and drafted the report; Lois Woods carried out the systematic review of test accuracy and clinical effectiveness, and drafted the report; Keith Cooper carried out the review of economic evaluations, developed the independent economic model and drafted the report; Lorna Hazel carried out the systematic review of test accuracy and clinical effectiveness, and drafted the report; David Scott developed the independent economic model and drafted the report; Jonathan Shepherd carried out the systematic review of test accuracy and clinical effectiveness, drafted the report and co-managed the project;

Keywords: Pregnancy management, pre-eclampsia, biomarker tests, diagnosis, test accuracy, cost effectiveness

Please note that: content highlighted in yellow and underlined is ‘academic in confidence’ (AIC). Commercial in confidence (CIC) information is in blue

ABSTRACT

Background

Predicting a diagnosis of pre-eclampsia is based on a combination of clinical assessment of blood pressure, presence of protein in the urine, symptoms, and laboratory test abnormalities. Accurately detecting pre-eclampsia is important to avoid false-positive diagnoses which could lead to unnecessary antenatal admissions and/or preterm delivery. Four blood tests that measure the biomarkers of placental growth factor (PlGF) or the ratio of soluble fms-like tyrosine kinase 1 (sFlt-1) to PlGF, are now available, of which two are currently used in UK clinical practice. Abnormal measurements of these biomarkers can be used as an aid to predict a diagnosis of pre-eclampsia.

Objectives

To evaluate the test accuracy, clinical effectiveness and cost-effectiveness of PlGF-based tests used in conjunction with standard clinical assessment for pregnant women referred to secondary care with suspected pre-eclampsia in weeks 20–37 of pregnancy.

Data sources and methods

A systematic review was conducted of studies of the diagnostic/prognostic accuracy and clinical effectiveness of PlGF-based tests used alongside standard clinical assessment.
An independent economic analysis was conducted using a decision tree model. The model includes short term cost and QALYs for the management of women, maternal and neonatal outcomes and long-term outcomes for severe neonatal complications.

Results

A total of 17 studies were included in the systematic review of test accuracy and clinical effectiveness. Two large randomised trials provided the most comprehenvsive and rigorous evidence to inform the economic model - The PARROT trial (Triage test) and the INSPIRE trial (Elecsys). The model estimates that the Triage PlGF test used as an add-on to standard clinical assessment would have a cost saving of £1,746 and an increase of 0.20 QALYs per woman with suspected pre-eclampsia compared with standard clinical assessment alone. Addition of the Elecsys test to standard clinical assessment would increase the cost by £621 per woman and a reduce QALYs by 0.14.

Limitations

Although the evidence base for PlGF tests is advancing there remains some uncertainty in cost effectiveness results particularly for the Elecsys test.

Conclusions

Use of PlGF-based testing alongside standard clinical assessment to help diagnose suspected pre-eclampsia and inform subsequent care decisions, compared to standard clinical assessment alone, can be cost saving based on current available evidence.

Study registration: This study is registered as PROSPERO CRD42020227085

Funding: NIHR Evidence Synthesis Programme as project number 132386

SCIENTIFIC SUMMARY

Background

Pre-eclampsia affects approximately 6% of pregnant women, usually from around 20 weeks of gestation, with severe cases affecting 1-2% of pregnant women. If the condition is undetected or left untreated it can result in serious, potentially fatal, maternal and neonatal complications, such as stroke or organ dysfunction or eclampsia or fetal growth restriction or intrauterine death. The only cure for pre-eclampsia is to deliver the placenta (and therefore the baby) so women are monitored until the optimum time for delivery.

Pre-eclampsia can be asymptomatic, and it can be difficult to detect in women with pre-existing hypertension, therefore assessment for pre-eclampsia is incorporated into routine antenatal assessments. Women are suspected of having pre-eclampsia if they have high blood pressure and/or proteinuria. Further signs and symptoms of suspected pre-eclampsia include swelling of the feet, ankles, face and hands, severe headache, vision problems, pain just below the ribs, and suspected fetal compromise.

If pre-eclampsia is suspected, current practice is to assess the person for blood pressure, proteinuria, other symptoms such as oedema or neurological disturbances, and abnormal laboratory results in order to diagnose the condition or decide whether and how to continue to monitor the pregnancy. In addition, blood tests have been developed that measure levels of two proteins in the blood: placental growth factor (PlGF), which occurs in abnormally low levels in women with pre-eclampsia; and soluble fms-like tyrosine kinase 1 (sFlt-1), which occurs in abnormally high levels in women with pre-eclampsia. Two of these tests (Triage and Elecsys) were recently incorporated into clinical practice to aid in predicting a diagnosis of pre-eclampsia. A further two tests which measure these proteins (BRAHMS and DELFIA) are now available for use which have not yet been evaluated for diagnostic or prognostic/predictive accuracy and cost-effectiveness for the NHS.

The four tests specified in the NICE scope for this diagnostic assessment and evaluation, are: Triage® PlGF test (Quidel Cardiovascular Inc; San Diego, CA, USA); the DELFIA® Xpress PlGF 1-2-3 test (PerkinElmer, Wallac Oy, Turku, Finland); the Elecsys® sFlt-1 to PlGF ratio test (Roche Diagnostics GmbH, Mannheim, Germany) and the BRAHMS® sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio test (Thermo Fisher Scientific GmbH, Hennigsdorf, Germany).

Objectives

The aim of this study is to investigate the test accuracy, clinical effectiveness and cost-effectiveness of the four biomarker tests at predicting a diagnosis of pre-eclampsia in pregnant women presenting with suspected pre-eclampsia between 20 and 36 weeks plus 6 days pregnancy who have received standard clinical assessment (including blood pressure and/or proteinuria assessment). Specifically, to:

- Assess any new evidence for the test accuracy and analytical validity of the BRAHMS and DELFIA tests (NICE research recommendation 1.3)
- Assess any new evidence for use of repeat testing for suspected pre-eclampsia: investigating test accuracy, intervals between tests, and scenarios when it might be used (NICE research recommendation 6.1).
- Assess any new evidence for the accuracy of the Triage and Elecsys tests to rule-in pre-eclampsia (NICE research recommendation 6.2).
- Assess the impact of the tests as an aid to diagnosis on clinical decision-making, investigating effect on outcome measures such as time to delivery or hospital admission, and on maternal and neonatal outcomes such as morbidity and mortality (NICE's 2020 evidence review identified studies reporting outcome measures and clinical outcomes).

Methods

Systematic review of test accuracy and clinical effectiveness

A systematic review of diagnostic and prognostic accuracy evidence was conducted following a peer-reviewed protocol. Searches were based on a comprehensive search strategy. Bibliographic databases, including MEDLINE, Embase, Web of Science, The Cochrane Library and the International HTA database, were searched for English-language references in November 2020, and these searches were updated in March 2021. Conferences, websites, and confidential company submissions were also obtained, and reference lists of identified systematic reviews and meta-analyses were checked.

Studies were eligible if they included women with suspected pre-eclampsia between 20 and 36 weeks plus 6 days pregnancy and reported accuracy of at least one of the specified tests for identifying pre-eclampsia when it was used alongside standard clinical practice. Risks of bias and generalisability of the included studies were assessed using the Quality

Assessment of Diagnostic Accuracy Studies 2 (QUADAS 2) instrument, which was tailored to this review.[1] Where included studies had outcomes additional to diagnostic and prognostic/predictive accuracy, they were assessed using the Cochrane Risk of Bias tool[2] or as appropriate for the study design. Study selection, data extraction and critical appraisal were each performed by two reviewers, with any disagreements resolved through discussion and referred to a third reviewer for resolution as necessary. Data were synthesised narratively, the option of conducting a pre-planned meta-analysis was not appropriate because the data was largely heterogeneous.

Review of economic evaluations

A systematic review was undertaken to identify economic evaluations of PlGF in addition to current management compared to standard clinical assessment only in women with suspect pre-eclampsia. The included population, interventions and comparators were the same as for the systematic review of clinical studies (as described in 3.2), but the study design and outcomes were differed for the economic review. Studies were included if they were full economic evaluations, assessing both costs and consequences, or cost studies for the specified index tests. Outcomes included are those consistent with full economic evaluations and cost studies, including measures of resource use (budget impact, cost per patient or cost per case of PE correctly managed) and health outcomes (life-years or QALYs gained).

We identified eleven economic evaluations of diagnostic tests that are within the scope of this assessment, i.e. diagnostic tests for pre-eclampsia administered to women between 20 weeks and 36 weeks plus 6 days of gestation. Six of the included studies are evaluations of the Elecsys sFlt-1/PlGF ratio test, two are evaluations of the Triage PlGF test, two assess more than one PlGF test and the other did not report which PlGF test(s) were evaluated. Four studies were conducted in the UK. The majority of the studies used a decision tree model. Only one study included QALYs. The studies suggest that including diagnostic tests alongside usual care has the potential to reduce maternal adverse events and reduce the number of women who receive inappropriate treatment (mainly hospitalisation) due to false-positive diagnoses. All studies reported cost saving when using the PlGF test and this varied between £26 and £2,896 per woman.

Independent economic assessment

We developed a new model to compare the use of PlGF in addition to standard clinical assessment versus standard clinical assessment alone for women with suspect pre-eclampsia, based upon one previously developed by Frampton et al.. The model includes a decision tree with components for management, maternal outcomes and neonatal outcomes.

Clinical parameters were taken from the PARROT RCT for the Triage test and the INSPIRE RCT for the Elecsys test. These trials were both conducted in the UK and evaluated the addition of PlGF-based tests to standard clinical assessment for women with suspected pre-eclampsia and are therefore relevant to the decision problem. They also reported maternal, fetal and neonatal outcomes, as well as intermediate clinical indicators and prognostic accuracy of the tests.

The costs are evaluated from the perspective of the NHS and Personal Social Services. Outcomes are expressed as QALYs. The lifetime time horizon was adopted in the base case with the discount rate of 3.5% applied to both costs and QALYs, in line with the NICE guidance. A shorter time horizon of up to six months post-partum was tested in a scenario analysis.

The costs considered in the economic analysis included:

- The cost of PlGF testing, including the cost of equipment, reagents and consumables, and the cost of staff and associated training
- The cost of managing gestational hypertension and pre-eclampsia from presentation to delivery, including the cost of antihypertensive treatment, magnesium sulphate to reduce the risk of seizure (for women with pre-eclampsia) and corticosteroids for fetal lung maturation
- Delivery cost
- The cost of maternal intensive care and ward stay
- The cost of neonatal unit stay including intensive care (NICU), high dependency (HDU) and special care (SCBU)
- The cost of follow-up up to 6 months post-partum
- Long-terms costs associated with complications in neonates

We estimated the total QALYs for the test and comparator arms by considering the quality of life associated with delivery, maternal adverse events, post-natal care and neonatal adverse events. These included the long-term QALY loss associated with adverse events and the QALYs associated with false positive results.

We also conducted scenario analyses for the Triage and Elecsys tests using the evidence from prospective observational comparisons of PlGF-based add-on tests versus standard clinical assessment alone: the analysis of MAPPLE/PELICAN cohort studies by Sharp and colleagues for the Triage test; and the PreOS before/after prospective study for the Elecsys test.

Results

Database searches identified 1974 unique bibliographic records and another 66 records were identified through searches of conference abstracts, company submissions and directly from study authors. After screening, the systematic review included 37 documents that reported 17 studies. Seven of these studies investigated use of the test alongside standard clinical assessment, and these are the focus of the review. The remaining ten studies investigated the test results independently of standard clinical assessment, and they include key studies from the previous DAR.

It was not feasible to perform a meta-analysis of either test accuracy or clinical effectiveness because of the heterogeneity of study outcomes. The diagnostic and prognostic/predictive accuracy outcomes varied according to rule-in or rule-out for differing time periods and different gestational age ranges. The various clinical outcomes for maternal and neonatal morbidity and mortality were numerous and not reported consistently across all the studies.

Evidence for the Elecsys test found that a test ratio cut-off of 85 had a PPV of 71% to rule-in pre-eclampsia within 4 weeks in women presenting between 24 and 37 weeks' pregnancy. The BRAHMS test using the same ratio cut-off of 85 had a PPV of 62% to rule-in pre-eclampsia within 4 weeks and a PPV of 46% to rule-in pre-eclampsia within 1 week in women presenting between 24 and 37 weeks' pregnancy (sensitivity and specificity were not reported). High NPVs were reported across the studies for the Elecsys test ratio cut-off of 38 so the evidence remains stronger for using the test to rule out pre-eclampsia. Other predictive accuracy evidence combined diagnosis of pre-eclampsia with other outcomes such as time to delivery, or requiring preterm delivery: the Triage test had a PPV of 100% (sensitivity 51%) to predict pre-eclampsia and a test to birth interval of 14 days using a test cut-off of <12pg/ml and a PPV of 87% (sensitivity 95%) using a test cut-off of <100pg/ml.

The EAG cost-effectiveness model estimates that the Triage PlGF test would have a cost saving of £1,746 and an increase of 0.20 QALYs per woman with suspected pre-eclampsia compared with current management only. Most of the savings in costs and improvement in QALYs were related to the long-term outcomes, which were based on the frequency of neonatal adverse outcomes. For the Elecsys test, there is an increase in cost of £621 per woman and a reduction of 0.14 QALYs with suspected pre-eclampsia compared with current management only. In the analysis for BRAHMS, assuming equal predictive accuracy to that of Elecsys, an increase in cost was £594.

Conclusions

Our analysis shows that the Triage PlGF test is likely to be cost effective, based on the outcomes from the PARROT trial. The test is cost saving and would improve QALYs compared to standard clinical practice only. In contrast, the Elecsys would not be cost-effective, based on the INSPIRE trial. However, data were not available for maternal and neonatal outcomes so results should be treated with caution. The analysis for BRAHMS suggests that standard clinical practice would be dominant. This analysis, however, is subject to uncertainty due to the context of the ROPE cohort study (standalone tests in a single US centre) which provided samples for an area-under-the-curve (AUC) analysis for BRAHMS and Elecsys, and has the same caveats as the cost-utility analysis for Elecsys.

Further research to compare more than one of the PlGF-based tests used as add-ons to the standard clinical assessment within the same trial would be useful, although there might be practical limitations. There is uncertainty around clinical utility of the BRAHMS and DELFIA tests, and the impact on maternal and neonatal outcomes of the use of Elecsys test in addition to standard clinical practice for diagnosis of pre-eclampsia. The clinical effectiveness systematic review identified limited evidence on the use of repeat testing which precluded a thorough economic evaluation of this testing strategy. Further research is needed to address the long-term impact of pre-eclampsia in women, for example future complications that could emerge and the related costs and utilities. More research is also needed on the impact of adverse maternal and neonatal outcomes on long-term quality of life and costs for mother and neonates, in particular the life-time costs related to intraventricular haemorrhage.

PLAIN ENGLISH SUMMARY

pre-eclampsia is a condition that affects some pregnant women and, if not detected or left untreated, can result in serious complications for the mother and/or the baby.
Four tests are now available (Triage, Elecsys, BRAHMS and DELFIA) that measure the level of certain proteins in the blood that can be abnormal in women with pre-eclampsia. We investigated the use of these tests in addition to clinical assessmentto help diagnose pre-eclampsia. These blood tests can help determine whether pregnant women suspected of having pre-eclampsia require admission to hospital or if they can be safely monitored as outpatients, potentially improving care and saving money.

We carried out expert medical evidence searches to update our knowledge of the accuracy and cost of these tests and to evaluate the impact on delivery-related outcomes for mother and baby. From the evidence we found we developed an economic model that estimated

costs and benefits to predict whether or not the tests would be good value for money for the NHS. Our results predict that the Triage and Elecsys tests improve care and save money when used in addition to routine clinical assessment of women with suspected pre-eclampsia.

Our model results suggested the Triage test is likely to reduce costs and improve health outcomes compared with standard clinical management only. In contrast the Elecsys is likely to improve costs and reduce health outcomes compared to standard clinical management only, although the results for this test varied depending on the clinical study used.
There is uncertainty around use of the BRAHMS and DELFIA tests, and on the usefulness and costs of repeat testing because of limited evidence, and research recommendations are made to reduce this uncertainty.

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LIST OF ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
AUC	Area under the curve
CE	Cost-effectiveness
CG107	Clinical guideline 107
CI	Confidence interval
DAP53	Diagnostics assessment programme 53
DAR	Diagnostic Assessment Report
DG23	Diagnostics guidance 23
EAG	External assessment group
eMiT	Drugs and pharmaceutical electronic market information tool national database
EQ-VAS	EuroQol Visual Analogue Scale
EQ-5D	EuroQol 5 dimension questionnaire
FGR	Fetal growth restriction
FP	False positive
FN	False negative
HAQ	Health Assessment Questionnaire
HCHS	Hospital and Community Health Services
HELLP	Haemolysis, elevated liver enzymes, low platelet count
HDU	High-dependency unit
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HT	Hypertension
HUI	Health Utilities Index
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
ISSHP	International Society for the Study of Hypertension in Pregnancy
IUGR	Intra-uterine growth restriction
LR	Likelihood ratio
N/A	Not applicable
NG133	NICE guideline 133

NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
NICU	Neonatal intensive care unit
NMB	Net monetary benefit
NPV	Negative predictive value
ONS	Office for National Statistics
OWSA	One-way sensitivity analysis
PE	Pre-eclampsia
PlGF	Placental growth factor
PPV	Positive predictive value
PSA	Probabilistic sensitivity analysis
RCT	Randomized controlled trial
ROC	Receiver–operator characteristics
RUQ	Right upper quadrant
QALY	Quality-adjusted life-year
SF-6D	Short-form six dimension questionnaire
SF-12	Short-form 12 dimension questionnaire
SF-36	Short-form 36 dimension questionnaire
sFLT-1	Soluble FMS-like tyrosine kinase-1
SGA	Small for gestational age
TN	True negative
TP	True positive
UtADV	Uterine artery Doppler velocimetry
UK	United Kingdom

1 BACKGROUND

1.1 Description of the health problem

Pre-eclampsia is a potentially serious complication commonly occurring during the second half of pregnancy (after 20 weeks' gestation). It is associated with placental dysfunction, whereby blood flow through the placenta is reduced, and is characterised by maternal hypertension and proteinuria, though not all women have both of these manifestations.[1] If pre-eclampsia is undetected and untreated it may result in complications including disseminated intravascular coagulation, stroke or organ dysfunction or can develop into eclampsia, a potentially life-threatening convulsive condition. The only cure for pre-eclampsia is to deliver the placenta (and therefore the baby). Women who have hypertension or pre-eclampsia during pregnancy may also have a higher risk of complications from placental abruption (when the placental lining separates from the uterus before delivery).[2] Gestational hypertension (high blood pressure that develops during pregnancy) and pre-eclampsia can also affect the fetus, increasing the risk of intrauterine growth restriction and intrauterine death.[3]

Pre-eclampsia is frequently asymptomatic and if so, may only be detected through routine antenatal testing. Symptoms of pre-eclampsia can include neurologic symptoms (headache, visual disturbances), epigastric or right upper quadrant pain,[5] oedema (swelling of the hands, face or feet) and oliguria (low output of urine).[6] Although most cases of pre-eclampsia are mild and cause no problems, the condition can worsen and be serious for both mother and baby.[7] Pre-eclampsia is classified as early-onset if it occurs before week 34 of pregnancy, or late-onset if it occurs after week 34.[4] However, pre-eclampsia is less common but often more severe if it occurs before week 34.[8] Pre-eclampsia can also develop in women with chronic hypertension before pregnancy, a condition known as superimposed pre-eclampsia.[4]

Epidemiology

Pre-eclampsia affects up to 5% of pregnancies, and severe cases develop in about 1-2% of pregnancies.[7] In 2012-13 there were 12,356 admissions to hospital in England for pre-eclampsia and 294 for eclampsia.[9] Maternal deaths due to pre-eclampsia have fallen,[10] and only nine deaths were caused directly by pre-eclampsia or eclampsia in the UK in 2010-12 (0.38 per 100,000) though there were additional deaths from related conditions including two deaths caused by placental abruption in the UK and Ireland in 2010-12 (0.49 per 100,000).[11] According to Action on Pre-eclampsia, fetal mortality is much higher and around 1,000

babies die each year as a result of pre-eclampsia, mostly due to complications associated with early delivery.[12]

Definitions of pre-eclampsia and related conditions

There is no international consensus on diagnostic criteria for pre-eclampsia and related conditions, though criteria used by organisations such as NICE, the American College of Obstetrics and Gynecology (ACOG), and the International Society for the Study of Hypertension in Pregnancy (ISSHP), overlap.[3-5] New onset hypertension plus proteinuria are key criteria for a diagnosis of pre-eclampsia, and these can be accompanied by a range of additional signs and symptoms indicative of pre-eclampsia.

The NICE clinical guideline on hypertension in pregnancy (NG133)[3] defines pre-eclampsia as new onset of hypertension (over 140 mmHg systolic or over 90 mmHg diastolic) after 20 weeks of pregnancy and the coexistence of one or more of the following new-onset conditions:

- proteinuria
- other maternal organ dysfunction:
    - renal insufficiency
    - liver involvement
    - neurological complications (e.g. eclampsia, altered mental status, stroke)
    - haematological complications (e.g. thrombocytopenia, disseminated intravascular coagulation or haemolysis)
- uteroplacental dysfunction such as fetal growth restriction, abnormal umbilical artery doppler waveform analysis, or stillbirth.

Women presenting with new-onset hypertension in pregnancy, but no other new conditions, may be classed as having suspected pre-eclampsia. Clinical practice varies with regard to whether new onset proteinuria alone is indicative of suspected pre-eclampsia. However, onset of proteinuria in women with chronic hypertension whose blood pressure is stable may indicate possible pre-eclampsia.

Pre-eclampsia is classed as severe if severe hypertension does not respond to treatment, or if there are ongoing symptoms such as severe headaches, nausea, vomiting, and epigastric pain, as well as deteriorating creatinine, liver transaminases or platelet counts, or limited fetal growth.

Impact of pre-eclampsia

Hypertension in pregnancy carries risks for mother and baby, and increases the mother's lifetime risk of hypertension, pre-eclampsia in subsequent pregnancies,[21] ischaemic heart disease, stroke, type 2 diabetes, and venous thromboembolism.[10,22] Negative consequences of pre-eclampsia for the baby include fetal growth restriction and preterm birth,[3] which can lead to complications including intracranial haemorrhage, nutritional compromise, necrotising enterocolitis, and breathing difficulties (neonatal respiratory distress syndrome),[7] requiring a stay in a neonatal intensive care unit.

Decisions about when to deliver the baby in the presence of pre-eclampsia involve a balance between the best outcomes for the mother and baby. Before 34 weeks of gestation, clinicians would aim to prolong the pregnancy so that the fetus has time to develop as much as possible before birth. Some babies die because of complications related to early delivery, and a few are stillborn.

Babies born early, or small-for-gestational-age, may also have pre-school developmental delays, and are at increased risk of adult disease. However, the baby may be delivered early if there is a risk that the mother may develop severe pre-eclampsia, HELLP syndrome (Haemolysis, elevated liver enzymes, low platelet count), disseminated intravascular coagulation, acute renal failure, hepatic failure, placental abruption, or eclampsia.

Suspected pre-eclampsia may have a negative impact in pregnancy if it involves hospitalisation, loss of work days, and/or anxiety. Women who have previously had pre-eclampsia, particularly those in whom pre-eclampsia was severe, have reported poorer quality of life compared to those with normotensive pregnancies. Pre-eclampsia can be stressful for both parents, due to worry about the condition of the unborn baby and the risk of morbidity and mortality due to preterm birth. Having a condition which can deteriorate rapidly, being kept in hospital for monitoring, uncertainty about what will happen, and undergoing emergency caesarean section can also cause fear, anxiety, loss of control over their situation and anxiety about future pregnancies. Partners and friends can also be affected due to fear of losing the mother or baby. Evidence is mixed, but generally pre-eclampsia or HELLP syndrome is associated with increased prevalence and severity of depression, and with post-traumatic stress disorder.

Significance for the NHS

Pregnant women have monitoring for high blood pressure and protein in their urine during routine antenatal care, and receive advice about action to take if they experience symptoms

indicative of pre-eclampsia.[13,32] If proteinuria is identified on a dipstick ('qualitative') test, a spot urinary protein:creatinine ratio or 24 hour urine collection is recommended to quantify the level of proteinuria. Twenty-four hour urine collection may require an overnight stay in hospital, refrigeration of the urine during collection and laboratory-based analysis. When pre-eclampsia is identified, referral to a specialist and hospital admission is recommended for maternal and fetal monitoring. If the woman is not admitted, ongoing regular monitoring is required to identify emergent signs and symptoms of pre-eclampsia.

NHS resource use associated with identification and management of pre-eclampsia is high. If case-finding is accurate, monitoring and appropriate care can improve health outcomes and reduce the need for treatment of adverse events. However, uncertainty around pre-eclampsia prediction increases the economic burden on the NHS. False positive diagnoses may lead to unnecessary antenatal admissions, fetal monitoring and pre-term delivery; and false negatives can provide inappropriate reassurance, increasing the risk of adverse events. More accurate methods of diagnosis therefore have the potential to reduce pressure on NHS resources, as well as to improve health outcomes.

1.2 Description of the diagnostic technologies under assessment

Current care pathway

The NICE pathway on pre-eclampsia is nested within a broader NICE pathway on hypertension in pregnancy. The pre-eclampsia pathway comprises a sequence of steps for patient care starting at the point at which pre-eclampsia is suspected and diagnosed, through subsequent steps involving clinical assessment, treatment, fetal monitoring, delivery and postnatal care (Figure 1). At each pathway step relevant recommendations are outlined based on available NICE clinical guidelines (e.g. NG133) and guidance (e.g. NICE DG23).

Step 3 is of particular relevance to this report as it describes the diagnosis of pre-eclampsia. The most widely used form of diagnosis is standard assessment of clinical signs and symptoms and subsequent clinical follow-up. NICE recommend the use of PlGF-based testing as an aid to standard clinical assessment and subsequent clinical follow-up to help rule out pre-eclampsia in women presenting with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation. This recommendation is based on NICE diagnostics guidance on PlGF-based testing to help diagnose pre-eclampsia (2016).

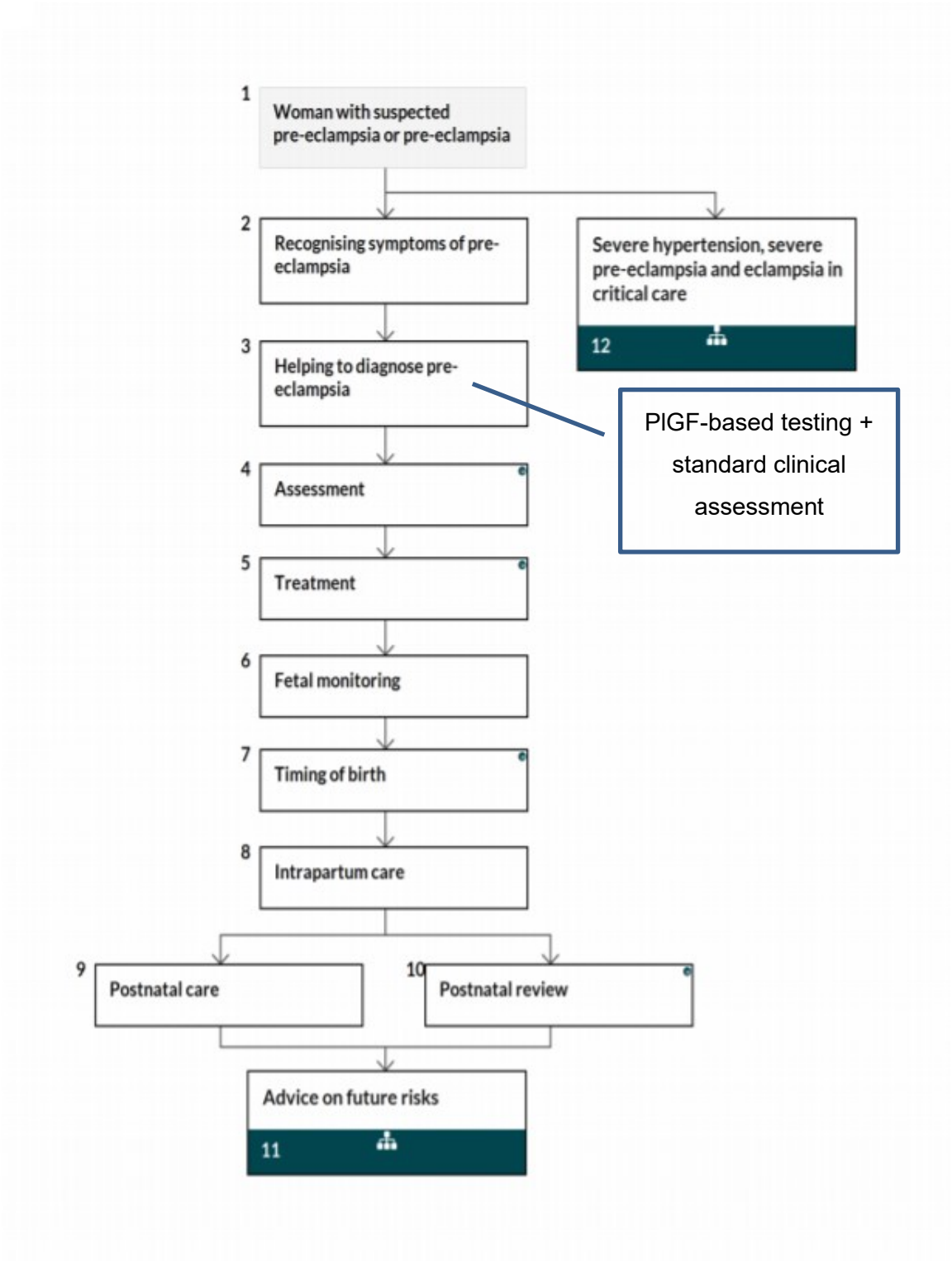

Figure 1 NICE pathway for pre-eclampsia

Two types of PlGF test are recommended for use in the NHS in England: the Triage PlGF test and the Elecsys immunoassay sFlt 1/PlGF ratio - for ruling out pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation. NICE do not currently recommend two other available tests - The DELFIA Xpress PlGF 1-2-3 test and BRAHMS sFlt-1

Kryptor/BRAHMS PlGF plus Kryptor PE ratio - for routine use (see 'PlGF-based testing' below for further information about each test).

NICE's guidance suggests that further research is done to find out if the DELFIA and BRAHMS tests are accurate in diagnosing pre-eclampsia (research recommendation 6.2). The guidance also recommends more research to find out if the Triage PlGF test and the Elecsys immunoassay sFlt-1/PlGF ratio test can accurately rule in pre-eclampsia.

The use of repeat PlGF-based testing for suspected pre-eclampsia was also considered in NICE DG23.[6] However, a practice recommendation could not be made due to the lack of diagnostic accuracy data for repeat use of the tests. Instead, a recommendation was made for research on the different scenarios in which repeat testing may be indicated; the appropriate intervals between PlGF-based tests; and the diagnostic accuracy of PlGF-based testing in women with suspected pre-eclampsia who have previously had one or more negative PlGF-based test results (research recommendation 6.1).

Women who are diagnosed with pre-eclampsia undergo clinical assessment at antenatal appointments (Step 4) to identify any concerns for their wellbeing or that of the baby, and thus inform decisions about potential hospital admission. A range of clinical signs and markers are assessed, including blood pressure monitoring, biochemical and hematological investigations (e.g. creatinine, alanine transaminase, platelet count), signs of eclampsia, pulmonary oedema, and fetal compromise amongst others.

Conservative outpatient management in hospital or the community continues until 34 weeks of pregnancy, unless there is clinical and test evidence of severe hypertension or potential harm to the baby. Antihypertensive drugs (labetalol, methyldopa or nifedipine) are given, with a target systolic blood pressure of 135 mmHg. Pre-eclampsia can only be cured by delivering the baby, so women are monitored until an appropriate time for delivery is reached.

NICE's guideline on hypertension in pregnancy (NG133) proposes optional use of risk prediction models to guide decisions about maternal care. Two validated models are recommended, the fullPIERS (to be used at any time during pregnancy) or the PREP-S (for use only up to 34 weeks of pregnancy). Use of these models should be in addition to the full clinical assessment that women receive to assess their risk of adverse outcomes.

PlGF-based testing

Tests are available that measure the amount of PlGF in blood plasma or serum during pregnancy. PlGF is a protein involved in placental angiogenesis (the development of new blood vessels) and levels rise during the course of pregnancy, reaching a plateau at 26 to 30 weeks gestation. Abnormally low levels of PlGF during pregnancy may indicate placental dysfunction associated with pre-eclampsia. Some PlGF tests measure soluble FMS-like tyrosine kinase-1 (sFlt-1), an anti-angiogenic protein which disables proteins, such as PlGF, which are associated with blood vessel formation. In cases of pre-eclampsia levels of sFlt-1 are higher than normal.

The purpose of PlGF-based testing (i.e. PlGF or sFlt-1/PlGF tests) is to aid standard clinical assessments that women with suspected pre-eclampsia receive, with the aim of providing an earlier and more accurate diagnosis. In turn, this diagnostic information can inform more appropriate care decisions, such as avoiding hospital admission in women with low risk of developing pre-eclampsia.

As mentioned above, NICE DG23 includes four commercially available tests to aid diagnosis of pre-eclampsia. We describe each of these below.

The **Triage PlGF test (Quidel)** is a fluorescence immunoassay to be used with the Quidel Triage Meter for the quantitative determination of Placental Growth Factor (PlGF) in EDTA anticoagulated plasma specimens. The company states that it can be used at the point of care and in the laboratory, taking less than 30 minutes to run. The test is used in conjunction with other clinical information as an aid in the diagnosis of preterm pre-eclampsia and as an aid in the prognosis of delivery, in women presenting with signs and symptoms of pre-eclampsia after 20 weeks and prior to 35 weeks of gestation. The test has a limit of detection of 9 pg/mLand a measurable range of 12 to 3000 pg/mL.

The **Elecsys immunoassay sFlt-1 / PlGF ratio (Roche Diagnostics Ltd)** measures the relative amounts of PlGF to soluble FMS-like tyrosine kinase-1 (sFlt-1; also known as VEGFR1) in serum samples from women with suspected pre-eclampsia. The ratio is formed by combining the results from two electrochemiluminescence immunoassays (the Elecsys PlGF and Elecsys sFlt-1 assays) which are compatible with the Roche Cobas e automated clinical chemistry analysers.

The sFlt-1/PlGF ratio is intended for use as an aid in the diagnosis of pre-eclampsia in conjunction with other diagnostic and clinical information. In addition, the sFlt-1/PlGF ratio is

intended for use as an aid in short-term prediction of preeclampsia (rule-out and rule-in) in pregnant women with suspicion of preeclampsia in conjunction with other diagnostic and clinical information.

The Elecsys sFlt-1 assay has a limit of detection of 10 pg/mL(measuring range 10 to 85,000 pg/mL) and a limit of quantitation of 15 pg/mL. The Elecsys PlGF assay has a limit of detection of 3 pg/mL(measuring range 3 to 10,000 pg/mL) and a limit of quantitation of 10 pg/mL.

The **DELFIA Xpress PlGF 1-2-3 (Perkin Elmer)** can be used as a standalone test or in combination with the **Perkin Elmer DELFIA Xpress sFlt-1 test.** The DELFIA Xpress PlGF 1-2-3 test is intended for the quantitative determination of PlGF in maternal serum using the 6000 DELFIA® Xpress clinical random access screening platform. The kit is described as being an aid in screening pregnant women for pre-eclampsia in all trimesters of pregnancy. In the second and third trimester (which is relevant to this diagnostic assessment), the company states that PlGF can be used for screening for risk of pre-eclampsia together with other relevant clinical information.

This DELFIA Xpress sFlt-1 kit is intended for the quantitative determination of sFlt-1 in maternal serum using the 6000 DELFIA® Xpress random access immunoanalyzer. The ratio of sFlt-1/PlGF may be used as an aid in diagnosis of pre-eclampsia and for short term prediction of suspected pre-eclampsia together with other biochemical and clinical information.

Using the DELFIA Xpress PlGF 1-2-3 test alone, the process time for first results is 30 minutes. Using both DELFIA Xpress PlGF 1-2-3 and sFlt-1 together takes approximately 31.5 minutes for the first sFlt-1/PlGF ratio result. The instrument is able to process samples simultaneously, leading to approximately 40 results per hour throughput.

The DELFIA Xpress PlGF 1-2-3 assay has a limit of detection of 1.9 pg/mLand a limit of quantitation of 3.3 pg/mL(measuring range 1.9 to 4000 pg/mL). The DELFIA Xpress sFlt-1 has a limit of detection of is 3.79 pg/mLand a limit of quantitation of 7.6 pg/mL(measuring range 3.79 to 19500 pg/mL).

The **BRAHMS PlGF plus Kryptor test (ThermoFisher)** can be used as a stand-alone test or together with **ThermoFisher BRAHMS sFlt-1 Kryptor test.** The BRAHMS sFlt-1 Kryptor / BRAHMS PlGF plus Kryptor PE ratio is formed by combining the results from 2 automated

immunofluorescent sandwich assays, the BRAHMS sFlt-1 Kryptor and BRAHMS PlGF plus Kryptor assays. The assays are indicated for the quantitative determination of sFlt-1 and PlGF in serum samples and are compatible with the BRAHMS Kryptor compact plus analyser and the Kryptor Gold immunoanalyser. The BRAHMS sFlt-1 Kryptor / BRAHMS PlGF plus KRYPTOR PE ratio is intended to be used to confirm or exclude diagnosis of pre-eclampsia after 20 weeks gestation.

When using the Kryptor Gold Immunoanalyser it takes 29 minutes for the first BRAHMS sFlt-1 Kryptor / BRAHMS PlGF plus Kryptor ratio result, and then a further 90 seconds for each additional result

The BRAHMS sFlt-1 Kryptor assay has a limit of detection of 22 pg/mL (measuring range 22 to 90,000 pg/mL) and a limit of quantitation of 34 pg/mL. The BRAHMS PlGF plus Kryptor assay has a limit of detection of 3.6 pg/mL (measuring range 3.6 to 7000 pg/mL) and a limit of quantitation of 6.9 pg/mL.

1.3 Current service provision

NICE's 2016 diagnostic guidance recommending PlGF-based testing applies to the Triage PlGF test and the Elecsys immunoassay sFlt 1/PlGF ratio test but, due to insufficient available evidence at that time, a recommendation for use of the two other available tests (-The DELFIA Xpress PlGF 1-2-3 test and BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio) was not made.

NICE's guidance makes recommendations for further research to inform aspects of PlGF-based testing where evidence to inform guidance was lacking. These were:

- The diagnostic accuracy and analytical validity of the DELFIA Xpress PlGF 1-2-3 test and BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio (Research recommendation 1.3).
- Rule in pre-eclampsia using the Triage PlGF test, and the Elecsys immunoassay sFlt-1/PlGF ratio (Research recommendation 6.2)
- Use of repeat PlGF-based testing for suspected pre-eclampsia (Research recommendation 6.1)

Since NICE's guidance was published in 2016, further research evaluating use of PlGF-based testing has been conducted, some of which has been published and some currently on-going. A scoping review of the evidence by NICE in the autumn of 2020 identified several relevant new studies, including large UK-based randomised controlled trials (RCTs)

reporting maternal, fetal, neonatal and perinatal outcome measures. New published data from existing studies was also identified. An update of the NICE guidance was therefore agreed (DAP53). Likewise, this report updates the Diagnostic Assessment Report (DAR) by Frampton et al. (2016)[7] which informed the 2016 NICE guidance (hereafter, we refer to this report as the previous DAR). This current report is based on a research protocol (registered on the PROSPERO database), which describes, a priori, the scope, decision problem and methods to be used. In the next section we describe the decision problem for this NICE appraisal.

2 DEFINITION OF THE DECISION PROBLEM

The decision problem is based on NICE's scope for this update appraisal, issued in November 2020.[8] The scope is similar to that of the original appraisal in terms of relevant diagnostic tests, population, comparator tests and outcome measures.

2.1 Decision problem

The tests under evaluation (the index test) are:

- The Triage PlGF test (Quidel)
- The Elecsys immunoassay sFlt-1 / PlGF ratio (Roche Diagnostics Ltd)
- The DELFIA Xpress PlGF 1-2-3 test / DELFIA Xpress sFlt-1 kit (Perkin Elmer)
- The BRAHMS sFlt-1 Kryptor / BRAHMS PlGF plus Kryptor PE ratio (ThermoFisher)

Scoping work undertaken by NICE and the EAG did not identify any other tests relevant to this appraisal which have become commercially available since 2015.

Each test will be evaluated when used in addition to standard clinical assessment, to diagnose pre-eclampsia in between 20 weeks and 36 weeks and 6 days of pregnancy. We interpret "use in addition to clinical assessment", as worded in the scope, to mean that the results of the test were assessed by the treating clinician(s) alongside observation of standard clinical signs and symptoms, and together this information informed subsequent care decisions, such as hospitalisation. As we will discuss later in this report, not all studies potentially relevant to the systematic review of test accuracy and clinical effectiveness provided clinicians with results of the PlGF tests to inform care decisions. We therefore categorize use of the tests in the studies as being:

- "**add-on**", in which the results of a test were used alongside standard clinical assessment to diagnose pre-eclampsia and inform subsequent care decisions. In these studies, test results are *revealed* to the clinician.

- "**standalone**", in which test results were used to diagnose pre-eclampsia but were not used alongside standard clinical assessment to inform care decisions. In these studies, test results are *concealed* from the clinician.

Both types of study are included in this report, with the primary focus on the evidence for add-on use of the tests to reflect how the test is used in clinical practice. We regard standalone test studies as providing supportive evidence of the diagnostic/prognostic accuracy of the tests.

The population of relevance to the decision problem is pregnant women, between gestation week 20 and gestation week 36 plus 6 days, who, on the basis of screening tests and clinical symptoms, are suspected of having pre-eclampsia. This is usually based on the presence of hypertension plus other signs or symptoms, including proteinuria, haematological abnormalities, frontal headache, severe pain just below the ribs, vision problems, vomiting, and/or sudden swelling of the face or hands.

Key relevant subgroups of interest include pregnant women with comorbidities such as chronic hypertension, severe hypertension, pre-existing or gestational diabetes, renal disease, and/or autoimmune disease; gestational stage (between 20 weeks and 34 weeks plus 6 days of pregnancy; between 35 weeks and 36 weeks and 6 days of pregnancy), and multiple pregnancy. Test results may be impacted by ethnicity and maternal weight, where data are available these variables will be taken into account.

The comparator of interest is no further clinical assessment (beyond assessments already done, such as blood pressure measurement, urinalysis and fetal monitoring) to diagnose pre-eclampsia and inform subsequent decisions about care.

The outcome measures of relevance fall into three main categories:

- Intermediate outcomes, including diagnostic/prognostic accuracy of the tests; concordance between PlGF-based tests; time to diagnosis; and clinical decisions (e.g. number of women admitted to hospital, length of in-patient hospital stay; time to delivery).
- Clinical outcomes, in terms of morbidity and mortality, at the maternal, fetal, and neonatal level.
- Patient-reported outcomes, including health related quality of life (HRQoL).

A list of all relevant outcome measures is given in section *3.2 Inclusion and exclusion criteria.*

2.2 Overall aims and objectives of assessment

The aim of this report is to assess the clinical effectiveness and cost-effectiveness of PlGF-based tests to aid the clinical diagnosis of pre-eclampsia in women presenting with suspected pre-eclampsia between 20 weeks and 36 weeks and 6 days of pregnancy.

The objectives of this report are to update the systematic review of diagnostic test evaluations, the systematic review of cost-effectiveness studies and the decision analytic model-based economic evaluation reported in Frampton et al.(2016)[7] and which informed NICE's 2016 diagnostic guidance (DG23).[6] This results of this update will inform NICE's 2021 review of the 2016 guidance (DAP53).

3 METHODS

3.1 Identification of studies

The comprehensive literature search strategy used in the previous DAR[7] was updated, refined, pilot tested and implemented by an experienced information specialist. This search strategy informs the systematic review of test accuracy and clinical effectiveness (Section 4, *Results of the systematic review of test accuracy and clinical effectiveness)* and the systematic review of cost-effectiveness *(Section 5.1 Systematic review of cost-effectiveness).*

The following sources were searched (search strategies for all sources are in Appendix 1):

- Bibliographic healthcare databases: MEDLINE (Ovid), including Epub Ahead of Print, In-Process & Other Non-Indexed Citations; Embase (Ovid); Cochrane Library (cochranelibrary.com) for the Cochrane Database of Systematic Reviews (CDSR) and the Central Register of Controlled Trials (CENTRAL); Web of Science for the Science Citation Index Expanded (SCI-EXPANDED) and the Conference Proceedings Citation Index – Science (CPCI-S); International HTA Database (INAHTA); Epistemonikos (epistemonikos.org).
- Citation searching: the references of all systematic reviews identified in the database searches were checked for relevant studies.
- Relevant conference proceedings: American Heart Association (formerly the American Society of Hypertension); British and Irish Hypertension Society; European Society of Hypertension; International Society for the Study of Hypertension in Pregnancy;

International Society for Prenatal Diagnosis (ISPD) International Conference on Prenatal Diagnosis and Therapy; Fetal Medicine Foundation.

- Relevant websites: British Maternal and Fetal Medicine Society; Royal College of Obstetricians and Gynaecologists; American College of Obstetricians and Gynaecologists; International Society of Perinatal Obstetricians; Society for Maternal-Fetal Medicine; Action on Pre-Eclampsia; Pre-Eclampsia Foundation; National Childbirth Trust; Cochrane Pregnancy and Childbirth Group; Tommy's; European Foundation for the Care of Newborn Infants; Fetal Medicine Foundation; British Association of Perinatal Medicine.
- Other grey literature and research in progress: PROSPERO register of systematic reviews; BePartOfResearch (formerly the UK Clinical Trials Gateway); Clinical Trials.gov; Pregnancy Research Review Subgroup of the UK Clinical Research Network Portfolio Database; NIHR Clinical Research Network Portfolio.
- Study authors: when it was necessary to contact a study author to request information not available in their study publications, we also took the opportunity to request details of any other published or unpublished reports of their study. We made requests for details of relevant ongoing studies and studies conducted by the test manufacturers, via NICE.

All databases were searched for the period at the start of 2015 to 18th March 2021. As the searches for the previous DAR covered the period up to March 2015, this brief overlap in search periods was intentional to reduce the likelihood of any studies published in early 2015 from being inadvertently missed by either review. We removed any duplicate references from our search which had been identified by the previous review search. Conference proceedings were hand-searched from 2016 to 2020. All searches were limited to the English language.

As the search strategy for the review of test performance did not limit to any particular study type or outcome, the same search results were reviewed for the economic evaluations. In addition, a separate search for health-related quality of life (HRQoL) was carried out. (see 5.1.1, *Systematic review of economic studies*)

3.2 Inclusion and exclusion criteria

The eligibility criteria for this systematic review are:

- **Study design:** primary research evaluations of PlGF-based tests, regardless of study design.

- **Population:** women presenting with suspected pre-eclampsia between 20 weeks and 36 weeks plus 6 days of pregnancy. Where a study a population comprised women with suspected pre-eclampsia and women suspected of other, related, conditions, we required that the study reported a subgroup analysis of those with suspected pre-eclampsia, or that ≥70% of the study population had suspected pre-eclampsia. Since 2019, the NICE guideline NG133[3] has included suspected fetal compromise as suggestive of pre-eclampsia and clinical experts to the EAG confirmed that fetal growth restriction (FGR) can also suggest possible pre-eclampsia. Therefore, studies comprising women with either suspected pre-eclampsia and/or suspected FGR were eligible for inclusion included in the review.
- **Index test**: any of the following four PlGF-based tests when used in addition to standard clinical assessment:
    - Triage PlGF test;
    - Elecsys immunoassay sFlt-1/PlGF ratio;
    - DELFIA Xpress PlGF 1-2-3 test with or without the DELFIA Xpress sFlt-1 test;
    - BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio.

  As stated earlier, our interpretation of "use in addition to standard clinical assessment" is that the results of the test were assessed by the treating clinician and used, alongside standard clinical assessment, to inform the diagnosis of pre-eclampsia and subsequent care plans. However, we note that key studies included in the previous DAR[7] including PELICAN, PETRA, and PROGNOSIS (and thus the evidence which informs the existing NICE guidance on PlGF testing in pre-eclampsia), did not evaluate the diagnostic accuracy of the tests when used alongside standard clinical assessment. These studies would therefore not be eligible for inclusion in this appraisal update. To ensure continuity between the original appraisal and the current appraisal we classify studies in which the tests are assessed for diagnostic or prognostic/predictive accuracy but the results did not inform care decisions, as being "standalone" test use studies. We include standalone studies in the review to provide supportive evidence to "add-on" studies which assess the use of the test alongside standard clinical assessment.
- **Reference standard:** for diagnostic accuracy of pre-eclampsia, the reference standard was standard clinical assessment according to local, national or international guidelines, including blood pressure measurement, urinalysis, and fetal monitoring. For prognostic accuracy of maternal and/or neonatal/fetal outcomes the reference standard should be appropriate to the particular outcome.
- **Test performance outcomes**, any one or more of the following: diagnostic accuracy; prognostic accuracy; concordance between tests; time to test result; impact of test result

on clinical decision making; test failure rate; time to diagnosis; proportion of people diagnosed with pre-eclampsia; time to onset of pre-eclampsia and/or eclampsia; proportion of people returned to less intensive follow-up; number of people admitted to hospital; length of in-patient hospital stay; time to delivery; gestation at diagnosis of pre-eclampsia; use of antihypertensive drugs, health related quality of life.

- **Maternal morbidity and mortality outcomes**, for example: biochemical abnormalities; haematological abnormalities; liver failure; renal failure; disseminated intravascular coagulation or thrombosis; stroke; eclampsia; HELLP syndrome; severe hypertension; emergency caesarean.
- **Neonatal/fetal morbidity and mortality outcomes**, for example: breathing difficulties; chronic lung disease; gestational age at delivery; growth at delivery; weight at delivery; intracranial haemorrhage; late onset infection; necrotising enterocolitis; neonatal unit length of stay, neonatal resuscitation; preschool developmental delays.

These criteria were applied using an inclusion/exclusion worksheet (Appendix 2) to the titles and abstract (where available) by two reviewers independently. Their screening decisions were compared and discrepancies resolved through discussion or with the opinion of a third reviewer where necessary. The full text articles of references judged to be potentially relevant were screened in further detail criteria by one reviewer and checked by a second, before reaching a final judgement (again, with the opinion of a third reviewer where necessary).

3.3 Data extraction strategy

Relevant data were extracted from each included study into a structured data extraction template in MS Word, customised, where necessary, to the type of study and evidence relevant to this review. Data extraction of each included study was performed by one reviewer, and checked for accuracy and interpretation by a second reviewer. Any discrepancies between the two reviewers were resolved through discussion, and instances where agreement between the two reviewers could not be reached the judgement of a third reviewer was sought. The finalised data extraction forms for each study are lengthy and it is not practical for them to be included in appendices to this report. However, in the interests of transparency, they will be considered for inclusion as supplementary information to this report in the NIHR Journals Library.

3.4 Risk of bias and study quality assessment

We critically appraised the risk of bias and methodological quality of the included add-on studies using criteria relevant to the type of study design and to the type of study findings

reported. (NB. It was not practical in the time available to critically appraise the included standalone studies. However, we describe the general methodological strengths and limitations of these studies, when relevant, later in this report (see section *4.1.1 Quantity and quality of research available* and *Appendix 5 Standalone test studies*).

Add-on studies reporting the diagnostic/prognostic accuracy of PlGF-based testing were appraised using the QUADAS 2 tool, tailored to the scope of this study (as recommended by the QUADAS 2 authors). QUADAS 2 is designed for assessing the methodological quality of a diagnostic evaluation study in terms of its potential risk of bias, and its applicability to the review question. Risk of bias and applicability are assessed across four key study domains: patient selection, index test, reference standard, and flow of patients through the study and timing of the index test(s) and reference standard.

Add-on studies reporting clinical effectiveness outcomes were appraised by one of two sets of criteria relevant to their design:

RCTs were appraised using the Cochrane Risk of Bias tool for randomised trials (version 1). This is a validated and widely used tool designed for use in systematic reviews to assess the potential risk of bias in RCTs of health interventions. The tool covers six domains of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias.

Non-randomised studies (observational studies) were appraised using the Cochrane Effective Practice and Organisation of Care (EPOC) risk of bias criteria for non-randomised studies. Where a study reports both diagnostic/prognostic accuracy and clinical effectiveness outcomes we appraised the evaluation of accuracy using QUADAS2 and the evaluation of clinical effectiveness outcomes using the tool most appropriate to the study design (i.e. RCT or observational study).

Each study was critically appraised by one reviewer and checked by a second reviewer, with any differences in judgement resolved through discussion. Where agreement between the two reviewers could not be reached through discussion, the judgement of a third reviewer was sought.

The results of the critical appraisal of the add-on studies are summarised in *Section 4.1.2.0 Critical appraisal of risk of bias and applicability of test accuracy*. The finalised critical appraisal forms for each study will be considered for inclusion as supplementary information to this report in the NIHR Journals Library.

3.5 Method of data synthesis

As we discuss later in this report (*see section 4*) the studies included in the systematic review are heterogeneous with regard to factors such as study design; population characteristics (e.g. gestational age at presentation); criteria used to define pre-eclampsia; measurement and definition of clinical effectiveness outcomes; whether or not PlGF test results were used alongside standard clinical assessment to inform diagnosis and subsequent care decisions. Our intention, as expressed in the study protocol, was to meta-analyse the study results where data allowed. Our assessment of the evidence meeting the review's inclusion criteria was that meta-analysis would not be feasible due to the limited availability of sufficiently similar outcome data across the studies. Furthermore, methodological guidance cautions against include random and non-randomised trial data from intervention studies within the same meta-analysis. Thus, separate meta-analyses would be required for the random and non-randomised evidence included in this review, and the resulting sparse distribution of clinical effectiveness outcome data across these two sets of analyses would increase uncertainty in effects. Therefore, in common with the previous DAR,[7] we provide a structured narrative synthesis of the included studies, summarising their results using textual description and data tables.

The synthesis of results of the add-on studies are presented from Section 4.1.2 *Assessment of test accuracy* to Section 4.1.13 *Assessment of health-related quality of life (HRQoL)* outcomes. Within these sections we also present brief key findings of the standalone studies, where available, alongside the add-on studies to provide context. The results of the standalone studies themselves are presented in more detail in *Appendix 5 Standalone test studies.*

4 ASSESSMENT OF DIAGNOSTIC TEST AND CLINICAL EFFECTIVENESS STUDIES

4.1 Results of the systematic review of test accuracy and clinical effectiveness

4.1.1 Quantity and quality of research available

After removing duplicate references, a total of 1902 potentially relevant references were identified from our literature searches (run in November 2020) and information submitted to NICE by the companies. Independent screening of titles and (where provided) abstracts by two reviewers determined that 1699 of these references did not meet the inclusion criteria,

whilst the full text reports of the remaining 154 references were obtained for further screening. Where necessary we contacted study authors for further information to enable us to determine whether or not their study met our inclusion criteria. Independent screening of the full text reports by two reviewers identified a total of 43 publications reporting a total of 21 studies which met the inclusion criteria for the systematic review.

We re-ran the database literature search on 18th March 2021 to identify any relevant literature published since the search we did in November 2020. We identified a further 130 unique references which were then independently screened by two reviewers, of which 121 did not meet the inclusion criteria. Screening the full text publications of the remaining nine references identified four that met the inclusion criteria for the systematic review, four that did not meet the inclusion criteria, and one reporting insufficient information to determine eligibility (NB. We did not receive a response from the study author to our request for clarification). Two of the four references that met the inclusion criteria provide analyses of studies already included in the review[9 10], and two which report studies not already identified[11 12].

In summary, the combined November 2020 and March 2021 literature searches identified a total of 1974 references, of which 1877 were excluded on title and abstract, and 163 were subjected to full-text screening (reasons for exclusion are given in Appendix 3). Twenty-four unique studies, reported in a total of 44 publications, met the inclusion criteria for the systematic review. Of the 24 included studies, seven were excluded post-hoc, primarily because of limited generalisability to practice in England (as explained below). The final total number of studies included in the systematic review is therefore 17 (Table 1).

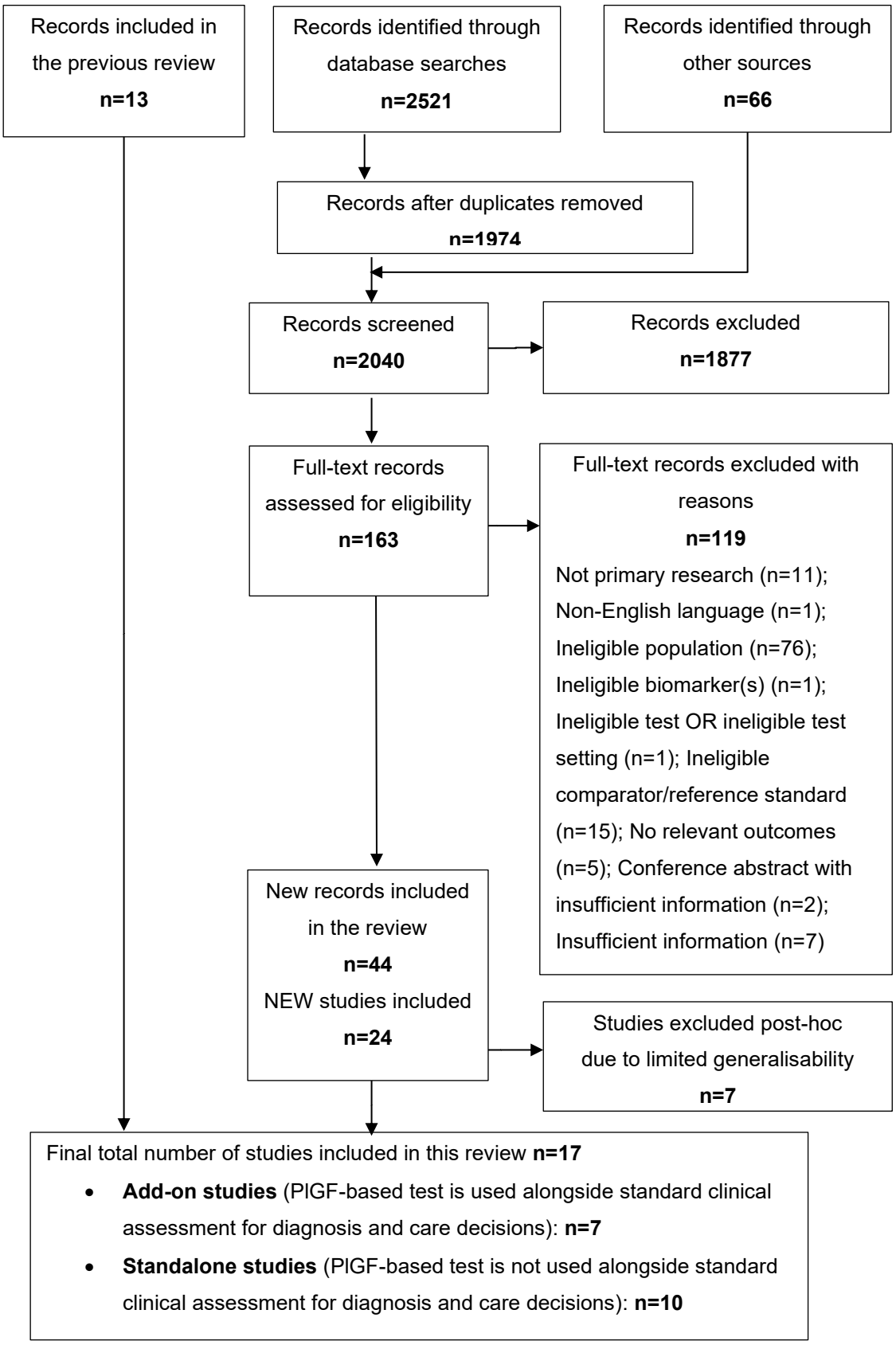

Figure 2 Flow chart for the identification of studies in the systematic review of test accuracy and clinical effectiveness

Table 1 Overview of studies included in the systematic review of test accuracy and clinical effectiveness

Test	Studies included (design) and type of outcomes assessed	
	Add-on test (result revealed to clinicians and used alongside standard clinical management)	**Standalone test** (result concealed from clinicians and used alone in statistical analyses for predicting outcomes)
Triage PlGF test	Test accuracy and comparative clinical outcomes: • **PARROT** [13-15] (cluster RCT) [a] Comparative clinical outcomes: • **MAPPLE** [16] (prospective cohort study, comparing to PELICAN cohort) [b] Test accuracy outcomes: • **Ormesher 2018** [17] (single group, prospective clinical evaluation; high-risk pregnancies only)	Test accuracy outcomes: • **PELICAN [18-23] / PEACHES** [24] (prospective observational study; PEACHES included a cohort of from the PELICAN study) • **PETRA** [25-29] (prospective cohort study) • **COMPARE** [30] (retrospective analysis of blood samples from three prospective cohort studies) [c]
Elecsys sFlt-1/PlGF ratio	Test accuracy and comparative clinical outcomes: • **INSPIRE** [31-33] (RCT) [a] Comparative clinical outcomes: • **PreOS** [34] (before- and after-study design) [d] Test accuracy outcomes: • **Binder 2020** [35] (single cohort; retrospective analysis; twin pregnancies only) [e]	Test accuracy outcomes: • **PROGNOSIS** [36-42] (prospective observational study) • **PROGNOSIS Asia** [43 44] (prospective observational study) • **ROPE** [45] (prospective cohort study) • **Baltajian 2016** [46] (prospective cohort study) • **Wang 2021** [11] (prospective cohort study) • **Salahuddin 2016** [47] (case control study) • **Saleh 2016** (prospective cohort study) • **COMPARE** [30] (retrospective analysis of blood samples from three prospective cohort studies) [c]
BRAHMS Kryptor sFlt-1/PlGF ratio	Test accuracy outcomes: • **Andersen 2019** [48] (single cohort; retrospective study)	Test accuracy outcomes: • **Salahuddin 2016** [47] (case control study)
Delfia Xpress test	No studies met the inclusion criteria	Test accuracy outcomes: • **COMPARE** [30] (retrospective analysis of blood samples from three prospective cohort studies) [c]

Underlining denotes studies from which test accuracy and clinical effectiveness data inform our economic model base case
'Comparative clinical outcomes' means that the study compared outcomes between the PlGF-based test used as an adjunct to standard clinical assessment (i.e. it was revealed to clinicians) to standard clinical assessment alone (i.e. when the PlGF-based test result was concealed from clinicians).
RCT, randomised controlled trial.

[a] compared outcomes between a trial arm where participants received standard clinical management and a PlGF-based test and the test result was revealed to clinicians and informed their clinical decision-making, and an arm where participants received standard clinical management and a PlGF-based test but the result was concealed from clinicians and did not inform clinical decision-making.
[b] included unadjusted and adjusted comparisons between the MAPPLE cohort where PlGF test results were revealed to clinicians and care was provided according to guidance that took into account the result and the PELICAN cohort where clinicians were not informed of the result. [18 21]
[c] blood samples collected during three prospective cohort studies (PEACHES, PELICAN-1 and PELICAN-2) were retrospectively tested using the Triage, Elecsys and DELFIA tests.
[d] clinicians recorded their intended clinical procedures for each participant before receiving the sFlt-1/PlGF ratio result. They were then informed of the result and they confirmed or revised their clinical decisions.
[e] study examined the use of the sFlt-1/PlGF ratio test to predict delivery due to pre-eclampsia. Results were revealed to clinicians, but the study authors state that due to the clinical guidance that clinicians followed, the result was unlikely to influence their decisions about delivery.

4.1.1.1 Studies excluded post hoc

As mentioned earlier, of the 24 studies which met the inclusion criteria, we subsequently excluded seven studies because, on further assessment, we judged them as being of limited generalisability to the diagnosis and management of suspected pre-eclampsia in England. All seven studies evaluated standalone use of the PlGF-based tests (i.e. the test result did not inform diagnosis or care decisions alongside standard clinical assessment). As we explain below, these studies do not appear to address evidence gaps not already covered by the included studies in this review:

- Three studies (Alvarez-Fernandez et al. 2014, [49] Alvarez-Fernandez al. 2016 [50] and Lafuente-Ganuza et al. 2020)[51] employed cut-offs for the Elecsys sFlt-1/PlGF ratio which are outside the companies' recommendations and the NICE scope (cut-offs 23, 45, 178 and/or 372). One of these, Alvarez-Fernandez et al. 2014,[49] was included in the previous DAR.
- Two studies (Ukah et al. 2017[52] and Manriquez Rocha 2018[53]) of the Triage PlGF test conducted in Mozambique are unlikely to reflect practice in England. Most of the outcomes reported in these studies were reported by other included studies (including UK-based studies), thus they did not address any key data gaps in our review.

- A study by Soundararajan et al. 2021[12] was conducted in a low healthcare resource setting in India and is unlikely to be reflective of the management of suspected pre-eclampsia in England.
- A study by Ohkuchi et al.[10] reported a subgroup analysis of the Elecsys sFlt-1/PlGF ratio for Japanese patients in the in the PROGNOSIS Asia study whose gestational age at enrolment was 18^{+0} to 36^{+6} weeks (NB. This is not fully consistent with the NICE scope) and who were enrolled according to specific local guidelines on blood pressure. The results of this study are consistent with those reported for the main PROGNOSIS Asia study and therefore this study does not address an evidence gap in this systematic review.

4.1.1.2 Classification of included studies as add-on (test results revealed) or standalone (test results concealed)

The 17 studies included in the systematic review were categorised according to whether or not the results of the tests were used alongside standard clinical assessment (Table 1), as follows:

- "**add-on**" studies n=7. The results of PlGF-based tests were used alongside standard clinical assessment to diagnose pre-eclampsia and inform subsequent care decisions. In these studies, test results are *revealed* to the treating clinician.
- **"standalone"** studies n=10. The results of PlGF-based tests were not used alongside standard clinical assessment to inform diagnosis and subsequent care decisions. In these studies, test results are *concealed* from the treating clinician.

As discussed earlier, the studies of add-on tests are directly relevant to the NICE scope and companies' recommendations, which specify that the PlGF-based test results should be used alongside standard clinical assessment for suspected pre-eclampsia.

The studies of standalone tests, though not directly relevant to the scope, provide the "next best" evidence for the diagnostic/prognostic accuracy of the tests. The standalone set of studies features three key studies included in the previous DAR[7] and thus which informed the original NICE guidance on this topic (NICE DG23) (PETRA[25 27], PELICAN[18 21] and PROGNOSIS [36-42]).

In the following sub-sections we describe the characteristics of the included studies and appraise their methodological quality and risk of bias, focusing primarily on the add-on

studies. In the final sub-section (4.1.1.12) we provide a narrative summary of two add-on studies: the PARROT study (Triage PlGF test) and the INSPIRE study (Elecsys sFlt-1/PlGF ratio test). These are two large UK-based RCTs which we have prioritised for their comprehensiveness, methodological rigour and relevance to the NHS, to inform the base case in our economic evaluation of the cost-effectiveness (see Section 4.1.1.12)

Further detail of the characteristics of the standalone studies can be found in Appendix 5.

4.1.1.3 Characteristics of the add-on test studies

Five of the seven add-on test (result revealed) studies were prospective, and the other two retrospective studies. Three of the seven studies, PARROT[15], MAPPLE[16] (Triage test) and INSPIRE[32] (Elecsys sFlt-1/PlGF ratio), included a comparison between a test result revealed arm and a test result concealed arm, either as separate randomised trial arms (PARROT[15], INSPIRE[32]) or as an indirect unadjusted comparison (MAPPLE[16]). In the concealed groups, participants had blood samples taken for a PlGF-based test, but the results were concealed from clinicians and were not incorporated into clinical decision making. Care for these participants followed standard clinical management.

Additionally, the PreOS study[34] compares the clinicians' decisions recorded both before and after receiving the test results, at which point they could chose to amend their original. All studies took place in Europe: Germany, Austria, Denmark and the UK (with one Australian site in the MAPPLE study[16]). The larger, comparative studies took place in the UK: PARROT[15] with a total study population of 1023 and INSPIRE[32] with a total study population of 370. An overview of the design of these add-on studies is in Table 2 below.

Table 2 Overview of the included studies of add-on tests (result revealed)

Study	Location (centres)	Design	Comparator	Total population analysed	Outcome types
Triage PlGF test					
PARROT[15]	UK (11 maternity units)	Multicentre, pragmatic, stepped-wedge cluster RCT	RCT: intervention arm for revealed result; comparator arm for concealed result.	Total: 1023 (allocated) Intervention: 576 Comparator: 447	Test accuracy; comparative clinical outcomes

MAPPLE[16]	UK, Germany, Austria, and Australia (4 centres)	Prospective cohort study	Unadjusted and adjusted analysis between the MAPPLE study cohort for revealed results and the PELICAN study cohort for concealed results.	Total pregnancies: 396 (Liverpool: 241; Osnabrück: 115; Salzburg: 26; Adelaide: 14) Total infants: 433	Comparative clinical outcomes
Ormesher 2018[17]	UK (1 hospital)	Prospective cohort study	N/A – single cohort study	260	Test accuracy
Elecsys sFlt-1/PlGF ratio					
INSPIRE[32]	UK (1 hospital)	Prospective randomized, parallel-group, controlled trial	RCT: intervention arm for revealed result; comparator arm for concealed result.	Total: 370 Intervention: 186 Comparator: 184	Test accuracy; comparative clinical outcomes
PreOS[34]	Germany (4 centres) and Austria (1 centre)	Multicentre, prospective, open, non-interventional study in routine clinical practice	Before- and after-design: before the sFlt-1/PlGF test result was known, clinicians documented their clinical decisions. Then the result was made available, and the decisions were revised or confirmed.	Total: 209 women enrolled Full analysis population: 192 women Per-protocol population: 118 women Safety population: 200 women	Comparative clinical outcomes

Binder 2020[35]	Austria (1 centre)	Retrospective analysis of a single cohort	N/A – single cohort study	164 (twin pregnancies)	Test accuracy
BRAHMS Kryptor sFlt-1/PlGF ratio					
Andersen 2019[48]	Denmark (1 centre)	Retrospective study	N/A – single cohort study	300	Test accuracy

The strongest evidence, therefore, comes from the large, UK-based, RCTs, PARROT[15] for the Triage test and INSPIRE[32] for the Elecsys test, supported by the cohort studies MAPPLE[16] for Triage and PreOS[34] for Elecsys. The Binder 2020[35] study provides data on multiple pregnancies and is discussed as a sub-group of interest in Section 4.2 of this report. The evidence for the BRAHMS Kryptor test is limited to a retrospective cohort study, conducted outside of the UK, currently available only as a conference abstract (Andersen 2019).[48] There is no available data for the DELFIA Xpress test used alongside standard clinical assessment, though we did identify a study of the DELFIA Xpress used as a standalone test - the COMPARE[30] study (see the next sub-section and also Appendix 5).

4.1.1.4 Characteristics of the standalone test studies

The standalone studies introduce a broader international study population to this systematic review with centres in the USA, Canada, The Netherlands, China, and several other countries in Asia. The only study to include a UK population is the PELICAN[18 21] study (also a comparator arm for the MAPPLE[16] add-on study, as noted above).

All, except one study, were prospective cohort studies with the main difference between them being whether they were single centre studies with small study populations (Baltajian 2016[46], Saleh 2016[54]), or whether they were large multicentre studies with larger study populations (PELICAN[18 21], PETRA[25 27], PROGNOSIS [36-42], PROGNOSIS Asia[43]).

The only standalone study providing data on the BRAHMS Kryptor test (Salahuddin 2016[47]) is also the only case control study, using the remaining evaluable samples from a defined recruitment period in the ROPE[45] cohort (a different recruitment period to the one reported in ROPE)[45] and a group of normative control participants which generated reference levels of angiogenic factors throughout gestation. Test ratio results were reported as a continuous variable except for a ROC analysis of a subgroup of women presenting <34 weeks (from the ROPE cohort only) where a cut-off of >85 was used. Therefore, for the purpose of this review, the relevant data is derived from a single cohort. The test concordance aspect of the study (BRAHMS/Elecsys) is discussed in section 4.1.3 of this report.

An overview of the design of the standalone studies is in Table 3 below.

Table 3 Overview of the included studies of standalone tests (result concealed)

Study	Location (centres)	Design	Total population analysed	Outcome types
Triage PlGF test				
PELICAN[18 21]	UK and Ireland (7 centres)	Prospective observational study	Enrolled: 649 Analysed: 625	Test accuracy; test concordance (PEACHES validation cohort)
PEACHES – validation cohort[24]	As above for PELICAN	Retrospective cohort study	Total: 579 No pre-existing disease: 456 Chronic hypertension: 94 Chronic kidney disease: 29	As above for PELICAN
PETRA[25 27]	USA and Canada (24 centres)	Prospective single cohort	20^{+0} to 35^{+0} weeks: Enrolled: N=757 Analysed: N=753 [redacted]	Test accuracy
Elecsys sFlt-1/PlGF ratio				
PROGNOSIS [36-42]	Argentina, Australia, Austria, Belgium, Canada, Chile, Germany, Netherlands, New Zealand, Norway, Peru, Spain, Sweden, UK. (30 centres; 1 centre in the UK)	Prospective, multi-center, observational study	Total: 1050 Development cohort: 500 Validation cohort: 550	Test accuracy
PROGNOSIS Asia[43]	China, Hong Kong,	Prospective, multi-center, blinded, non-	Enrolled: 764 Analysed: 700 evaluable for the	Test accuracy

	Japan, Singapore, South Korea, and Thailand. (25 centres)	interventional study	primary endpoint analysis. Analysed: 690 evaluable for analysis of fetal adverse outcomes.	
ROPE[45]	USA (1 centre)	Prospective cohort study	Total: 402	Test accuracy
Baltajian 2016[46]	USA (1 centre)	Prospective cohort study	Enrolled: 103 Analysed: 100	Test accuracy
Saleh 2016[54]	The Netherlands (1 centre)*	Prospective cohort study	Total: 107	Test accuracy
Wang 2021[11]	China (1 centre)	Prospective cohort study	Enrolled: 200 Analysed: 196	Test accuracy
BRAHMS Kryptor sFlt-1/PlGF ratio				
Salahuddin 2016[47]	USA (1 centre)	Case control study using evaluable participants from a different recruitment period (to that reported above in Rana 2018[45]) within the ROPE cohort and normative controls.	Available samples from previous cohort: 412 Normative controls: 434	Test accuracy; test concordance
DELFIA Xpress PlGF 1-2-3				
COMPARE[30]	UK and Ireland (combined total of 20 centres)	Retrospective analysis of samples collected as part of three prospective cohort studies (PEACHES, PELICAN-1 and PELICAN-2).	Total: 396 women Plasma samples: 396; Serum samples: 244	Test accuracy; test concordance

*Study centre location(s) not reported, based on author affiliations				

In summary, the standalone test studies mainly report test accuracy results and to a lesser extent test concordance data. Notably, standalone studies provide data for tests where evidence from add-on studies was limited: BRAHMS Kryptor test (Salahuddin 2016)[47] and the DELFIA Xpress PlGF 1-2-3 test (COMPARE)[30]

4.1.1.5 Approach to add-on test use

There was slight variation between the add-on studies in their approach to testing, in terms of timing of the test; cut-offs values used; how the revealed test results were used to inform in patient care; and definitions of pre-eclampsia (Table 4)

- **Gestational age at testing**. This varied from 20^{+0} weeks (PARROT[15], MAPPLE[16], Ormesher 2018[17]), to 24^{+0} weeks (INSPIRE[32], PreOS[34], Andersen 2019[48]), and in one study testing was performed on a population with a gestational age within an interquartile range of 30 to 35 weeks (Binder 2020[35]). Samples were taken at presentation or during triage for suspected pre-eclampsia.
- **Test cut-off values**. All studies used the cut-offs recommended by the respective manufacturers. The Binder 2020[35] study additionally investigated ratio cut-offs of >80 and >67 and intermediate values of 38 to 80 and 38 to 67 as it was investigating different sFlt-1/PlGF ratio measures in twin pregnancies. However, only the cut-off of 38 in the Binder 2020[35] study is assessed in this review because the others do not match the cut-offs recommended by the manufacturer. Andersen 2019[48] used cut-offs of 33 and 85 with the BRAHMS Kryptor test: the cut-off of 85 is in keeping with the manufacturer recommendations that a measurement >85 is suggestive of pre-eclampsia and the patient should be delivered within two weeks; the cut-off of 33 correlates with the Roche Elecsys use of the sFlt-1/PlGF ratio to rule out pre-eclampsia in the short term.
- **Use of test results to inform care.** Four studies (PARROT[15], MAPPLE[16], Ormesher 2018[17], INSPIRE[32]) incorporated test results into local clinical care algorithms; one study (PreOS[34]) allowed clinicians to confirm or amend their decisions according to the test result where the only care recommendations available were the test package inserts; two studies (Binder 2020[35], Andersen 2019[48]) stated the test results were available to physicians or used as an aid to clinical diagnosis but no care algorithms or care recommendations were reported as being used.

- **Diagnostic criteria.** The studies that used the test results to aid diagnosis of pre-eclampsia additionally referred to the following published diagnostic criteria for pre-eclampsia: two studies (PARROT[15], Binder 2020[35]) used the ISSHP 2014 criteria[55]; one study (Andersen 2019[48]) used the Danish guidelines based on the ISSHP criteria, which version is not reported; two studies (INSPIRE[32], Ormesher 2018[17]) referred to both ISSHP 2014[55] and ACOG 2013[56] criteria; one study (PreOS[34]) referred to their protocol definitions which reference ISSHP 2001[57] criteria for pre-eclampsia and ACOG 2002[58] for severe pre-eclampsia.
  The updated ISSHP 2014[55] criteria and ACOG 2013[56] criteria include proteinuria, but its concomitant presence alongside other criteria is not required. Therefore, the PreOS study[34], and potentially the Andersen 2019 study[48], used a narrower definition of pre-eclampsia than the other studies.

Table 4 Overview of the approach to add-on test use

Study	Timing of the tests (GA weeks)	Test diagnostic cut-off(s)	Use of the test in the revealed arm/cohort	Reference standard diagnostic criteria
Triage PlGF test				
PARROT[15]	20^{+0} to 36^{+6}	PlGF test: Normal: > 100 pg/mL. Low: PlGF < 100 pg/mL. Very low: <12 pg/mL.	A clinical management algorithm was used in which the PlGF result was integrated into NICE guidance for the management of hypertensive pregnancies.	ISSHP 2014 Statement[55].
MAPPLE[16]	20^{+0} to 34^{+6}	Derived from PELICAN[18] study: - <12 pg/ml (very low) - 12–100 pg/ml (low; representing <5th percentile of normal) - >100 pg/ml (normal)	Care was provided according to the Liverpool Pre-eclampsia PlGF Protocol for Maternity Assessment Unit which provides guidance according to PlGF level cut-offs in addition to blood pressure and other test results.	N/A*
Ormesher 2018[17]	20^{+0} to 36^{+6}	PlGF was classified as either normal (> 100 pg/ml), intermediate	A care pathway was developed incorporating standard clinical management	ISSHP 2014[55] and ACOG 2013[56] criteria.

		(13–100 pg/ml) or low (< 12 pg/ml).	guidelines (NICE CG107[59] and RCOG Greentop Guideline no. 31)[60] with inclusion of the PlGF result.	
Elecsys sFlt-1/PlGF ratio				
INSPIRE[32]	24^{+0} to 36^{+6}	- ≤38 for low risk of developing pre-eclampsia within 7 days. - >38 elevated risk of developing pre-eclampsia within 7 days. Post-hoc analysis: - ≥85 for ruling in pre-eclampsia within 4 weeks.	The sFlt-1/PlGF ratio was incorporated into a local protocol of clinical decision pathways for care of suspected pre-eclampsia using a clinical algorithm.	In line with ISSHP 2014[55] and ACOG 2013[56] criteria.
PreOS[34]	24^{+0} to birth	Investigators were aware that ≥85 was "useful in confirming the diagnosis of pre-eclampsia" (p. 3). They received no clinical management guidelines based on sFlt-PlGF ratio test cut-offs beyond those in the package inserts.	Investigators recorded intended clinical procedures on a device that was data locked and time stamped. On receipt of the sFlt-1/PlGF ratio test result they were free to confirm or revise their decisions. There were no care recommendations other than the test package inserts.	Concomitant occurrence of proteinuria ≥2+ by dipstick urinalysis and elevated blood pressure (≥140 mmHg systolic and/or ≥90 mmHg diastolic, reproducible on two occasions).
Binder 2020[35]	IQR 30 to 35	Cut-off <38 assessed for ruling out delivery within 1 and 2 weeks Cut-offs of >80 and >67 and intermediate values of 38 to 80 and 38 to 67 also assessed for predicting delivery within 1 and weeks, but results are not data extracted, as these cut-offs do not reflect those specified for the Elecsys	It is reported that the test results were available to the physicians. No clinical care algorithm or care recommendations are referred to.	ISSHP 2014 Statement.[55]

BRAHMS Kryptor sFlt-1/PlGF ratio				
Andersen 2019[48]	24^{+0} to 37^{+0}	33 and 85 (rationale and purpose not reported)	Women had had a s-Flt1/PlGF ratio test before being included in the study. It was used as an aid to diagnosis in conjunction with clinical assessment.	Danish guidelines based on ISSHP criteria.
* MAPPLE was not a diagnostic accuracy study, comparison of clinical outcomes only.				

4.1.1.6 Approach to standalone test use

An overview of the diagnostic test aspects of the standalone studies is in Table 5 below.

- **Gestational age at testing**. Testing was performed from 20+0 weeks in three studies (PELICAN[18 21], PETRA[25 27], PROGNOSIS Asia[43]), and slightly later in other studies, from 22 weeks (Saleh 2016[54]), and from 24 weeks (PROGNOSIS [36-42]).
- **Test cut-off values.** All the standalone studies used PlGF and sFLT-1/PlGF ratio cut-offs according to the manufacturer recommendations.
- **Timing of tests.** The blood samples were taken at presentation or triage for suspected pre-eclampsia, but the immunoassays were run at different timepoints across the studies: in one study (PELICAN[18 21]) the tests were run but the results were masked from the clinicians and participants; for most studies (PROGNOSIS [36-42], PROGNOSIS Asia[43], ROPE[45], Baltajian 2016[46], Salahuddin 2016[47]) the tests were not run until after all deliveries and clinical outcomes measured.
- **Diagnostic criteria**. Criteria used to define pre-eclampsia varied more than for the add-on studies, including the earlier ACOG 2002[58] and ISSHP 2001[57] criteria and/or the updated ACOG 2013 criteria[56] and ISSHP 2014 statement[55] (likely due to study start date). This indicates less consistency in the use of proteinuria as a diagnostic criterion across the studies.

Table 5 Overview of the approach to standalone test use

Study	Timing of the tests (GA weeks)	Test diagnostic cut-off(s)	Use of the test	Reference standard diagnostic criteria
Triage PlGF test				
PELICAN[18 21]	20^{+0} to 34^{+6} 35^{+0} to 36^{+6}	Normal: PlGF ≥5^{th} centile for gestational age. Positive,	All test meters were programmed to produce a masked result, indicating	ACOG practice bulletin 2002[58] for pre-eclampsia, severe pre-

		low: <5th centile. Positive, very low: <12 pg/mL.	satisfactory test completion only, without revealing the value. All adjudicators of pregnancy outcome were masked to PlGF values so that the test result could not influence delivery decisions.	eclampsia and superimposed pre-eclampsia. ISSHP 2001[57] for atypical pre-eclampsia.
PEACHES – validation cohort[24]	As above for PELICAN	PlGF less than fifth centile for gestation	Samples were taken at the time of suspected disease to assess the diagnostic performance of the test at the time of presentation and were categorized according to outcome at delivery. Plasma samples were tested without awareness of clinical outcomes.	As above for PELICAN
PETRA[25 27]	20^{+0} to 34^{+6} [redacted]	Pre-term pre-eclampsia: 12 pg/mL Pre-term pre-eclampsia delivering within 7 or 14 days: 100 pg/mL.	Blood samples were frozen and sent to a central Alere site for PlGF measurement.	Diagnostic classification based on modified ACOG criteria 2002[58] and 2013[56], and pre-specified in the protocol.
Elecsys sFlt-1/PlGF ratio				
PROGNOSIS [36-42]	24^{+0} to 36^{+6}	sFlt-1/PlGF ratio cut-off of 38	sFlt-1/PlGF ratio measurements were not available until after the study. Results could not influence clinical decisions.	Diagnostic criteria for each pre-eclampsia-related disorder were based on international guidelines, including: ISSHP 2001[57]; ACOG Practice Bulletin 2002[58].

PROGNOSIS Asia[43]	20^{+0} to 36^{+6}	sFlt-1/PlGF ratio cut-off of 38	The maternal serum samples were analyzed retrospectively at 2 independent central laboratories. Results were transferred at the end of the study to the Roche biostatistics department (Penzberg, Germany) where the sFlt-1/PlGF ratio was calculated.	Based on ISSHP 2001[57] diagnostic criteria to align with the PROGNOSIS study.
ROPE[45]	up to 36^{+0}	>38 and >85, based on accuracy data from prior studies, to predict pre-eclampsia with severe features.	Blood samples were collected upon arrival at triage and stored at -70°C. Immunoassays were run after all patients had delivered and outcomes occurred.	ACOG criteria 2013[56], including ACOG criteria for diagnosing pre-eclampsia with severe features.
Baltajian 2016[46]	<37 (IQR 31 to 35)	Normal angiogenic profile was defined as patients with sFlt1/PlGF ratio of <85 and abnormal angiogenic profile was defined as sFlt1/PlGF ratio of ≥85.	The samples were analyzed in a single batch for measurement of angiogenic factors in blinded fashion after delivery and after all the outcomes were achieved by all the patients.	ACOG criteria 2013[56].
Saleh 2016[54]	22 to 36	Cut-off of ≥85 for diagnosing pre-eclampsia and for predicting adverse	Blood samples were taken at time of admission, centrifuged and stored at -80°C until analysis. Values of	PE was defined according to the ISSHP 2001[57] criteria and based on clinical judgement and

		outcomes and prolongation of pregnancy.	sFlt-1 and PlGF were determined after delivery to prevent any influence on clinician decision making.	routine laboratory findings.
Wang 2021[11]	20 to 36	Ratio of ≥38 predicts pre-eclampsia within 4 weeks. Ratio of <38 predicts no pre-eclampsia within 4 weeks.	Maternal blood from each participant was drawn when they were enrolled, left to clot and then centrifuged, The serum aliquots were separated and stored at −80°C until being tested.	2019 ACOG Practice Bulletin[61]
BRAHMS Kryptor sFlt-1/PlGF ratio				
Salahuddin 2016[47]	IQR 28.7 to 33 (<34 group) IQR 33.6 to 38.0 (total)	sFlt1/PlGF ratio cut-off of 85	Available samples from the ROPE study were thawed from frozen and assays performed. Test results were not available to clinicians or research staff at the time of data collection and entry.	ACOG criteria 2013[56].
DELFIA Xpress PlGF 1-2-3				
COMPARE[30]	20^{+0} to 36^{+6}	<150 pg/mL Optimally derived from data in this study.	Available samples from the PEACHES, PELICAN-1 and PELICAN-2 studies were processed on each platform. Both serum and plasma samples were analysed where available. Whole aliquots were used for each index test, and no sample had been exposed to a freeze–thaw cycle.	ISSHP 2014[55]

4.1.1.7 Definition of suspected pre-eclampsia in the study populations

The inclusion criteria of this review specify that ≥70% of the study population should have suspected pre-eclampsia as the presenting condition. In six of the seven add-on studies all patients had suspected pre-eclampsia: PARROT[15], MAPPLE[16], Ormesher 2018[17], INSPIRE[32], PreOS[34], Binder 2020[35]. (Table 6) This list contains MAPPLE[16] and Ormesher 2018[17] which included suspected fetal growth restriction as a presenting condition, which in itself is a sign of suspected pre-eclampsia as the current NICE guidance includes 'suspected fetal compromise'.[3] Andersen 2019[48], for the BRAHMS Kryptor test, included high risk pregnancies referred for observation of pre-eclampsia and it was not reported what constituted high risk. All of the standalone studies comprised only women with suspected pre-eclampsia.

Table 6 Reasons for suspecting pre-eclampsia, add-on studies (result revealed)

Study	Proportion of population with suspected pre-eclampsia	Reasons for suspected pre-eclampsia
Triage PlGF test		
PARROT[15]	[All.] Presenting condition was suspected pre-eclampsia.	Suspected pre-eclampsia was defined as new or worsening hypertension, dipstick proteinuria, epigastric or right upper-quadrant pain, a headache with visual disturbances, fetal growth restriction, or abnormal maternal blood tests that indicated disease. Proportions are reported in participant characteristics.
MAPPLE[16]	[All.] Suspected pre-eclampsia or fetal growth restriction <35 weeks gestation.	Symptoms/signs included headache, visual disturbances, epigastric or right upper quadrant pain, hypertension, dipstick proteinuria, or suspected fetal growth restriction.
Ormesher 2018[17]	[All.] High-risk pregnant women with suspected pre-eclampsia or fetal growth restriction.	A change in maternal condition noted after 20 and <37 weeks' gestation in women with pre-existing maternal disease and/or an ultrasound scan identified concerns regarding placental function.
Elecsys sFlt-1/PlGF ratio		
INSPIRE[32]	[All.] Presenting condition was suspected pre-eclampsia.	A clinical suspicion of pre-eclampsia, defined as new onset elevated blood pressure, or worsening of pre-existing hypertension or new onset proteinuria/worsening of existing proteinuria or new onset headache, visual disturbance, edema or right upper quadrant pain or any other suspicion of pre-eclampsia.

PreOS[34]	[All.] Presenting condition was suspected pre-eclampsia.	Suspected based on a variety of reasons, including new onset of elevated blood pressure, abnormal uterine Doppler ultrasound result, suspected IUGR, headache and/or new onset of protein in urine. A fuller list of reasons is provided in Table 1 in the paper.
Binder 2020[35]	[All.] Presenting condition was suspected pre-eclampsia.	Symptoms of pre-eclampsia including epigastric pain, new-onset edema, new-onset proteinuria (positive dipstick urine test), elevated liver enzymes (transaminase levels above the reference range), low platelet count (<100 000/ μ L), high blood pressure (⩾ 140/90mmHg), dyspnea, or neurological symptoms of pre-eclampsia.
BRAHMS Kryptor sFlt-1/PlGF ratio		
Andersen 2019[48]	High risk pregnancies referred for observation for pre-eclampsia; 51/300 (17%) had pre-eclampsia at the time of the test.	Not reported (conference abstract with limited information).

Table 7 Reasons for suspecting pre-eclampsia, standalone studies (result concealed)

Study	Proportion of population with suspected pre-eclampsia	Reasons for suspected pre-eclampsia
Triage PlGF test		
PELICAN[18 21]	[All.] Inclusion criteria was all women requiring evaluation for pre-eclampsia.	Symptoms or signs of pre-eclampsia included headache, visual disturbances, epigastric or right upper quadrant pain, hypertension, dipstick proteinuria, or suspected FGR.
PEACHES – validation cohort[24]	[All.] The validation cohort derived from the PELICAN study therefore consisted of all women requiring evaluation for pre-eclampsia. Women were selected if they had chronic kidney disease or chronic hypertension (or both) or no pre-existing disease.	As above for PELICAN.
PETRA[25 27]	[All.] Inclusion criteria required signs or	Not stated which of the signs and symptoms listed in the population baseline characteristics raised suspicion of pre-eclampsia.

	symptoms of pre-eclampsia.	
Elecsys sFlt-1/PlGF ratio		
PROGNOSIS [36-42]	[All.] Inclusion criteria specifies women with suspected pre-eclampsia.	At least one of the following: New onset of elevated blood pressure (did not need to be defined hypertension), aggravation of pre-existing hypertension, new onset of protein in urine (did not need to be defined proteinuria), aggravation of pre-existing proteinuria, epigastric pain, excessive edema/severe swelling (face, hands, feet), headache, visual disturbances, sudden weigt gain (>1 kg/week in the third trimester, low platelets, elevated liver transaminases, (suspected) intrauterine growth restriction, abnormal uterine perfusion detected by Doppler sonography with mean pulsatility index >95th percentile in the second trimester and/or bilateral uterine artery notching.
PROGNOSIS Asia[43]	[All.] Inclusion criteria specifies women with suspected pre-eclampsia.	One or more of the following, new onset of hypertension (systolic blood pressure [BP] ⩾140 mm Hg or diastolic BP ⩾90 mm Hg, single measurement), aggravation of pre-existing hypertension (systolic BP ⩾160 mm Hg or diastolic BP ⩾110 mm Hg, single measurement), new onset of proteinuria, aggravation of pre-existing proteinuria, severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses, new onset of visual disturbances (e.g. blurred vision, diplopia), suspected FGR or abnormal uterine perfusion detected by Doppler sonography with mean pulsatility index >95th percentile or bilateral notch, and partial HELLP syndrome (1 or 2 of the 3 features of HELLP syndrome present).
ROPE[45]	[All.] Women presenting with symptoms and signs of suspected pre-eclampsia at time of initial evaluation in triage.	Symptoms and signs of pre-eclampsia included elevated blood pressure, proteinuria, headache, visual symptoms, right upper quadrant pain, or edema.
Baltajian 2016[46]	[All.] Women admitted for evaluation of pre-eclampsia.	Reasons for suspecting pre-eclampsia were not reported.
Saleh 2016[54]	[All.] Women were recruited at time of admission for suspected pre-eclampsia.	Patients were suspected of PE if they presented with new onset hypertension and or proteinuria at or after 18 weeks gestation, developed an aggravation of their pre-existing hypertension and or pre-existing proteinuria or if they presented with symptoms such as right upper quadrant abdominal pain or headache with visual disturbances.
Wang 2021[11]	[All.] Women presenting with	At least one of the following: new onset of hypertension

	suspected pre-eclampsia.	(systolic BP >120 and <160 mmHg and/or diastolic BP >80 and <110 mmHg) or proteinuria (≥2+ by dipstick); aggravation of pre-existing hypertension or proteinuria; or persistent symptoms of upper abdominal pain, edema, visual impairment, abnormal weight gain (>1 kg/week), decreased platelets (<150 × 109/L), elevated liver transaminase (alanine transferase >55 U/L or aspartate transaminase >34 U/L), fetal growth restriction (estimated fetal weight or abdominal circumference <10th percentile according to the charts routinely used by Obstetric Department at our institute), increased pulsatility index (PI) of the uterine artery (PI > 0.878), or uterine artery flow notching.
BRAHMS Kryptor sFlt-1/PlGF ratio		
Salahuddin 2016[47]	[All.] As above for the ROPE study.	As above for the ROPE study.
DELFIA Xpress PlGF 1-2-3		
COMPARE[30]	[All.] As above for the PELICAN and PEACHES studies.	As above for the PELICAN and PEACHES studies.

4.1.1.8 Characteristics of participants in the add-on studies

The key demographic and maternal health characteristics of the participants are shown in Table 8 and Table 9 below, except for Andersen 2019[48] for the BRAHMS Kryptor test which does not report participant characteristics.

The mean (or median) age of participants in the add-on test studies was around 31 years except in the study by Binder 2020[35] which had a median age of 37, 36, or 34 years depending on the outcome group. The gestational age at presentation was similar across all studies. The PreOS[34] study did not report parity. The other studies, however, all reported at least the proportion of participants who were nulliparous, which was broadly similar across the studies except for Binder 2020[35] which had a slightly greater proportion of nulliparous participants at 55%, 60% or 71% depending on the outcome group. Binder 2020[35] also reports a slightly lower BMI for participants and the range does not reach 30 kg/m^2, whereas participants in the other studies reach a BMI of up to 34 kg/m^2. It is not possible to determine the overall BMI range across all studies due to the different variance measures used in each study.

The majority of participants in the studies were of white ethnicity: PARROT[15] (66% revealed arm, 65% concealed arm), MAPPLE[16] (91% revealed arm, 66% concealed arm) and INSPIRE[32] (89% revealed arm, 90% concealed arm). Other ethnicities are not reported

consistently across studies. The PreOS study[34], with centres in Germany and Austria, reports only Hispanic/Latino or non-Hispanic/non-Latino categories for ethnicity, with 96% in the non-Hispanic/non-Latino category. Binder 2020[35] did not report ethnicity.
Only MAPPLE[16] and INSPIRE[32] report smoking status, showing that between 9% and 11% of participants were current smokers.

Singleton or multiple pregnancies were accounted for in each study's inclusion or exclusion criteria. One study included only multiple pregnancies (Binder 2020[35]); some studies had a mixture of singleton and multiple pregnancies (MAPPLE[16], PreOS[34]) (although in MAPPLE[16] women with twin pregnancies were excluded from the adjusted comparison with PELICAN[18]); whilst other studies included singleton pregnancies only (PARROT[15], INSPIRE[32]). A recent study demonstrated that maternal plasma PlGF in twin pregnancy follows the same gestational pattern as described in singletons and therefore we need not discount evidence from studies including multiple pregnancies in the population.[62] However, some studies have suggested that the sFlt-1/PlGF ratio is higher in twins across all gestational ages compared with singleton pregnancies and that different ratio cut-offs may need to be applied.[63-66] A clinical expert to the EAG advised that including twins in a study but using thresholds defined for singletons can affect the results. However, in studies comprising mixed singleton and multiple pregnancies the number of multiple pregnancies was low.

Table 8 Characteristics of participants in the add-on test studies

Population characteristic	PARROT[15] Revealed arm	PARROT[15] Concealed arm	MAPPLE[16] Revealed arm	MAPPLE[16] Concealed arm	Ormesher 2018[17]
Measure (variance)	Mean (SD)		Median (quartiles)		Median (range)
Age, years	31.9 (5.9)	31.5 (6.0)	31 (27-35)	32 (27-36)	Not reported
Gestational age, weeks	32.3 (3.8)	32.7 (3.9)	30.7 (27.7 – 33.1)	31.0 (27.9 – 33.4)	*No PE/SGA:* 33+4 (23+0 – 40+0) *PE:* 31+6 (23+1 – 41+2) *SGA:* 32+4 (23+1 – 38+3)
Parity, n (%)	0: 317 (55) 1: 133 (23) 2: 59 (10)	0: 211 (47) 1: 120 (27) 2: 65 (15)	0: 208 (52.7)	0: 164 (57.1)	Not reported

	≥3: 67 (12)	≥3: 51 (11)			
BMI, kg/m^2, median (IQR)	27.9 (23.9–33.1)	28.4 (24.2–34.1)	27 (24 – 32)	29 (24 – 34)	*No PE/SGA:* 26.13 (18.79–44.08) *PE:* 30.43 (20.20–50.07) *SGA:* 24.21 (17.21–41.28)
Ethnicity, n (%)	White: 378 (66) Black: 76 (13) "Indian, Pakistani, Bangladeshi, or Sri Lankan": 67 (12) Mixed: 13 (2) Other (incl. Chinese): 39 (7)	White: 292 (65) Black: 63 (14) "Indian, Pakistani, Bangladeshi, or Sri Lankan": 52 (12) Mixed: 11 (2) Other (incl. Chinese): 26 (6%)	White: 357 (91.1) Black: 12 (3.1) Asian: 8 (2.0) Other: 19 (4.8)	White: 187 (65.6) Black: 70 (24.6) Asian: 19 (6.7) Other: 11 (3.8)	*Total:* White: 121 (46.5) Black: 54 (20.8) Asian: 70 (26.9) Other: 15 (5.8)
Smoking status, n (%)	Not reported		43 (11.3)	24 (8.6)	Not reported

Table 9 Characteristics of the participants in the Elecsys add-on test studies

Population characteristic	**INSPIRE[32] Revealed arm**	**INSPIRE[32] Concealed arm**	**PreOS*[34]**	**Binder 2020[35]**
Measure (variance)	Median (IQR)		Median (min-max)	Median (IQR)

Age, years	30.9 (27.4–35.8)	31.1 (26.7–34.7)	31.2 (19–45)	*Delivery ≤1 week due to PE:* 37.0 (33.0-39.0) *Delivery ≤2 week due to PE:* 36.0 (31.2–38.0) *Delivery >2 week due to PE or other:* 34.0 (30.2–37.0)
Gestational age, weeks	34.3 (31.3–36.0)	34.4 (31.4–35.7)	32+4*	*Delivery ≤1 week due to PE:* 35.0 (33.0-36.1) *Delivery ≤2 week due to PE:* 34.3 (32.9–36.0) *Delivery >2 week due to PE or other:* 33.0 (29.3–35.0)
Parity, n (%)	0: 86 (46.2) ≥1: 86 (46.2)	0: 94 (51.1) ≥1: 90 (48.9)	Not reported	*Delivery ≤1 week due to PE:* 0: 16 (55.2) *Delivery ≤2 week due to PE:* 0: 25 (59.5) *Delivery >2 week due to PE or other:* 0: 86 (70.5)
BMI, kg/m^2, median (IQR)	28.3 (24.3–32.4)	26.7 (23.1–31.7)	26.2 (17–60)	*Delivery ≤1 week due to PE:* 24.5 (21.8-26.0) *Delivery ≤2 week due to PE:* 25.1 (21.9–29.1) *Delivery >2 week due to PE or other:* 23.4 (21.3–26.9)
Ethnicity, n (%)	White: 166 (89.2) Other: 18 (9.7) Not recorded: 2 (1.1)	White: 166 (90.2) Other: 15 (8.2) Not recorded: 3 (1.6)	Hispanic/Latino: 3 (1.6) Non-Hispanic/non-Latino: 184 (95.8) Unknown: 5 (2.6)	Not reported

Smoking status, n (%)	*Revealed:* Current smoker: 17 (9.1) Never smoker: 107 (57.5) Previous smoker: 62 (33.3)	Current smoker: 16 (8.7) Never smoker: 118 (64.1) Previous smoker: 50 (27.12)	Not reported	Not reported
*data shown here for the full analysis population of the PreOS study, except for gestational age which was only reported for the safety population.				

4.1.1.9 Prognostic characteristics of participants in the add-on studies

Four of the add-on studies reported prognostic characteristics of the participants: both of the Triage test studies (PARROT[15], MAPPLE[16]) and two of the Elecsys test studies (PreOS[34] and Binder 2020[35]).

All four studies reported either new-onset hypertension, worsening hypertension, new-onset elevated blood pressure, or more than one of these. The proportion of participants with new onset hypertension was lower in PreOS[34] (14%) than in PARROT[15] (52% revealed arm) or MAPPLE[16] (80% revealed arm), however, PreOS[34] additionally reported new onset of elevated blood pressure (36%) whereas the other studies did not. All four studies reported the proportion of participants with new-onset proteinuria for which the proportion was much higher in the PARROT[15] study at 59% (both study arms) compared to 4% in PreOS[34]. The PreOS study[34] additionally reported aggravation of pre-existing proteinuria (0.5%) and new onset of protein in urine (15%). All four studies reported the proportion of participants with epigastric pain (3% to 15.9%). Three studies reported on abnormal blood test results, with two studies specifically reporting low platelet counts and elevated liver enzymes. Three studies reported on suspected fetal growth restriction. All other prognostic characteristics were only reported by one or two studies, see Table 8 below. Ormesher 2018, which only reports suspected FGR (51%) and both suspected pre-eclampsia and suspected FGR (20%), is not included in Table 8.

The studies report differing aspects of medical history relevant to pre-eclampsia (NB. INSPIRE[32] does not report any). These include:

- previous pre-eclampsia, range 7% to 39% (PARROT[15], MAPPLE[16], PreOS[34])
- previous hypertensive disorder of pregnancy (excluding pre-eclampsia), range 2% - 6% (MAPPLE[16])
- previous eclampsia, 1% (PreOS[34])
- previous HELLP, 4% (PreOS[34])
- family history of pre-eclampsia, 1% (PreOS[34])
- chronic hypertension, range 14% to 16% (PARROT[15], MAPPLE[16])
- pre-existing hypertension, range 14% to 55% (Ormesher 2018[17])
- pre-existing renal disease, range 4% to 7% (PARROT[15], MAPPLE[16])
- diabetes, range 2% to 17% (PARROT[15], MAPPLE[16], Ormesher 2018[17])
- gestational diabetes, range 12%/12% (PARROT[15])
- being prescribed prophylactic aspirin, range 41%/40% (PARROT[15])
- antihypertensive medication, 14% (Binder 2020[35])
- systemic lupus erythematosus/antiphospholipid syndrome, range 2% 4% (MAPPLE[16])
- early pregnancy proteinuria, range 4% to 23% (Ormesher 2018[17])

Three of the studies report blood pressure levels at baseline, but they use different measures of variance so it is difficult to compare (PARROT[15], INSPIRE[32], Binder 2020[35]), and two studies report proteinuria at baseline, either the proportion of participants with proteinuria (MAPPLE[16]), or by level of proteinuria (PARROT[15]).

Table 8 Prognostic characteristics of participants in the Triage and Elecsys add-on studies

Prognostic characteristic	Triage		Roche Elecsys	
	PARROT*[15]	**MAPPLE[16]**	**PreOS[34a]**	**Binder 2020[35]**
New-onset hypertension, n (%)	*Revealed:* 299 (52) *Concealed:* 209 (47)	*Revealed:* 314 (79.5) *Concealed:* 155 (54.0)	27 (14.1)	Not reported
Worsening of existing hypertension, n (%)	*Revealed:* 100 (17) *Concealed:* 79 (18)	Not reported	24 (12.5)	Not reported

New onset of elevated blood pressure, n (%)	Not reported	Not reported	69 (35.9)	*Delivery ≤1 week due to PE:* 25 (86.2) *Delivery ≤2 week due to PE:* 38 (90.5) *Delivery >2 week due to PE or other:* 71 (58.2)
New-onset proteinuria, n (%)	*Revealed:* 341 (59) *Concealed:* 263 (59)	*Revealed:* 59 (14.9) *Concealed:* 161 (56.1)	7 (3.6)[b]	*Delivery ≤1 week due to PE:* 15 (51.7) *Delivery ≤2 week due to PE:* 18 (42.8) *Delivery >2 week due to PE or other:* 19 (15.6)
Epigastric or right upper-quadrant pain, n (%)	*Revealed:* 47 (8) *Concealed:* 47 (11)	*Revealed:* 12 (3.0) *Concealed:* 18 (6.3)	26 (15.9)	*Delivery ≤1 week due to PE:* 2 (6.9) *Delivery ≤2 week due to PE:* 2 (4.7) *Delivery >2 week due to PE or other:* 16 (13.1)
Neurological symptoms, n (%)	*Revealed:* 187 (32) *Concealed:* 150 (34)	Not reported	Not reported	*Delivery ≤1 week due to PE:* 4 (13.8) *Delivery ≤2 week due to PE:* 6 (14.3) *Delivery >2 week due to PE or other:* 9 (7.4)
New onset edema	Not reported	Not reported	Not reported	*Delivery ≤1 week due to PE:* 16 (55.2) *Delivery ≤2 week due to PE:* 24 (57.1) *Delivery >2 week due to PE or other:* 36 (29.5)
Dyspnea, n (%)	Not reported	Not reported	Not reported	*Delivery ≤1 week due to PE:* 0 (0.0) *Delivery ≤2 week due to PE:* 0 (0.0) *Delivery >2 week due to PE or other:* 5 (4.1)
Abnormal blood test results, n (%)	*Revealed:* 19 (3)	Not reported	*Low platelets:* 14 (8.5)	*Delivery ≤1 week due to PE:*

	Concealed: 8 (2)		*Elevated liver transaminases :* 12 (7.3)	Low platelets: 3 (10.3) Elevated liver enzymes: 2 (6.9) *Delivery ≤2 week due to PE:* Low platelets: 3 (7.1) Elevated liver enzymes: 3 (7.1) *Delivery >2 week due to PE or other:* Low platelets: 6 (4.9) Elevated liver enzymes: 6 (4.9)
Suspected fetal growth restriction, n (%)	*Revealed:* 103 (18) *Concealed:* 62 (14)	*Revealed:* 66 (16.7) *Concealed:* 25 (8.7)	49 (29.9)	Not reported
Reduced fetal movement, n (%)	*Revealed:* 6 (1) *Concealed:* 5 (1)	Not reported	Not reported	Not reported
Andersen 2019[48] for the BRAHMS Kryptor test is a conference abstract and did not report prognostic characteristics and is therefore not included in this table. The INSPIRE study[32] and Ormesher 2018[17] did not report prognostic characteristics of participants and are not included in this table. [a] A further breakdown of prognostic characteristics by PlGF level and trial arm is also reported for this study[9] [b]PreOS additionally reports aggravation of pre-existing proteinuria (1/192, 0.5%) and new onset of protein in urine (29/192, 15.1%) whereas the other studies do not report this.				

4.1.1.10 Critical appraisal of risk of bias and applicability of test accuracy in the add-on studies

We applied the QUADAS-2[1] quality assessment tool to assess the risk of bias and applicability of test accuracy data in the add-on studies, where reported (Table 9). QUADAS -2 appraises the likelihood of bias arising from: the selection of participants; the conduct and

interpretation of the index test and the reference standard; the flow of participants through a study and the timing of the index test and reference standard. It also assesses the applicability of the participants selected and the index test and reference standard the review's research question. shows our assessments of the add-on studies identified in this review.

Table 9 Overview of QUADAS-2 assessments (add-on studies)

Study	Risk of bias				Applicability concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Triage PlGF test							
PARROT	Unclear	Low	Low	Low	Low	High [a]	Low
Ormesher 2018	Unclear	Low	Low	Low	Low	Low	Low
Elecsys sFlt-1/PlGF ratio							
INSPIRE	Low	Low	Low	Low	Low	Low	Low
Binder 2020	Unclear	Low	Low	Unclear	Low	Unclear	Low
BRAHMS Krytpor sFlt-1/PlGF ratio							
Andersen 2019	Unclear	Low	Low	Unclear	Low	Low	Low

Note: Of the seven identified add-on studies, no accuracy data was reported in the PreOS and MAPPLE study publications.
[a] Accuracy was assessed in the concealed trial arm only, so the PlGF test was not used alongside standard clinical assessment.

For all but one of the five studies appraised (INSPIRE), we judged there to be an unclear risk of participant selection bias, due to either a lack of information provided in the study reports about whether or not a consecutive or random sample of participants were enrolled and/or the study's exclusion criteria (meaning we could not assess if any inappropriate participant exclusions had been made). In the PARROT trial, maternity units were randomised as to when they could start introducing PlGF testing, but it was unclear how pregnant women were individually approached and enrolled in the study, resulting in an unclear risk of bias. Across the other domains of bias, we generally judged that the studies were of a low risk of bias.

In terms of applicability of the studies' findings to the review question, we did not identify any concerns. We noted, however, that test accuracy was assessed in the concealed trial arm

only in the PARROT RCT. This means that the accuracy of the PlGF test result was examined as a standalone test only, so the results have more limited applicability to the decision problem.

We note that the purpose of the Binder 2020 study was to identify cut-offs in twin pregnancies that optimised positive predictive values (PPV) and negative predictive values (NPV) for this population, and by default the cut-offs were not pre-specified. The paper also did not generally clearly report the cut-offs for which the test accuracy findings were presented, so the applicability of the findings to this review were unclear. We also noted the study authors stated that due to the clinical guidance that clinicians followed, the sFlt-1/PlGF ratio result, although used in conjunction with standard clinical assessment, was unlikely to influence their decisions about delivery.
Although we did not identify any applicability issues in how the index test was used in the Ormesher 2018 study, we note it used the PlGF test in a slightly different way to the other studies. In this study, the test was repeated if the initial result was normal or intermediate but there was an ongoing suspicion of pre-eclampsia or concerns about the fetus. The test closest to delivery was then used in the test accuracy analyses. Other studies used the PlGF-based tests once.

4.1.1.11 Critical appraisal of risk of bias of clinical effectiveness outcomes in RCTs (add-on)

We used the Cochrane risk of bias tool for randomised trials (version 1) to assess potential risk of bias, with respect to the clinical effectiveness outcomes in the two add-on RCTs included in the review (INSPIRE and PARROT). The results of the appraisal show that, overall, both trials can be considered to be a low risk of bias, with a couple of exceptions in each trial (Table 10) which we discuss below.

First, in both trials, due to the ‘revealed’ nature of the intervention (i.e. the use of PlGF-based testing alongside standard clinical assessment to inform diagnosis and subsequent care) compared to the ‘concealed’ comparator (standard clinical assessment to inform diagnosis and subsequent care without knowledge of the test result) it was not possible to blind the clinicians or study participants to intervention/comparator status. Thus, the trials are at high risk of performance bias (i.e. bias arising from differences in the care received by the intervention and control groups in a trial other than the intervention that being compared). However, in both trials there was evidence that outcome assessors were unaware of

intervention/comparator arm assignment (thus, they are at low risk of detection bias). In the INSPIRE trial it appears that all outcome measures were assessed without knowledge of trial arm assignment, whilst for PARROT it wasn't explicitly stated whether or not the assessment of clinical outcomes (all of which were secondary outcomes) was without knowledge of assignment. Detection bias is less likely for clinical outcomes which, by their nature, are indisputable 'hard' endpoints (e.g. mortality, hospitalisation, delivery, stillbirth).

Table 10 Risk of bias assessments for add-on RCTs

	Random sequence generation	**Allocation concealment**	**Blinding (participants; personnel)**	**Blinding (outcome assessors)**	**Incomplete outcome data**	**Selective reporting**
Study						
INSPIRE	Low	Low	High	Low	Low	High
PARROT	Low	High	High	Low	Low	Low

Risk of bias judgments: Low, High, or unclear

In PARROT the second concern relates to lack of apparent concealment of the random allocation, suggesting a potential for selection bias (i.e. biased allocation of participants to trial arms). The method of random sequence generation in this trial was complex due to the design of the study (a stepped-wedge cluster RCT). Randomisation of site clusters was done by the trial statistician, and from the information in the trial publications, it appears that the only influence the statistician had on the random allocation was to ensure sites of different sizes were balanced by trial arm. This does not, however, guarantee against any conscious or unconscious biased selection of sites for randomisation. We also note, however, that the study participants' baseline characteristics, and the proportion diagnosed with pre-eclampsia, were similar between the trial arms, suggesting a lack of selection bias (at least for measured variables). Thus, although we judged this study as high risk of bias for concealment of allocation (as per the Risk of Bias criteria) taking other factors into consideration, it appears unlikely that the results are affected by selection bias.

In the INSPIRE trial the second concern was that results were not presented for all of the outcome measures the authors intended to measure (as stated in the trial protocol).

4.1.1.12 Narrative summary of the INSPIRE and PARROT studies

Of the seven add-on studies included in this review, the PARROT and INSPIRE RCTs provide the most rigorous, comprehensive and relevant evidence on the impact of the tests, used alongside standard clinical assessment, on clinical effectiveness outcomes in pre-eclampsia. Both trials were conducted in UK hospitals and followed local care protocols as well as national maternity care guidelines including those produced by NICE. They can therefore be considered reflective of contemporary 'real world' NHS clinical practice, and for all of the above reasons we prioritise PARROT and INSPIRE to inform the assumptions and input parameters used in our base case economic modelling of the cost-effectiveness of the Triage PlGF test and the Elecsys sFlt-1/PlGF ratio, respectively (Section 5.4).

In this sub-section we summarise the design and key findings of each trial in turn, focusing on the outcomes our experts advised are of particular clinical importance. The purpose is to give the reader an overview of the 'end to end' test accuracy and clinical effectiveness evidence for the Triage PlGF test and the Elecsys sFlt-1/PlGF ratio in the respective trials. The 'whole trial' summaries of PARROT and INSPIRE which follow are complementary to the more detailed 'outcome-by-outcome' synthesis of all seven add-on studies, presented from Section 4.1.2 onwards.

The PARROT trial

The PARROT trial [9 15] was a pragmatic, stepped wedge cluster RCT of the Triage PlGF test conducted in 11 UK maternity units with 1023 participants with suspected pre-eclampsia who were between 20^{+0} and 36^{+6} weeks of gestation. The units initially used usual care to assess and manage pre-eclampsia, with PlGF measures taken but the result concealed from clinicians. The units were then randomised over time to start revealing the PlGF test results to clinicians, who used the results alongside usual care to make clinical decisions. Usual care followed local hospital practice, NICE's guidelines for the management of hypertension in pregnancy, and national guidance for the management of fetuses suspected to be small for gestational age. When revealed testing took place, clinicians used a clinical management algorithm that integrated the PlGF test result with NICE's hypertension in pregnancy guidelines, with guidance on clinical decisions to take according to the PlGF result.

The PlGF cut-offs used (>100, 12-100, and <12 pg/mL) were in line with those recommended by the company. If a participant had a PlGF of < 12 pg/mL, the algorithm defined this as 'very low' and instructed clinicians to 'assess as pre-eclampsia'. Pre-

eclampsia was defined by the International Society for the Study of Hypertension in Pregnancy (ISSHP) 2014 statement. The trial compared clinical outcomes between participants who had received usual care plus revealed testing (n = 576) to those who had received usual care with concealed testing (n = 447). The trial assessed a range of clinical and test accuracy outcomes. The study's primary outcome was time from trial entry to a documented diagnosis of pre-eclampsia.

The following sections summarise the key findings of the trial and selection of these is presented in Table 11.

Pre-eclampsia diagnoses and time to diagnosis

The trial found that, after diagnosis adjudication, 44% of the participants in revealed testing group and 44% in the concealed testing group met the diagnostic criteria for pre-eclampsia. Time to diagnosis was statistically significantly shorter in the revealed than the concealed group (a median of 1.9 days versus 4.1 days). The authors stated this corresponded to a 64% reduction in time to diagnosis.

Use of the Triage PlGF Test to rule-in pre-eclampsia

In DG23, NICE recommended research on the use of a positive Triage PlGF test result (< 12pg/mL), when the test was used with standard clinical assessment, to rule-in pre-eclampsia among people presenting between 20 weeks and 34 weeks plus 6 days of gestation. NICE stated the focus of research should be on how this "would affect management decisions on time to delivery and the outcomes associated with this" (NICE DG23).[6] The PARROT trial reported a Triage PlGF test result of <12 pg/mL, when used alone and not in conjunction with standard clinical assessment (that is, the test accuracy analysis was performed in the concealed arm only) had a PPV of 44.6% (95% CIs 32.3% to 57.5%) for predicting pre-eclampsia requiring delivery within 14 days in a subgroup of women who presented between 20^{+0} and < 35 weeks of gestation.

Time to delivery and preterm delivery

In the whole trial population of between 20^{+0} and 36^{+6} weeks of gestation, the time to delivery in days was longer in the revealed PlGF test result arm than in the concealed PlGF test arm, but the difference did not quite reach statistical significance (Table 11). The authors stated there were no differences in the rates of pre-term delivery (< 37 weeks) between the trial arms.

Maternal and fetal outcomes

The key findings from the PARROT trial regarding maternal outcomes were:

- The adjusted odds of women having an adverse outcome (a composite outcome as defined by the fullPIERS consensus) was 68% lower in the revealed arm than the concealed arm.
- There was no statistically significant difference between the revealed and concealed groups in the number of nights they spent in inpatient care.

The key findings from the PARROT trial regarding fetal and neonatal outcomes were:

- There was no statistically significant difference in mean gestational age at delivery between the revealed group and the concealed group.
- There were no statistically significant differences between the revealed and concealed groups in the odds of perinatal adverse outcomes (a composite outcome) or perinatal deaths. There were three late neonatal deaths (1%) in the reveal arm and one in the concealed arm (<1%) (statistical significance not reported).
- Data from PARROT on neonatal unit admissions (stratified by PE risk level), inpatient nights in ICU/HDU and SCBU are used in the base case economic model. The paper states that there were no statistically significant differences in neonatal unit admissions (34% of the babies in the revealed testing arm were admitted versus 33% in the concealed testing arm). The mean number of inpatient nights in the neonatal unit and SCBU appeared to be similar between groups (data not presented here; see section 4.1.11.2 for results). The mean number of inpatient nights in the ICU/HDU was lower in the revealed (15.2, SD 1.7) than concealed group (24.2, SD 3.8), with a statistically significant difference based on the confidence interval of the mean difference.
- There were no apparent differences in rates of intraventricular haemorrhage or respiratory distress between the groups.

Labour and mode of delivery

Findings from the trial on onset of labour and mode of delivery inform our base case economic model. The trial found no apparent differences between groups in how labour started or mode of delivery (data not presented here; see sections 4.1.9.3 and 4.1.9.4 for results).

Table 11 Summary of the PARROT trial key findings

PARROT trial outcome	Revealed PlGF test result n = 573	Concealed PlGF test result n = 446	Difference
Trial's primary outcome			
Time to diagnosis, median days (IQR)	1.9 (0.5-9.2)	4.1 (0.8-14.7)	Time ratio = 0.36 (95% CI 0.15 to 0.87; p=0.027), corresponding to a 64% reduction in time to diagnosis (13 – 85%)
Time to delivery and preterm delivery			
Time to delivery (all diagnoses), days, geometric mean (SD)	19.0 (3.1)	17.8 (3.1)	Ratio of means 1·10 (CI 0·99-1·24)
Preterm deliveries <37 weeks, n/N (%)	234/573 (41)	167/446 (37)	Paper states no differences observed
Maternal outcomes			
Number of nights in inpatient care, mean (SE)	7.43 (0.36)	7.26 (0.38)	-0.06 [a] (95% -0.22 to 0.09)
Number of women with adverse outcomes, defined by the fullPIERS consensus, n/N (%)	22/573 (4)	24/446 (5)	Adjusted OR 0·32, 95% CI 0·11 to 0·96; p=0·043
Perinatal and neonatal outcomes			
Perinatal adverse outcomes, n/N (%) [post-hoc]	86*/573 (15)	63/446 (14)	aOR 1.45, 95% CI 0.73–2.90
Perinatal deaths, n/N (%) [b]	6/573 (1)	4/446 (1)	aOR 1.00, 95% CI 0.61–1.63
Late neonatal deaths (8–27 complete days of life), n/N (%) [b]	3/573 (1)	1/446 (<1)	Not reported
Any grade of intraventricular haemorrhage [perinatal], n/N (%)	7/573 (1)	11/446 (3)	Not reported
Respiratory distress syndrome [perinatal], n/N (%)	78/573 (14)	54/446 (12)	Not reported

Delivery gestation, mean weeks (SD)	36.6 (3.0)	36.8 (3.0)	Mean difference -0·52 (CI -0·63 to 0·73)

Underlining shows the trial outcomes used in our economic model base case.

[a] Authors do not report what statistic this is.

[b] In the base case economic model, fetal and neonatal deaths results from PARROT are categorised as follows: stillbirth, neonatal death and in-hospital death.

The INSPIRE trial

The INSPIRE trial[32] was a pragmatic RCT of the Elecsys sFlt-1/PLGF ratio test conducted in one tertiary referral hospital in the UK. The study included 370 participants with suspected pre-eclampsia who were between 24^{+0} and 37^{+0} weeks of gestation. The design was similar to the PARROT trial, but women, rather than maternity units, were randomly allocated to receive standard clinical management with concealed testing (n = 184) or standard clinical management with the sFlt-1/PlGF ratio result revealed (n = 186). Standard clinical management included blood pressure and proteinuria assessment, and a range of blood tests and other examinations. Blood pressure was managed according to NICE's guidelines.

Clinicians followed a clinical management algorithm, and in the revealed testing group, the sFlt-1/PlGF ratio result was integrated into this. The study used cut-offs of ≤38 to suggest a low risk of developing pre-eclampsia within seven days and of >38 to suggest elevated risk of developing pre-eclampsia within seven days. These cut-offs are the same as those recommended by the company for ruling out or ruling in the development of pre-eclampsia within one and four weeks, respectively. The study's primary outcome was preeclampsia-related inpatient admission (hospitalisation) within 24 hours of the test. The following sections summarise the key findings of the trial and selection of these is presented in Table 12.

Pre-eclampsia diagnoses and time to diagnosis

Across the entire trial duration, 25.2% of the participants in revealed testing group and 20.6% in the concealed testing group were diagnosed with pre-eclampsia. A post-hoc analysis showed there was no statistically significant difference between the trial arms in the time to the pre-eclampsia diagnosis (revealed arm: 7 days, IQR 0-29; concealed arm: 9.5 days, IQR 0-32; p = 0.6387; days assumed to be reported as the median, but unit not stated in paper).

Use of the Elecsys sFlt-1/PLGF ratio test to rule-in pre-eclampsia

In DG23, NICE recommended research on the use of the Elecsys sFlt 1/PlGF ratio of < 38 to rule-in pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation. For a gestation age of 24+0 to 37+0 weeks, the INSPIRE study reported in a post-hoc analysis of the revealed arm that the Elecsys sFlt-1/PLGF ratio test cut-off of >38 had a PPV of 0.411 (95% CIs 0.281 – 0.550) for ruling in the development of pre-eclampsia within one week of testing, when it was used alone (that is, not as an adjunct to standard clinical management). The INSPIRE trial did not, therefore, assess the ability of this test cut-off to rule-in pre-eclampsia in-keeping with the scope of this appraisal.

Time to delivery and preterm delivery

The INSPIRE trial did not report any findings related to time to delivery or preterm delivery.

Maternal and fetal outcomes

The key findings from the INSPIRE trial regarding maternal outcomes were:

- No statistically significant difference between the revealed and concealed testing arms in hospital admission for suspected pre-eclampsia within 24 hours of the test.
- No statistically significant difference between arms in hospital admission for suspected pre-eclampsia any time, up to the point of delivery (data not shown in Table 12, but available in Section 4.1.10.1).

Our base case economic model uses data from the INSPIRE trial to estimate severe/major maternal complications. As Table 12 shows, there were no statistically significant differences between the trial arms on any of these outcomes. There were no other statistically significant differences between trial arms on any of the other maternal outcomes reported in the trial (data not shown in Table 12; see section 4.1.6.2 for results).

Regarding fetal and neonatal outcomes, the trial found no statistically significant difference in gestational age at delivery between the trial arms (Table 12), nor in the other four outcomes assessed: birthweight, APGAR score, SCBU admissions and SGA.

Table 12 Summary of the INSPIRE trial key findings

INSPIRE trial outcome	Revealed PlGF test result n = 186	Concealed PlGF test result n = 184	Difference

Trial's primary outcome			
Admission for suspected PE within 24 hours of the test, n/N (%)	60/186 (32.3)	48/184 (26.1)	Risk ratio (95% CI) 1.24 (0.89 to 1.70) Risk difference (95% CI) 0.06 (−0.03 to 0.15)
Maternal outcomes			
Pulmonary edema, n/N (%)	1/186 (0.54)	1/184 (0.54)	*p*=0.994
Abruption, n/N (%)	2/186 (1.1)	5/184 (2.7)	*p*=0.246
Eclampsia	0	0	-
Perinatal and neonatal outcomes			
Gestational age (weeks) at delivery, median (IQR)	38.4 (37.3-39.6)	38.1 (37.1-39.3)	*p*=0.479

Underlining shows the trial outcomes that are used in our economic model base case.

4.1.2 Assessment of test accuracy (add-on studies)

This section describes the test accuracy results from studies in which the PlGF or sFlt-1/PlGF ratio test was used alongside standard clinical assessment (add-on studies). In addition, supporting data on test accuracy from studies in which the test was not used alongside routine clinical care (standalone studies) are summarised briefly (further data for these studies is in Appendix 5).

An overview of the test accuracy data available from the seven included add-on studies is summarised in Table 13.

Table 13 Test accuracy data reported in add-on studies

Test	**Study identifier**	**Relevant study population**	**Prognostic/diagnostic outcome reported Prediction of:**
Triage PlGF test	PARROT	Revealed test arm	None reported
		Concealed test arm	-Pre-eclampsia requiring delivery within 2 weeks -Preterm delivery (<37 weeks)
	MAPPLE	Revealed test arm only	None reported
	Ormesher 2018	Women with test-birth interval <14 days	-Pre-eclampsia

		Women with any test-birth interval	-Pre-eclampsia
		Women <37 weeks gestation with test-birth interval <14 days	-Preterm delivery
		Women <37 weeks gestation with any test-birth interval	-Preterm delivery
Elecsys sFlt-1/PlGF ratio	INSPIRE	Revealed test arm	-Pre-eclampsia within 1,2,3 and 4 weeks
		Revealed test arm using test only	-Pre-eclampsia within 1 week
		Concealed test arm	-Pre-eclampsia within 1,2,3 and 4 weeks
	PreOS	Whole study population (before and after test result revealed)	None reported
	Binder 2020	Whole study population (all twin pregnancies)	-Pre-eclampsia requiring delivery within 1 and 2 weeks -Prediction of severe maternal morbidity
BRAHMS Kryptor sFlt-1/PlGF ratio	Andersen 2019	Whole study population	-Pre-eclampsia within 1 and 4 weeks
Delfia Xpress test	No add-on studies identified	N/A	N/A

N/A = Not applicable

4.1.2.1 Testing to predict pre-eclampsia

Triage PlGF test

Ormesher et al[17] report test accuracy data for the Triage PlGF test in the diagnosis of pre-eclampsia, with the highest PPVs achieved when using a test cut-off of 12 pg/ml (Table 14).

Table 14 Diagnosis of pre-eclampsia by test-birth interval (Triage PlGF test)

Test-birth interval	Cut-off (pg/ml)	Total (n)	Sensitivity (95% CI) [a]	Specificity (95% CI) [a]	PPV[b] (95% CI) [a]	NPV[b] (95% CI) [a]	Prevalence % (95% CI) [a]
Ormesher et al;[17] Triage PlGF test, result concealed, after 20 and <37 weeks' gestation							
Within 14 days	<12	50	0.512	1.000	1.000	0.310	82.0
	<100	50	0.951	0.333	0.867	0.600	82.0
At any time	<12	128	0.500	1.000	1.000	0.562	60.9
	<100	128	0.771	0.333	0.893	0.792	60.9
NPV: negative predictive value; NR: not reported; PPV: positive predictive value [a] 95%CI not reported; [b] calculated by reviewer							

Two standalone studies (PETRA, PELICAN)[22 25] reported NPVs ranging from 0.530 to 0.901 in patients <35 weeks gestation when using this test at a cut-off PlGF level of 100 pg/mL to predict PE at any time point (Appendix 5, Table 81).

Elecsys sFlt-1/PlGF ratio test

In a post-hoc analysis of the INSPIRE study with women who presented with suspected pre-eclampsia from 24^{+0} to 36^{+6} weeks, an unpublished manuscript (academic in confidence)[31] reported the NPVs using an sFlt-1/PlGF ratio cut off of <38 for ruling out pre-eclampsia within 1, 2, 3 weeks and 4 weeks. Results were provided for the test result revealed (N=186) and test result concealed (N=184) arms of the study as well as for the whole study population (N=370). In all cases NPVs were [redacted]. However, no further test accuracy statistics are reported for this analysis. In the original published manuscript,[32] test accuracy data is provided only for the use of the test cut-off of <38 for ruling out pre-eclampsia within 1 week, with an NPV of 0.992 (Table 15).

Positive predictive values may be used to assess the accuracy of a test in ruling in a disease. PPVs of 0.714 and 0.720 were reported in the revealed and concealed arms of the INSPIRE study,[33] respectively, when a higher cut-off of 85 was applied to predict pre-eclampsia within 4 weeks (Table 15).

Table 15 Prediction of pre-eclampsia by timepoint (Elecsys sFlt-1/PlGF ratio test)

Time point	Cut -off	Total (n)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Prevalence % (95% CI)
INSPIRE, [32] Elecsys ratio (result revealed arm, using test result only), 24^{+0} to 37^{+0} weeks							
Within 1 week	>38	186	0.958 (0.789-0.999)	0.796 (0.726-0.855)	0.411 (0.281-0.550)	0.992 (0.958-1.000)	12.90 [b] (8.45-18.59)
INSPIRE,[33] Elecsys ratio plus standard clinical interpretation (result revealed arm), 24^{+0} to 37^{+0} weeks							
Within 4 weeks (rule in) [a]	≥85	186	0.571 (0.394-0.737)	0.947 (0.898-0.977)	0.714 (0.513-0.868)	NR	NR
INSPIRE, [32] Elecsys ratio (result concealed arm), 24^{+0} to 37^{+0} weeks							
Within 4 weeks (rule in) [a]	≥85	184	0.643 (0.441-0.814)	0.955 (0.910-0.982)	0.720 (0.506-0.879)	NR	NR
Andersen et al, [48] BRAHMS Kryptor sFlt-1/PlGF ratio used alongside clinical care, 24^{+0} to 37^{+0} weeks							
Within 1 week	33	300	NR	NR	NR	0.960	20 [b]
	85	300	NR	NR	0.460	NR	20 [b]
Within 4 weeks	33	300	NR	NR	NR	0.940	20 [b]
	85	300	NR	NR	0.620	NR	20 [b]

NPV: negative predictive value; NR: not reported; PPV: positive predictive value
[a] author emphasis; [b] calculated by reviewer

Similarly, high NPVs (>0.9) were reported at a cut-off of 38 for prediction of pre-eclampsia at various time points in standalone studies: PROGNOSIS[36 39 67] (within 1, 2, 3 and 4 weeks), PROGNOSIS Asia[43] (within 1 and 4 weeks), Wang[11] (within 4 weeks), and ROPE[45] (PE with severe features within 2 weeks). At the lower cut-off (<38), PPVs ranged from 0.367 to 0.407 across the study populations within the PROGNOSIS study. At a higher cut-off (cut-off >85), PPVs ranged from 0.594 to 0.769 in the ROPE study and were highest in the subgroup of women admitted to hospital and at less than 34 weeks gestation (Appendix 5, Table 80 and Table 83). Saleh et al[54] reported high PPVs (>0.9) at a test cut off >85 for the diagnosis /prediction of PE at study inclusion and at final diagnosis (Appendix 5,Table 82).

BRAHMS Kryptor sFlt-1/PlGF ratio test

Andersen et al[48] assessed the use of the test to predict pre-eclampsia within 1 or 4 weeks at a cut-off of 33. NPVs were high (>0.9) while PPVs were 0.460 and 0.620 respectively when a higher cut-off of 85 was used (Table 15).

DELFIA Xpress PlGF test

We did not identify any relevant add-on studies or standalone studies reporting on this outcome.

4.1.2.2 Testing to predict delivery

Triage PlGF test

Ormesher et al[17] provide test accuracy data for the prediction of preterm delivery by test-birth interval in women at less than 37 weeks gestation (**Table 16**). Higher PPVs were achieved when the lower test cut-off of 12 pg/ml was used and were similar between women who delivered within 14 days of the test (0.969) and those who delivered at any time after the test (0.951).

Table 16 Prediction of preterm delivery (<37 weeks) by test-birth interval (Triage PlGF test)

Test-birth interval	Cut-off (pg/mL)	Total (n)	Sensitivity (95% CI)[a]	Specificity (95% CI) [a]	PPV [b] (95% CI) [a]	NPV [b] (95% CI) [a]	Prevalence % (95% CI) [a]
Ormesher et al,[17] Triage PlGF; test concealed < 37 weeks gestation							
Within 14 days	<12	88	0.449	0.947	0.969	0.321	78.4
	<100	88	0.841	0.263	0.806	0.313	78.4
At any time	<12	255	0.742	0.977	0.951	0.665	48.2
	<100	255	0.797	0.727	0.731	0.793	48.2
NPV: negative predictive value; NR: not reported; PPV: positive predictive value [a] 95%Cis not reported [b] calculated by reviewer.							

Data from the concealed arm only of the PARROT[15] study provided high NPV values (>0.95) for prediction of PE requiring delivery within 2 weeks (in women <35 weeks gestation) at test cut-offs of <12 pg/ml and <100 pg/ml (Table 17) while PPVs were 0.446 and 0.257 respectively. (NB. These data inform a scenario analysis for the Triage test in this population in our economic evaluation, see section 5.4 and section 5.5).

Table 17 Prediction of pre-eclampsia requiring delivery by timepoint (Triage test and Elecsys ratio test)

Time point	Cut-off	Total (n)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Prevalence % (95% CI)
PARROT, [15] Triage test, result concealed, 20^{+0} to 35^{+0} weeks							
Within 2 weeks	<100 pg/mL	265	0.949 (0.827-0.994)	52.7 (0.459-0.593)	0.257 [a] (0.228-0.288)	0.983 [a] (0.939-99.6)	14.72 (10.68-19.57) [b]
	<12 pg/mL	265	0.744 (0.579-0.870)	0.841 (0.786-0.886)	0.446 [a] (0.362-0.534)	0.950 [a] (0.917-0.970)	14.72 (10.68-19.57) [b]
Binder et al.,[35] Elecsys ratio, result revealed, median GA at assessment 33.6 weeks							
Within 1 week	<38 [d] [e]	164	0.965 (0.822-0.999)	0.711 (0.627-0.786)	0.418 (0.353-0.485)	0.990 (0.933-0.999)	NR

(rule out)[c]	<38 (adj) [d] [f]	164	0.862 (0.683-0.961)	0.763 (0.682-0.832)	0.439 (0.358-0.522)	0.963 (0.912-0.985)	NR
Within 2 weeks (rule out)[c]	<38 [d] [e]	164	0.881 (0.744-0.960)	0.770 (0.686-0.842)	0.569 (0.494-0.651)	0.949 (0.891-0.977)	NR
	<38 (adj) [d] [f]	164	0.982 (0.838-0.994)	0.713 (0.624-0.791)	0.533 (0.461-0.604)	0.977 (0.918-0.994)	NR

NPV: negative predictive value; NR: not reported; PPV: positive predictive value
[a] confidence interval as calculated by reviewer; differs slightly from reported value; [b] calculated by reviewer;
[c] author emphasis; [d] EAG assumes a cut-off of 38 but not clear from publication
[e] unadjusted model
[f] adjusted for mean arterial pressure and gestational age at assessment based on a method by Perry et al.[68]

For the prediction of pre-eclampsia requiring preterm delivery (<37 weeks) in women at 35 - 36^{+6} weeks' gestation, the PARROT study reported a higher NPV for the 100pg/ml test cut-off (0.971) than for the 12 pg/ml cut-off (0.868) while PPVs were 0.185 and 0.244 respectively (Table 18). (NB. These data inform the base case analysis for the Triage test in our economic evaluation, see section 5.4 and section 5.5).

Table 18 Prediction of pre-eclampsia requiring preterm delivery (<37 weeks) (Triage test)

Time point	Cut-off	Total (n)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Prevalence % (95% CI)
PARROT, [15] *Triage test, result concealed, 35^{+0} to 36^{+6} weeks*							
Before 37 weeks gestation	<100 pg/mL	170	0.962 [a] (0.804-0.999)	0.236 [a] (0.169-0.314)	0.185 [a] (0.168-0.204)	0.971 [a] (0.830-0.996)	15.29 (10.24% to 21.60%) [c]
	<12 pg/mL	170	0.370 (0.194-0.576)	0.783 (0.707-0.848)	0.244 [b] (0.153-0.366)	0.868 [b] (0.830-0.899)	15.88 (10.74-22.26) [c]

NPV: negative predictive value; NR: not reported; PPV: positive predictive value
[a] data as calculated by reviewer, to correct a slight discrepancy in the publication (see explanation in data extraction form). Applies to point estimate and confidence interval for sensitivity, specificity and PPV; and to confidence interval for NPV.
[b] confidence interval as calculated by reviewer; differs slightly from reported value.
[c] calculated by reviewer.

Two standalone studies (PETRA, PELICAN),[22 25-27 69] in patients <35 weeks gestation, evaluated the accuracy of the Triage test for prediction of delivery, pre-eclampsia requiring delivery and/or prediction of preterm pre-eclampsia requiring delivery within 1 and 2 weeks, with NPVs ranging from [redacted] when a cut-off of 100pg/ml was used. In contrast, this test had [redacted] and [redacted]

[redacted] for the prediction of any preterm delivery when the lower test cut-off of 12pg/ml was used (Appendix 5, Table 84 and Table 86). Another standalone study, 'COMPARE'[30] also reported high NPVs (>0.872) for the Triage test for a variety of different delivery outcomes (Appendix 5, Tables 90-93).

Elecsys sFlt-1/PlGF ratio test

Binder et al[35] reported high NPVs for the use of this test as part of routine care in ruling out of PE requiring delivery within 1 and 2 weeks in a retrospective analysis of women with twin pregnancies with a median gestational age of 33.6 weeks (Table 17). The authors commented that it was unlikely that clinicians intervened because of the biomarker test results, although no information is provided on the extent to which clinicians made decisions with or without the test results.

Additional prognostic accuracy data for the Elecsys sFlt-1/PlGF ratio test for prediction of delivery outcomes are reported by the following standalone studies: ROPE, Baltajian and PROGNOSIS Asia in (Appendix 5, Tables 85-87). While the results from the PROGNOSIS Asia[43] study support the use of the test for ruling out PE requiring delivery within 1 week (NPV:1.00), Baltajian et al[46] reported a relatively high PPV (0.91) for the prediction of indicated delivery within 2 weeks. Results from the ROPE study[45] varied by test cut-off and gestational age group with the highest NPV (0.947) reported for predicting indicated delivery within 2 weeks using a test cut-off of 38 in women at <34 weeks gestation. The COMPARE study[30] also reported high NPVs (>0.866) for the Elecsys ratio test for a variety of different delivery outcomes (Appendix 5, Tables 90-93).

BRAHMS Kryptor sFlt-1/PlGF ratio test

No data are available for prediction of delivery outcomes for this test from add-on or standalone studies.

DELFIA Xpress PlGF test

No data were available from add-on studies, however, one standalone study, COMPARE[30] reported NPVs >0.912 for a range of delivery-related outcomes.

4.1.2.3 Repeat testing to rule in/out pre-eclampsia

No data were provided by the add-on studies on the test accuracy of repeat PlGF-based testing. Zeisler et al.[36] conducted a post-hoc analysis of the PROGNOSIS validation cohort (N=550), a standalone study, to investigate whether repeat testing after 2-3 weeks could

identify women at risk of developing pre-eclampsia (sFlt-1/PlGF ratio >38) after initially being ruled out (sFlt-1/PlGF ratio ≤38).

4.1.2.4 Other test accuracy predictions

Binder et al[35] reported high NPVs (>0.962) for the use of the Elecsys ratio as part of routine care in predicting severe maternal morbidity in a retrospective analysis of women with twin pregnancies with a median gestational age of 33.6 weeks (Table 19). No further test accuracy data were provided from the add-on studies for the other three tests.

Table 19 Prediction of severe maternal morbidity

Outcome	Cut-off	Total (n)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Prevalence % (95% CI)
Binder et al.,[35] Elecsys ratio, result revealed, median GA at assessment 33.6 weeks							
Severe maternal mortality (rule out)	<38 [a b]	164	0.857 (0.637-0.970)	0.531 (0.446-0.615)	0.212 (0.174-0.256)	0.962 (0.898-0.987)	NR
	<38 (adj) [a c]	164	0.952 (0.762-0.999)	0.489 (0.405-0.574)	0.215 (0.185-0.248)	0.986 (0.911-0.998)	NR

NPV: negative predictive value; NR: not reported; PPV: positive predictive value
[a] EAG assume cut-off of 38 used; paper not clear.
[b] unadjusted model
[c] adjusted for mean arterial pressure and gestational age at assessment based on a method by Perry et al.[68]

Two standalone studies (Saleh et al[54] and Salhuddin et al[47]) provide additional accuracy data for the Elecsys sFlt-1/PlGF ratio test for the prediction of adverse outcomes (see Appendix 5 for further details).

4.1.3 Assessment of the concordance between tests

4.1.3.1 Analytical concordance

According to the EAG's clinical experts, all PlGF-based tests require quality assurance of their long-term performance for UKAS accreditation. An external quality assurance (EQA) scheme administered by NEQAS involves sending standard serum samples to hospitals for reference calibration and checking. The Roche, Perkin Elmer and ThermoFisher tests are included in this scheme but the Quidel Triage test is not. Users of the Quidel test therefore must use an alternate approach for demonstrating long-term consistency of the analyses.

4.1.3.2 Predictive concordance

The previous DAR[7] found no studies which compared the predictive accuracy of the four tests in a relevant population who had suspected pre-eclampsia. Our literature search 11 studies published since the previous DAR which compared two or more of the Triage PlGF, Elecsys, BRAHMS Kryptor and DELFIA Xpress PlGF 1-2-3 tests (Appendix 4). Some of these have limited relevance because they employed test cut-offs other than those recommended by the test manufacturers or were correlational analyses that did not include predictive outcomes. The most relevant studies are summarised briefly below. There were no studies that compared all four of the tests.

Cheng et al.[70] identified inter-test differences in determining measured PlGF and sFlt-1 concentrations and concluded that the rule-in/rule-out decision levels are test-specific and not interchangeable, although their study population was healthy pregnant Chinese women at 20-39 weeks of gestation, some of whom developed PE. Cheng et al. noted that in the Elecsys test, assay interference led to 0.6% of PlGF and sFlt-1 assay samples being not reportable. The rule-out and rule-in cut-offs of the Elecsys sFlt-1/PlGF ratio of 38 and 110 respectively were estimated to have equivalent values of 55 and 188 for the BRAHMS Kryptor sFlt-1/PlGF ratio test.

McCarthy et al.[30] conducted a secondary analysis, called the COMPARE study, which utilised PlGF samples from women in the PEACHES study[24] and in parts 1 and 2 of the PELICAN study[18 21] who had presented with suspected PE or a suspected SGA fetus before 37 weeks of gestation. NB Part 1 of PELICAN (included in our review) focused on women with suspected pre-eclampsia, while part 2 of PELICAN (excluded from our review) focused on women suspected of having an SGA infant. McCarthy et al. compared the commercially

recommended cut-offs for the Alere (now Quidel) Triage PlGF test (<100 pg/mL), Roche Elecsys test sFlt-1/PlGF ratio (>38) and an optimally derived cut-off for the Perkin Elmer DELFIA Xpress PlGF 1-2-3 test (<150 pg/mL). A trade-off was seen between sensitivity and specificity, with the Triage PlGF and DELFIA Xpress tests both having higher sensitivity, but lower specificity, than the Elecsys test. However, McCarthy et al. concluded that the tests' ability to predict delivery within 2 weeks did not differ significantly when using the specified cut-offs, with areas under the ROC curve being similar among the tests (full test accuracy statistics for the three tests are provided in the publication). The results from the Triage PlGF and Elecsys ratio tests were similar to those previously reported. Note that the population analysed in the COMPARE study does not fully match the NICE scope for the current review since it comprises women suspected of having pre-eclampsia as well as those suspected of having an SGA infant.

Giblin et al.[71] conducted a further secondary analysis of PlGF samples from women in the PELICAN and PEACHES studies who presented with suspected PE or a suspected SGA infant (as assessed in the COMPARE study[30]). Giblin et al. reported the test performance statistics (sensitivity, specificity, PPV, NPV and likelihood ratios) for PlGF or the sFlt-1/PlGF ratio for predicting delivery within 14 days using the Quidel Triage, Roche Elecsys and Perkin Elmer DELFIA Xpress tests. They concluded that the Quidel and Roche tests have slightly different sensitivities and specifies, but AUCs were similar and the test had similar clinical applicability for prediction of delivery. That said, there was a 3-fold difference in the rule-in thresholds for the Triage and DELFIA Xpress tests, 12 pg/mL and 50 pg/mL respectively, and the authors recommended the assessments could be standardised across tests, e.g. by converting biomarker concentrations to multiples of the median, to reduce the possibility of confusion.

4.1.4 Assessment of clinical effectiveness outcomes

Numerous clinical effectiveness outcome measures are reported across the included studies, with heterogeneity in the way they have been assessed and reported. Some clinical effectiveness outcomes are reported by only a handful of studies and are thus sparsely distributed across the evidence base. The three single arm observational cohort studies (Binder 2020[68], Ormesher 2018[17] and Andersen 2019[48]) did not assess the effect of using the PlGF or sFlt-1/PlGF ratio tests on clinical outcomes because they lack a control arm in which the test result is concealed. Any clinical outcomes reported in these studies are not presented in this report. Similarly, clinical outcomes reported in standalone test accuracy

studies are not discussed here since these also lack a control group and do not assess the use of the test alongside standard clinical assessment.

The subsequent sections therefore focus on a selection of clinical outcomes reported in the four add-on studies which compare use of the test alongside standard clinical assessment (test result revealed) with standard clinical assessment only (test result concealed): the PARROT and MAPPLE studies (Triage PlGF test) and the INSPIRE and PreOS studies (Elecys sFlt-1/PlGF ratio test). [9 15 16 32 34] We selected outcomes for presentation based on their clinical relevance, as informed by our expert clinical advisors. These include clinical effectiveness outcomes which inform our assessment of cost-effectiveness.

No clinical outcome data is available for the BRAHMS Kryptor sFlt-1/PlGF ratio test or DELFIA Xpress PlGF tests.

4.1.5 Assessment of time to event outcomes

4.1.5.1 Time to pre-eclampsia diagnosis

In the PARROT study, use of the Triage PlGF test alongside standard clinical assessment ('test result revealed') was associated with a 64% reduction in time to diagnosis of pre-eclampsia (95% CI:13% to 85%; p=0.027).[9 15] Time to diagnosis was numerically shorter in the revealed trial arm in all three PlGF level subgroups (Table 20).

Time to diagnosis was also numerically shorter in the INSPIRE study for those in whom the Elecsys sFlt-1/PlGF ratio test result was revealed (Table 20).[32]

Time to pre-eclampsia diagnosis was not reported in the MAPPLE or PreOS studies.[16 79]

Table 20 Time to diagnosis of pre-eclampsia, test result revealed versus concealed

Study	Outcome	Group	Revealed	Concealed	Difference (as reported in study)
Triage PlGF test					
PARROT[9 15]	Time (days) to diagnosis, median (IQR); N	Total	1.9 (0.5-9.2); N=573	4.1 (0.8-14.7); N=446	Adjusted time ratio = 0.36 (95% CI 0.15 to 0.87; p=0.027),
		PlGF <12	1.0 (0.3-4.5); n=130	2.0 (0.3-9.0); n=106	Adjusted time ratio = 0.17 (95% CI 0.03 to1.06)

		PlGF 12-100	2.0 (0.9-8.70); n=212	4.6 (1.0-14.5); n=173	Adjusted time ratio =0.66 (95% CI 0.09 to 4.95)
		PlGF >100	22.8 (8.4-39.2); n=229	30.3 (5.9-65.1); n=156	Adjusted time ratio =0.13 (95% CI 0.16 to 1.07)
Elecsys sFlt-1/PlGF ratio test					
INSPIRE[32]	Time (days) to PE diagnosis within 7 days, median (IQR); N	Total	0 (0-2); N=186	0 (0-3); N=184	0 days; [a] p=0.7777
	Time (days) to PE diagnosis within 28 days, median (IQR); N	Total	2 (0-9); N=186	4 (0-10.5); N=184	2 days; [a] p=0.5641
	Time (days) to PE diagnosis at any time, median (IQR); N	Total	7 (0-29); N=186	9.5 (0-32); N=184	2.5 days; [a] p=0.6387
[a] absolute difference as calculated by reviewer					

4.1.5.2 Time to delivery

For the Triage PlGF test, time to delivery was slightly longer overall in the revealed arm of the PARROT study compared to the concealed arm (19 versus 17.8 days) but when stratified by PlGF level the time to delivery was shorter in women with very low levels of PlGF (<12 pg/ml) in the revealed group compared to the concealed group regardless of gestational age (Table 21).[9 15] In general, time to delivery was longer in women at less than 35 weeks gestation. In the MAPPLE study, time to delivery was 6 days shorter in the revealed arm compared to the concealed arm (95% CI 2.0 to 10.0 days shorter) and was also shortest in women with very low PlGF levels (Table 21).[16]

Time to delivery was not reported in the INSPIRE or PreOS studies.[32 79]

Table 21 Time to delivery, test result revealed versus concealed

Study	Outcome	Group	Revealed	Concealed	Difference (as reported in study)
Triage PlGF test					
PARROT	Time to delivery (days), geometric mean (SD); N	Total	19.0 (3.1); N=573	17.8 (3.1); N=446	Adjusted ratio of means: 1·10 (CI 0·99-1·24)

	Time to delivery (days), median (IQR)[a]	In women <35 weeks gestation at testing:			
		PlGF <12 [b]	12 (6-22)	17 (7-25)	Not reported
		PlGF 12-100 [b]	26 (16-36)	27 (18-35)	Not reported
		PlGF >100 [b]	50 (32-75)	50 (35-76)	Not reported
		In women 35^{+0} to 36^{+6} weeks gestation at testing:			
		PlGF <12 [b]	4 (2-8)	8 (5-12)	Not reported
		PlGF 12-100 [b]	13 (7-18)	11 (4-18)	Not reported
		PlGF >100 [b]	20 (13-28)	21 (11-28)	Not reported
MAPPLE[16] [c]	Interval (days) from first test to delivery, median, (quartiles); N	Total	24 (4–52); N=397	29 (11–59); N=287	Median Difference: −6.0 (−2.0 to −10.0)
		PlGF <12 [b]	3 (1-13); n=116	9 (3-16); n=69	Not reported
		PlGF 12-100 [b]	19 (6-43); n=137	23 (11-40); n=97	Not reported
		PlGF >100 [b]	48 (32-69); n=143	61 (37-90); n=121	Not reported
[a] n not reported for subgroups [b] pg/ml [c] unadjusted indirect comparison					

4.1.6 Assessment of maternal outcomes

4.1.6.1 Pre-eclampsia diagnosis

Triage PlGF test

In the PARROT study, a slightly higher proportion of women were diagnosed with pre-eclampsia by a clinician (1% higher) or severe eclampsia (3% higher) in the test revealed arm compared to the concealed arm, with the highest numerical differences observed in women with very low PlGF levels (Table 22).[9 15] In contrast, the MAPPLE study observed a lower proportion of women diagnosed with pre-eclampsia in the revealed arm compared to the concealed arm (8.4%) with larger differences between the study arms observed when stratified by PLGF level (Table 22).[16]

Elecsys sFlt-1/PlGF ratio test

The proportion of women diagnosed with pre-eclampsia within 7 days, 28 days or at any time was numerically higher in the revealed arm compared to concealed arm in the INSPIRE study (Table 22).[32] Of those with a pre-eclampsia diagnosis, a higher proportion of the test revealed group (9% higher) were diagnosed with severe pre-eclampsia than the test concealed group(Table 23). Klein et al[79] did not report the frequency of pre-eclampsia

diagnoses for women in the PreOS study before and after knowledge of the test results was available to clinicians.

Table 22 Pre-eclampsia diagnosis by time point, test result revealed versus concealed

Study	Outcome	Group	Revealed	Concealed	Difference (as reported in study)
Triage PIGF test					
PARROT[9] [15]	PE diagnosis by clinician at any time, % (n/N)	Total	36 (205/573)	35 (155/446)	1.0 [b]
		PIGF <12 [c]	73.8 (96/130)	66.0 (70/106)	7.0 [b]
		PIGF 12-100 [c]	39.6 (84/212)	37.0 (64/173)	4.5 [b]
		PIGF >100 [c]	10.0 (23/229)	12.2 (19/156)	0.4 [b]
MAPPLE[16] [a]	PE diagnosis at any time, % (n/N)	Total	52.9 (193/397)	61.3 (176/287)	8.4; [b] Risk ratio (95% CI) 0.86 (0.75–0.99)
		PIGF <12 [c]	48.6 (51/116)	97.1 (67/69)	48.5 [b]
		PIGF 12-100 [c]	53.1 (69/137)	74.2 (72/97)	21.1 [b]
		PIGF >100 [c]	56.2 (73/143)	30.6 (37/121)	25.6 [b]
Elecsys sFlt-1/PlGF ratio test					
INSPIRE[32]	PE within 7 days, % (n/N)	Total	12.9 (24/186)	9.7 (18/184)	3.2; [b] p=0.344
	PE within 28 days, % (n/N)	Total	18.8 (35/186)	15.2 (28/184)	3.6; [b] p=0.357
	PE at any time, % (n/N)	Total	25.2 (47/186)	20.6 (38/184)	4.6; [b] p=0.291

[a] unadjusted indirect comparison [b] absolute % difference as calculated by reviewer [c] pg/mL

Table 23 Severe pre-eclampsia, test result revealed versus concealed

Study	Outcome	Group	Revealed	Concealed	Difference (as reported in study)
Triage PIGF test					
PARROT[9] [15]	Severe PE (ACOG definition), n/N (%)	Total	27 (155/573)	24 (106/446)	3.0; [b] aOR 1.22 (95% CI 0.71–2.12)
		PIGF <12 [c]	56.2 (73/130)	46.2 (49/106)	10.0 [b]
		PIGF 12-100 [c]	30.2 (64/212)	28.3 (49/173)	1.9 [b]
		PIGF >100 [c]	7.9 (18/229)	4.5 (7/156)	3.4 [b]
Elecsys sFlt-1/PlGF ratio test					
INSPIRE[32]	Severe PE (ACOG criteria), %[a] (n/N)	Total	72.3 (34/47)	63.3 (24/38)	9.0 [b]; p=0.366

	Severe PE with 2 or more criteria for severity, %[a] (n/N)	Total	12.7 (6/47)	18.4 (7/38)	5.7; [b] p=0.471
aOR: adjusted odds ratio [a] as a proportion of those diagnosed with PE [b] absolute % difference as calculated by reviewer [c] pg/ml					

4.1.6.2 Severe maternal adverse outcomes

Triage PlGF test

Our economic model primarily uses the composite outcome of severe maternal adverse outcomes reported in the PARROT trial.[9 15] This outcome is defined by the fullPIERS consensus and includes the number of women with one or more of the following events:

- maternal death, eclampsia, a Glasgow Coma Scale score of less than 13, stroke, transient ischaemic attack, cortical blindness or retinal detachment, posterior reversible encephalopathy, a requirement for positive inotropic support, a requirement for parenteral infusion of a third-line antihypertensive, myocardial ischaemia or infarction, blood oxygen saturations of less than 90%, 50% FiO2 (or higher) for more than 1 h, a requirement for intubation (other than for caesarean section), pulmonary oedema, a requirement for transfusion of blood products, a platelet count of less than 50 × 10^9 platelets per L, hepatic dysfunction, haematoma or hepatic rupture, severe acute kidney injury (defined as concentrations of creatinine >150 µmol/L or >200 µmol/L in chronic kidney disease, a requirement for dialysis), or placental abruption.

In the PARROT study, the frequency of any fullPIERS maternal outcomes was slightly lower in the trial arm where the Triage PlGF test results were revealed compared to the concealed arm (3.8% vs 5.4%; adjusted OR 0·32, 95% CI 0·11 to 0·96; p=0·043; Table 24).

Table 24 Severe maternal adverse outcomes: composite, test result revealed versus concealed

Study	Outcome	Group	Revealed	Concealed	Difference (as reported in study)
Triage PlGF test					
PARROT[9 15]	Severe maternal adverse	Total	3.8 (22/573)	5.4 (24/446)	1.0; [a] aOR 0·32, 95% CI 0·11 to 0·96; p=0·043

	outcomes (defined by the fullPIERS consensus), % (n/N)	PlGF <12 [b]	6.2 (8/130)	5.7 (6/106)	aOR 0.87 (0.09 to 8.02)
		PlGF 12-100 [b]	3.8 (8/212)	6.9 (12/173)	aOR: 0.15 (0.03 to 0.92)
		PlGF >100 [b]	2.6 (6/229)	3.8 (6/156)	a OR: 0.29 (0.02 to 4.34)
MAPPLE[16]	Adverse maternal outcomes, % (n/N)	Total	11.9 (47/396)	10.1 (29/287) (10.1)	Risk ratio (95% CI) 1.17 (0.76-1.82)
		PlGF <12 [b]	21.6 (25/116)	17.4 (12/69)	4.2 [a]
		PlGF 12-100 [b]	11.7 (16/137)	8.2 (8/97)	3.5 [a]
		PlGF >100 [b]	4.2 (6/143)	7.4 (9/121)	3.2 [a]
aOR: adjusted odds ratio a absolute % difference as calculated by reviewer b pg/ml					

The PARROT study also reported separate results for each individual component of the fullPIERS composite outcome of severe maternal adverse outcomes.[9 15] The majority of these outcomes were reported in less than 1% of women in both trial arms. Exceptions were the need for blood transfusion(s) which were reported in 9 (1.6%) and 14 (3.1%) of women, severe acute kidney injury reported in 7 (1.2%) and 6 (1.3%) of women and placental abruption reported in 4 (0.7%) and 5 (1.1%) of women in the revealed and concealed arms respectively. Major postpartum haemorrhage occurred less frequently in women for whom the PlGF test result was revealed (49; 8.6%) than in those for whom it was concealed (48;10.8%).

In the MAPPLE study, the composite outcome 'maternal adverse outcomes' was reported in 47 (11.9%) of women in the revealed Triage PlGF test results arm and 29 (10.1%) of women in the comparator (risk ratio:1.17; 95% CI:0.76–1.82).[16] Although not explicitly stated by the study authors, we have assumed that this composite includes the fullPIERS-defined outcomes since many of the individual fullPIERS outcomes were also reported separately in the MAPPLE study. The majority of these individual outcomes were reported in less than 1% of women in both trial arms with the following exceptions: hepatic dysfunction was reported at a higher frequency in the revealed arm (38; 9.6%) compared to the concealed arm (23; 8.0%) risk ratio, elevated creatinine (>150 µmol/L) was reported in 7 (1.8%) and 2 (0.7%) and placental abruption was reported in 1 (0.2%) and 4 (1.4%) of women in the revealed and concealed arms respectively.

No maternal deaths were reported in either trial arm in the PARROT or MAPPLE studies.

Elecsys sFlt-1/PlGF ratio test

Maternal outcomes were reported in the PreOS study in relation to different sFlt-1/PlGF ratios but not for the comparison of interest to this systematic review (revealed versus concealed) and are therefore not presented in this report.[79] The INSPIRE study reported the frequency of selected outcomes only and are summarised in **Table 25** with severe hypertension and hepatic dysfunction the most frequently reported of these outcomes.[32] No statistically significant differences were observed between trial arms for these outcomes, however these results should be interpreted with caution as the study was not powered to detect differences for these outcomes. Our economic model assumes that pulmonary oedema, placental abruption and eclampsia were the major maternal complications in this study and that they were independent.

Table 25 Maternal adverse outcomes: individual; test result revealed versus concealed

Study	Outcome	Revealed	Concealed	Difference[a]
Elecsys sFlt-1/PlGF ratio test				
INSPIRE[32]	Pulmonary oedema, % (n/N)	0.5 (1/186)	0.5 (1/184)	0; p=0.994
	Placental abruption, % (n/N)	1.1 (2/186)	2.7 (5/184)	1.6; p=0.246
	Severe hypertension (in women with a PE diagnosis only), % (n/N)	46.8 (22/47)	52.6 (20/38)	5.8; p=0.59
	Creatinine >97, % (n/N)	4.8 (9/186)	4.4 (8/184)	0.4; p=0.822
	Platelets <100, % (n/N)	2.2 (4/186)	3.8 (7/184)	1.6; p=0.349
	ALT double the normal, % (n/N)	17.7 (33/186)	12.5 (23/184)	5.2; p=0.159
	Eclampsia, % (n/N)	0 (0/186)	0 (0/184)	Not applicable
ALT: alanine transaminase [a] absolute % difference as calculated by reviewer				

4.1.7 Assessment of fetal outcomes

4.1.7.1 Fetal mortality

The PreOS and INSPIRE studies did not report data for this outcome for the Elecsys sFlt-1/PlGF ratio test.[32 79] Rates of intrauterine fetal death (including pre-viable and viable stillbirths) were similar for the revealed and concealed arms of Triage PlGF test from the PARROT study [9 15] but slightly higher stillbirth rates were observed in the concealed arm of the MAPPLE study, particularly in the subgroup of women with very low PlGF levels (<12 pg/ml) (Table 26).[16]

Table 26 Fetal mortality, test results revealed versus concealed

Study	Outcome	Group	Revealed	Concealed	Difference [a]
Triage PIGF test					
PARROT[15]	Intrauterine death, % (n/N)	Total	1.2 (7/573)	1.3 (6/446)	0.1
		PIGF <12 [b]	3.1 (4/130)	3.8 (4/106)	0.7
		PIGF 12-100 [b]	0.5 (1/212)	1.2 (2/173)	0.7
		PIGF >100 [b]	0 (0/229)	1.3 (2/156)	1.3
MAPPLE	Stillbirth, % (n/N[a])	Total	0.2 (1/433)	2.3 (7/299)	2.1
		PIGF <12 [b]	0.8 (1/124)	5.8 (4/69)	5.0
		PIGF 12-100 [b]	0 (0/158)	2.9 (3/105)	2.9
		PIGF >100 [b]	0 (0/151)	0 (0/125)	Not applicable
[a] number of infants [b] pg/ml [c]absolute % difference as calculated by reviewer					

4.1.8 Assessment of neonatal/perinatal outcomes

4.1.8.1 Gestational age at delivery

Triage PIGF test

In the PARROT study there was no difference in mean gestational age at delivery between revealed and concealed trial arms overall or within subgroups of women stratified by PlGF level. However, women with very low PlGF levels (<12 pg/ml) delivered earlier, on average, in both trial arms (mean <35 weeks gestation) (Table 27).[9 15] In the MAPPLE study, women delivered, on average, at a gestational age 1.4 weeks earlier in the revealed arm than women in the concealed arm (95% CI: 0.9 to 2.0 weeks earlier). Again, women with a very low PlGF levels (<12 pg/ml) delivered at an earlier gestational age in both trial arms (median <32 weeks) (Table 27).[16]

Table 27 Gestational age at delivery, test result revealed versus concealed

Study	Outcome	Group	Revealed	Concealed	Difference (as reported in study)
Triage PIGF test					
PARROT[9 15]	Gestational age (weeks) at delivery, mean (SD); N	Total	36.6 (3.0); N=573	36.8 (3.0); N=446	Mean difference: -0·52 (CI -0·63 to 0·73)
		PIGF <12 [a]	33.4 (3.13); n=130	34.4 (3.72); n=106	Mean difference (95% CI): -0.03 (-1.72 to 1.66)

		PlGF 12-100 [a]	36.71 (2.48); n=212	37.06 (2.04); n=173	Mean difference (95% CI): -0.40 (-1.25 to 0.45)
		PlGF >100 [a]	38.30 (1.75); n=229	38.23 (2.33); n=156	Mean difference (95% CI): 0.36 (-0.44 to 1.16)
MAPPLE[16]	Gestational age (weeks) at delivery, median, (quartiles); N [b]	Total	34.9 (32.0–37.1); N=433	36.7 (33.6–38.6); N=299	Median difference −1.4 (−0.9 to −2.0)
		PlGF <12 [a]	31.2 (29.0 – 33.4); n=124	31.9 (29.3 – 34.1); n=69	Not reported
		PlGF 12-100 [a]	35.0 (33.3 – 36.8); n=158	35.7 (34.1 – 37.9); n=105	Not reported
		PlGF >100 [a]	37.4 (36.1 – 38.4); n=151	38.4 (37 – 39.9); n=125	Not reported
Elecsys sFlt-1/PlGF ratio test					
INSPIRE[32]	Gestational age (weeks) at delivery, median (IQR); N	Total	38.4 (37.3-39.6); N=186	38.1 (37.1-39.3); N=184	0.3; [c] p=0.479
[a] pg/ml [b] number of infants [c] absolute % difference as calculated by reviewer					

Elecsys sFlt-1/PlGF ratio test

No statistically significant different in gestational age at delivery was observed between revealed and concealed arms in the INSPIRE study (Table 27).[32] Klein et al (PreOS study)[34] performed an analysis of intended clinical decisions made before and after sFlt-1/PlGF ratio test results were revealed to the clinical team in 188 women. In women for whom a decision was changed after the test result was revealed, the gestational age at delivery was generally lower for those women where the change was in favour of an intervention (to hospitalise, use of steroids to induce fetal lung maturity) compared to those women where the clinical decision was reverses (not to hospitalise or induce lung maturity).

4.1.8.2 Perinatal and neonatal mortality

Data were available for this outcome for the Triage PlGF test only. Perinatal deaths defined (or assumed by the EAG) to include deaths from 24 weeks of gestation, including those defined as stillbirths, until 7 completed days after birth, were reported at a lower frequency in the revealed arm (0.5%) compared to the concealed arm (3.0%) in the MAPPLE study[16] but at similar frequencies (1.0%) in both arm of the PARROT study (**Table 28**).[9 15]

Overall, less than 1% of women experienced early or late neonatal death in the MAPPLE and PARROT studies respectively (Table 29). Late neonatal deaths were reported at the highest frequency if women with very low PlGF levels in the concealed arm of the PARROT

study (1.0%). Data were not stratified by PlGF level for these outcomes in the MAPPLE study.

Neonatal and perinatal mortality was not reported in the INSPIRE or PreOS studies.[32 79]

Table 28 Perinatal mortality of fetus/neonate, test result revealed versus concealed

Study	Outcome	Group	Revealed	Concealed	Difference (as reported in study)
Triage PlGF test					
PARROT[15]	Perinatal deaths [b] % (n/N)	Total[e]	1.0 (6/573)	1.0 (4/446)	0; [f] aOR 1.00, 95% CI 0.61–1.63
MAPPLE[16a]	Perinatal deaths [c] % (n/N[d])	Total[e]	0.5 (2/433)	3.0 (9/299)	2.5; [f] Risk Ratio (95% CI) 0.16 (0.03–0.74)

aOR: adjusted odds ratio
[a] unadjusted indirect comparison [b] defined as deaths from 24 weeks of gestation, including those defined as stillbirths, until 7 completed days after birth
[c] definition not reported; assumed by EAG to be the same as for PARROT study
[d] N=number of infants
[e] data not stratified by PlGF level for these outcomes
[f] absolute % difference as calculated by reviewer

Table 29 Early and late neonatal mortality test result revealed versus concealed

Study	Outcome	Group	Revealed	Concealed	Difference (as reported in study)
Triage PlGF test					
PARROT[9 15]	Early neonatal death; n/N[b]	Total	0 0 (9/573)	0 (0/446)	Not applicable
	Late neonatal deaths (8–27 complete days of life); n/N	Total	0.5 (3/573)	0.2 (1/446)	0.3 [c]
		PlGF <12 [c]	0.8 (1/130)	1.0 (1/106)	Not reported
		PlGF 12-100 [c]	0.9 (2/212)	0.0 (0/173)	Not reported
		PlGF >100 [c]	0.0 (0/229)	0.0 (0/156)	Not reported
MAPPLE[16a]	Early neonatal death; n/N[b]	Total	0.2 (1/433)	0.7 (2/299)	0.5 [d]

[a] unadjusted indirect comparison [b] assumed to be within 7 days of birth; N=number of infants [c] pg/ml
[d] absolute % difference as calculated by reviewer

4.1.8.3 Perinatal and neonatal adverse composite outcomes

Data were available for this outcome for the Triage PLGF test only. The composite 'perinatal adverse outcomes' was reported in the PARROT study[9 15] and included the following:

- any grade of intraventricular haemorrhage, seizure, any grade of retinopathy of prematurity, respiratory distress syndrome, bronchopulmonary dysplasia or necrotising enterocolitis (stage 2 or 3), perinatal death and late neonatal death.

Frequencies of this composite outcome were not significantly different between revealed and concealed arms but were higher in the group of women with very low PlGF levels (<12 pg/ml) (Table 30). In contrast, the composite perinatal adverse outcome (assumed by EAG to include the same components as for PARROT) was reported at a higher frequency in the revealed arm of the MAPPLE study (30.4%) compared to the concealed arm (20.1%) with a similar difference between study arms (28.4% versus 18.9%) reported for the subgroup with singleton pregnancies only.[16] The composite including neonatal outcomes only was reported at a higher frequency in the revealed arm than in the concealed arm, both in total study population and in each PlGF level subgroup. This composite outcome was more commonly reported with lower PlGF levels and the difference between revealed and concealed arms was also greater with lower PlGF levels.

Table 30 Perinatal and neonatal adverse outcomes: composite, test result revealed versus concealed

Study	Outcome	Group	Revealed	Concealed	Difference (as reported in study)
Quidel Triage PIGF test					
PARROT[9 15]	Perinatal adverse outcomes,[a] % (n/N)	Total	15 (86[b]/573)	14 (63/446)	1.0; [d] aOR 1.45, 95% CI 0.73–2.90
		PIGF <12 [c]	37.7 (49/130)	25.5 (27/106)	aOR (95% CI): 1.95 (0.64 to 6.00)
		PlGF 12-100 [c]	11.8 (25/212)	13.3 (21/173)	aOR (95% CI): 1.62 (0.45 to 5.89)
		PlGF >100 [c]	5.2 (12/229)	5.8 (9/156)	aOR (95% CI): 3.84 (0.29 to 51.31)
MAPPLE[16a]	Perinatal adverse	Total	30.4 (131/433)	20.1 (60/299)	10.3; [d] Risk ratio (95% CI)

	outcomes,[b] % (n/N)				1.51 (1.15–1.98)
	Perinatal adverse outcomes,[b] % (n/N)	Singleton pregnancies only	28.4 (101/356)	18.9 (52/275)	9.5; [d] Unadjusted odds ratio 1.74 (1.20–2.51) aOR ratio 1.51 (0.93–2.43).
	Neonatal adverse outcomes, [e] % (n/N)	Total	30.4 (131/433)	17.1 (51/299)	13.3 [d] Risk ratio (95% CI) 1.78 (1.32–2.41)
		PlGF <12 [c]	60.7 (74/124)	39.1 (27/69)	21.6 [d]
		PlGF 12-100 [c]	23.4 (37/158)	13.3 (14/105)	10.1 [d]
		PlGF >100 [c]	13.3 (20/151)	7.2 (9/125)	6.1 [d]

aOR: adjusted odds ratio
[a] unadjusted indirect comparison [b] N=number of infants; perinatal death or neonatal adverse outcome [c] pg/ml
[d] absolute % difference as calculated by reviewer
[e] EAG assumes this excludes perinatal death but notes minor inconsistencies in numbers reported between text and tables within MAPPLE publication.

4.1.8.4 Neonatal adverse outcomes: individual components

The PARROT and MAPPLE studies report the frequencies of the individual components of the composite adverse neonatal outcome (**Table 31**).[9 15 16] Overall frequencies for these outcomes were comparable in the PARROT study but were generally higher for the revealed arm of the MAPPLE study compared to the concealed arm. Effect estimates were not reported. The PARROT study also reports the frequency of seizures in the total study population (<1%) but the EAG are not confident of the accuracy of the reported data since the figures reported for the total number of cases appear to be are lower than that of individual subgroups.

Table 31 Neonatal outcomes: individual components

Outcome	**Group (pg/ml)**	**PARROT[9 15]**		**MAPPLE[16]**	
		Revealed	**Concealed**	**Revealed**	**Concealed**
Triage PlGF test					
Respiratory distress syndrome,% (n/N)	Total	14 (78/573)	12 (54/446)	30.5 (28/433)	15.4 (46/299)
	PlGF <12	34.9 (44/130)	22.9 (24/106)	62.1 (72/124)	33.3 (23/69)
	PlGF 12-100	11.8 (25/212)	12.3 (21/173)	23.4 (36/158)	13.3 (14/105)
	PlGF >100	4.4 (10/229)	3.8 (8/156)	13.3 (20/151)	7.2 (9/125)
Bronchopulmonary dysplasia, % (n/N)	Total	0.9 (5/573)	0.7 (3/446)	6.7 (28/433)	2.0 (6/299)
	PlGF <12	3.2 (4/130)	1.8 (2/106)	16.4 (19/124)	8.7 (6/69)

	PIGF 12-100	0.5 (1/212)	0.6 (1/173)	2.6 (4/158)	0.0 (0/105)
	PIGF >100	0.0 (0/229)	0.0 (0/156)	3.3 (5/151)	0.0 (0/125)
Intraventricular haemorrhage % (n/N) [a]	Total	1.2 (7/573)	2.5 (11/446)	0.9 (4/433)	0.0 (0/299)
	PIGF <12	NR	NR	1.6 (2/124)	0.0 (0/69)
	PIGF 12-100	NR	NR	1.3 (2/158)	0.0 (0/105)
	PIGF >100	NR	NR	0.0 (0/15)	0.0 (0/25)
Necrotising enterocolitis [b]	Total	1 (7/573)	2 (7/446)	1.7 (7/433)	1.3 (4/299)
	PIGF <12	3.2 (4/130)	4.8 (5/106)	3.4 (4/124))	4.3 (3/69)
	PIGF 12-100	1.4 (3/212)	0.6 (1/173)	1.3 (2/158)	0.0 (0/105)
	PIGF >100	0.0 (0/229)	0.6 (1/156)	0.7 (1/151)	0.8 (1/125)
Retinopathy of prematurity	Total	2 (9/573) [c]	2 (9/446) [c]	2.6 (11/433)	2.0 (6/299)
	PIGF <12	0.0 (0/130)	0.0 (0/106)	6.0 (7/124)	7.2 (5/69)
	PIGF 12-100	0.0 (0/212)	0.6 (1/173)	1.9 (3/158	1.0 (1/105)
	PIGF >100	0.0 (0/229)	0.6 (1/156)	0.7 (1/151)	0.0 (0/125)

NR: not reported
[a] Grade 3 or 4 in MAPPLE [b] stage 2 or 3 in PARROT
[c] EAG notes subgroup counts do not sum to reported total

4.1.9 Assessment of delivery and related perinatal outcomes

4.1.9.1 Corticosteroid use

Use of antenatal steroids to induce fetal lung maturity was reported at a numerically higher frequency in the revealed arm compared to the concealed arm in both the PARROT and MAPPLE studies with the greatest differences between study arms observed in women with very low PlGF levels (Table 32).[9 15 16]

Table 32 Antenatal corticosteroids, test result revealed versus concealed

Study	Outcome	Group	Revealed	Concealed	Difference (as reported in study)
Triage PIGF test					
PARROT[9 15]	Use of antenatal corticosteroids for fetal lung maturity, % (n/N)	Total	34.9 (200/573)	29.6 (132/446)	5.3; [c] OR 1.26 (CI 0.75 to 2.11)
		PIGF <12 [b]	75.4 (98/130)	50.9 (54/106)	24.5 [c]
		PIGF 12-100 [b]	31.6 (67/212)	29.5 (51/173)	2.1 [c]
		PIGF >100 [b]	15.3 (35/229)	14.1 (22/156)	1.2 [c]
MAPPLE[16a]	Use of antenatal corticosteroids for fetal lung	Total	59.9 (236/397)	30.7 (88/287)	29.2; [b] Risk ratio (95% CI) 1.95 (1.61–2.37)
		PIGF <12 [b]	89.6 (103/116)	59.4 (41/69)	30.2 [c]

	maturity, % (n/N)	PlGF 12-100 [b]	59.6 (81/137)	35.1 (34/97)	24.5 [c]
		PlGF >100 [b]	36.4 (52/143)	10.7 (13/121)	25.7 [c]
[a] unadjusted indirect comparison [b] pg/ml [c] absolute % difference as calculated by reviewer					

No data on use of steroids were reported in the INSPIRE study.[32] In the PreOS study, the majority of intended clinical decisions were unchanged after the sFlt-1/PlGF ratio test result was revealed however, 6.0% changed in favour of inducing fetal lung maturity compared to 1.7% changing in favour of not induction lung maturity.[79]

4.1.9.2 Magnesium sulphate

Use of magnesium sulphate was reported in the PARROT study only[9 15] where this was more frequently reported with lower PlGF levels, however, the proportions in the revealed and concealed arms were similar across all PlGF subgroups (Table 33).

Table 33 Use of magnesium sulphate, test result revealed versus concealed

Study	Outcome	Group	Revealed	Concealed	Difference (as reported in study)
Triage PlGF test					
PARROT[9 15]	Use of magnesium sulphate, % (n/N)	Total	NR	NR	NR
		PlGF <12 [a]	36.2 (47/130)	36.9 (39/106) (36.9%)	0.7 [b]
		PlGF 12-100 [a]	9.0 (19/212)	11.1 (19/173)	2.1 [b]
		PlGF >100 [a]	2.6 (6/229)	3.2 (5/156)	NR
NR: not reported [a] pg/ml [b] measure of effect undefined in publication; absolute difference calculated by reviewer					

4.1.9.3 Onset of labour

Onset of labour was reported in the PARROT study only.[9 15] A higher proportion of women had a pre-labour caesarean section in the revealed arm (40%) compared to the concealed arm (35%) (Table 34).

Table 34 Onset of labour, test result revealed versus concealed

Study	Outcome	Group	Revealed	Concealed	Difference [a]
Triage PlGF test					

PARROT[9] [15]	Spontaneous	Total	14 (79/573)	17 (78/446)	3
	Induced	Total	46 (263/573)	47 (210/446)	1
	Pre-labour caesarean section	Total	40 (230/573)	35 (158/446)	5
[a] absolute % difference calculated by reviewer					

4.1.9.4 Mode of delivery

In the PARROT study, higher numerical proportions of women delivered by emergency caesarean section in the revealed arm compared to the concealed arm overall (26% versus 21%) and across all subgroup of PlGF level with the highest rates reported in women with very low PlGF levels (Table 35).[9] [15]

Table 35 Mode of delivery, test result revealed versus concealed

Study	Outcome	Group	Revealed	Concealed	Difference (as reported in study)
Triage PIGF test					
PARROT[9] [15]	Spontaneous vaginal cephalic, % (n/N)	Total	37 (210/573)	41 (182/446)	aOR 1.05, 95% CI 0.59–1.86
		PlGF <12 [a]	20.8 (27/130)	23.6 (25/106)	2.8 [b]
		PlGF 12-100 [a]	36.8 (78/212)	43.9 (76/173)	7.1 [b]
		PlGF >100 [a]	45.9 (105/229)	50.0 (78/156)	4.1 [b]
	Assisted vaginal (forceps or vacuum, % (n/N)	Total	7 (42/573)	9 (38/446)	2 [b]
		PlGF <12 [a]	3.8 (5/130)	3.9 (4/106)	0.1 [b]
		PlGF 12-100 [a]	8.5 (18/212)	8.7 (15/173)	0.2 [b]
		PlGF >100 [a]	8.2 (19/229)	12.8 (20/156)	4.6 [b]
	In-labour caesarean section, % (n/N)	Total	26 (150/573)	21 (94/446)	aOR 0.78, 95% CI 0.48–1.25
		PlGF <12 [a]	35.4 (46/130)	37.9 (39/106)	2.5 [b]
		PlGF 12-100 [a]	28.3 (60/212)	19.7 (34/173)	8.6 [b]
		PlGF >100 [a]	18.8 (43/229)	12.2 (19/156)	6.6 [b]
aOR: adjusted odds ratio [a] pg/ml [b] absolute % difference calculated by reviewer					

The MAPPLE study also reported a higher frequency of caesarean section (other modes of delivery not reported) in the Triage PlGF test result revealed arm than in the concealed arm (73.8% versus 64.5%; risk ratio (95% CI)1.14 (1.03–1.26).[16]

No data on delivery mode were reported in the INSPIRE or PreOS studies.[32] [79]

4.1.9.5 Preterm and early preterm delivery

The rates of preterm delivery (<37 weeks gestation) were similar between trial arms in the PARROT study but the MAPPLE study reported higher proportions of women delivering before 37- or 34 weeks gestation in the revealed arm compared to the concealed arm (Table 36).[9 15 16] No date for this outcome was available from the INSPIRE or PreOS studies.[32 79]

Table 36 Preterm delivery and early preterm delivery, test result revealed versus concealed

Study	Outcome	Revealed	Concealed	Difference
Triage PlGF test				
PARROT[9 15]	Preterm delivery <37 weeks, % (n/N)	41 (234/573)	37 (167/446)	4.0; [b] Paper states no differences observed
MAPPLE[16] [a]	Preterm delivery < 37 weeks, % (n/N) [c]	70.2 (304/433)	52.8 (158/299)	17.4 [b]
	Early preterm delivery < 34 weeks, % (n/N) [c]	38.6 (167/433)	27.8 (83/299)	10. 8[b]
[a] unadjusted indirect comparison [b] absolute difference as calculated by reviewer [c] paper reports frequencies by PlGF level subgroup only; frequencies summed by reviewer for whole study population				

4.1.10 Admission to hospital or specialist care unit

4.1.10.1 Maternal admissions

No statistically significant difference in maternal admissions was observed at any time point measured in the INSPIRE study (Table 37) although the proportions of women admitted within 24 hours or 7 days due to suspected pre-eclampsia were numerically higher in the revealed arm compared to concealed arm.[32] In the PreOS study, the majority of intended clinical decisions were unchanged after the sFlt-1/PlGF ratio test result was revealed, however, 5.9% changed in favour of hospitalisation compared to 11.0% changing in favour of not hospitalising the mother.[34]

No data on maternal admissions were reported in the PARROT or MAPPLE studies.[9 15 16] The INSPIRE study[32] did not report on the proportion of women admitted to different levels of care, e.g. intensive care units or other critical care units.

Table 37 Maternal admissions at different times, test result revealed versus concealed

Study	Outcome	Revealed	Concealed	Difference	
				Risk ratio (95% CI)	Risk difference (95% CI)
Elecsys sFlt-1/PlGF ratio test:					
INSPIRE[32]	Any maternal admission, % (n/N)	38.7 (72/186)	31.5 (58/184)	1.22 (0.93 to 1.62)	0.07 (-0.02 to 0.17)
	Admission for suspected PE within 24 hours, % (n/N)	32.3 (60/186)	26.1 (48/184)	1.24 (0.89 to 1.70)	0.06 (−0.03 to 0.15)
	Admission for suspected PE within 1 week, % (n/N)	37.6 (70/186)	35 (65/184)	1.06 (0.1 to 1.39)	0.02 (−0.07 to 0.12)
	Admission for suspected PE until delivery, % (n/N)	67 (126/186)	72.8 (134/184)	0.93 (0.82 to 1.06)	−0.05 (−0.14 to 0.04)

4.1.10.2 Neonatal admission

No difference in rates of admission to a neonatal unit were observed between revealed and concealed arms in the PARROT and MAPPLE studies when the effect of the Triage PlGF test was assessed (**Table 38**).[9 15 16] Admission rates were higher for babies born to mothers with lower PlGF levels. The INSPIRE study also reported no difference in admission rates to the special care baby unit (SCBU) between revealed and concealed arms when the Elecsys sFlt-1/PlGF ratio test was assessed (Table 38).[32]

Table 38 Admission to neonatal unit, test result revealed versus concealed

Study	Outcome	Group	Revealed	Concealed	Difference (as reported in study)
Triage PlGF test					
PARROT[9 15]	Neonatal unit admission, % (n/N)	Total	34.0 (195/573)	32.7 (146/446)	Paper states no differences observed
		PlGF <12 [a]	71.5 (93/130)	58.5 (62/106)	aOR (95% CI): 2.37 (0.63–7.92)

		PlGF 12-100 [a]	34.4 (73/212)	31.2 (54/173)	aOR (95% CI): 2.37 (0.76–7.37)
		PlGF >100 [a]	12.7 (29/229)	17.3 (27/156)	Not reported
MAPPLE[16]	Neonatal unit admission, % (n/N) [b]	Total	45.5 (190/433)	39.8 (117/299)	Risk ratio (95% CI) 1.14 (0.95–1.37)
		PlGF <12 [a]	81.7 (94/124)	82.8 (53/69)	Not reported
		PlGF 12-100 [a]	46.4 (71/158)	43.8 (46/105)	Not reported
		PlGF >100 [a]	16.7 (25/151)	14.4 (18/125)	Not reported
Elecsys sFlt-1/PlGF ratio test					
INSPIRE[32]	SCBU admission, % (n/N)	All women	18.3 (34/186)	15.2 (28/184)	*p*=0.430
aOR: adjusted odds ratio SCBU: special care baby unit [a] pg/ml [b] number of infants					

4.1.11 Length of stay in hospital or unit

4.1.11.1 Length of stay (maternal)

There was no difference in the mean number of inpatients nights in women admitted to hospital between the revealed and concealed arms in the PARROT study (Table 39).[9 15]

Table 39 Inpatient nights, test result revealed versus concealed, by test cut-off

Study	Outcome	Revealed	Concealed	Difference
Triage PlGF test				
PARROT[15]	Number of nights in inpatient care, mean (SE); N	7.43 (0.36); N=573	7.26 (0.38); N=446	-0.06 (-0.22 to 0.09) [a]
[a] effect measure not specified				

4.1.11.2 Length of stay (neonatal)

There was no difference in the mean length of stay for babies admitted to the neonatal unit or SCBU between the revealed and concealed arms in the PARROT study, however, the length of stay in the neonatal intensive care or high dependency unit was 10.6 days shorter in the revealed arm than for the concealed arm (Table 40).[15]

Table 40 Nights in neonatal unit, test result revealed versus concealed

Study	Outcome	Revealed	Concealed	Difference
Triage PlGF test				
PARROT[9 15]	Number of nights in neonatal unit[a] mean (SE); N	22.1 (25.9); N=573	24.6 (35.2); N=446	Not reported
	Number of nights in SCBU, mean (SE); N	14.7 (14.4); N=573	13.09 (12.6); N=446	Paper states no difference between groups
	Number of nights in NICU/HDU, mean (SE); N	15.2 (1.7); N=573	24.2 (3.8); N=446	Mean difference -10.6 (95% CI -20.81 to -0.47)
SCBU: special care baby unit; NICU: Neonatal intensive care unit: HDU: high dependency unit [a] level of neonatal care not specified				

4.1.12 Assessment of test on clinical decision making and monitoring intensity

Klein et al[34] (PreOS study) compared intended clinical decisions made before and after sFlt-1/PlGF ratio test results were revealed to clinicians in 118 pregnant women ≥24 weeks gestation with suspected pre-eclampsia. The majority of intended clinical decisions remained unchanged after the test was revealed, however, the proportion of women intended for hospitalisation reduced by 4.9% while induction of fetal lung maturity increased by 4.3% (Table 41). Decisions to change monitoring within one week reduced by 15% although it is not explicit as to whether this includes both increases and decreases in monitoring intensity. Additional intended decisions relating to drug therapy, ultrasound scans and other monitoring tests in mothers and neonates were also reported in the paper (for brevity, not presented in this report). For the majority of these additional decisions, there was a reduction in the proportion of women intended for the monitoring test in question after the result was revealed to clinicians.

Table 41 Changes in intended clinical decisions before and after test results revealed

Intended Clinical Decision	Before (test concealed)	After (test revealed)
Elecsys sFlt-1/PlGF ratio test		
Hospitalisation, % (n/N)	34 (40/118)	28.8 (34/118)
Induction of delivery, % (n/N)	3.4 (4/116)	5.2 (6/116)
Induction of fetal lung maturity, % (n/N)	9.4 (11/117)	13.7 (16/117)

Change in monitoring within one week, % (n/N)	65.8 (75/114)	52.6 (60/114)

4.1.13 Assessment of health-related quality of life (HRQoL) outcomes

No HRQoL outcomes were reported in the published studies. However, we note that the ongoing PARROT Ireland trial is assessing HRQoL – see Section 4.3 and Appendix 6).

4.2 Subgroups of interest

Subgroups of interest to this appraisal, as specified to the NICE scope, include pregnant women with comorbidities such as chronic hypertension, severe hypertension, pre-existing or gestational diabetes, renal disease, and/or autoimmune disease; gestational stage (between 20 weeks and 34 weeks plus 6 days of pregnancy; between 35 weeks and 36 weeks and 6 days of pregnancy), and multiple pregnancy.

Subgroup analysis data reported by the studies included in this systematic review is limited to the following:

- Test accuracy data is reported by gestational age group in the ROPE, PELICAN and McCarthy (COMPARE) [22 30 45] standalone studies for prediction of delivery-related outcomes (see Appendix 5).
- Test accuracy data is reported for subgroups of participants with chronic kidney disease and/or hypertension in the PEACHES (PELICAN cohort) standalone study[24] for the prediction of delivery within 2 weeks due to pre-eclampsia or superimposed pre-eclampsia (see Appendix 5).
- Time to delivery outcomes are stratified by gestational age (and PlGF level) in the add-on PARROT study[9 15] (see Section 4.1.5.2)
- All results for the Elecsys sFlt-1/PlGF ratio in the add-on study Binder et al[35] are for twin pregnancies only (See Section 4.1.2).

4.3 Ongoing studies

The EAG identified ongoing studies from several sources, including trial registries, conference abstracts, and company submissions. From the information available, it is likely that seven studies would meet the eligibility criteria for this systematic review, of which at least five are RCTs. Four studies will provide further data on the Elecsys test; one study, PARROT-Ireland which has already completed, will provide data on the Triage test; one

company study will provide data on the DELFIA Xpress test; and one study, Fernández Oliva, does not give details of the index test used.

The company studies for the BRAHMS Kryptor test which reported AIC data to the EAG for the purpose of this review (PRAECIS and REPORTS) were both excluded on population, and no further ongoing studies for this test were identified. One study (PARROT-2) will provide data on the use of repeat testing; two studies (DELFIA Xpress and Fernández Oliva) will provide diagnostic accuracy data; and five studies (PARROT-Ireland, PARROT-2, PreRisk, PRECOG, EuroPE) will assess the impact of testing on maternal and fetal/neonatal outcomes. Further details of the ongoing studies are listed in Appendix 6.

5 ECONOMIC ANALYSIS

This chapter assesses the evidence on the cost-effectiveness of the PlGF tests when used in addition to standard clinical assessment, based on a systematic review of economic analyses and an independent economic model. Parameters for the model were identified from the systematic review of test accuracy and clinical effectiveness (in particular the PARROT[15 9] and INSPIRE[32] RCTs for the base case), the systematic review of economic studies (section 5.1.1), a review of utility estimates (section 5.1.5) and targeted searches for data on relevant costs and resource use.

5.1 Systematic review of cost-effectiveness evidence

5.1.1 Methods for review of economic studies

The methods detailed in Chapter 3 were used to systematically search for the economic evidence. The relevant population, interventions and comparators were the same as for the systematic review of test accuracy and clinical effectiveness (as described in Section 3.2), but differed in terms of relevant the study design and outcomes.

Studies were included if they were full economic evaluations, assessing both costs and consequences, or cost studies for the specified index tests. Outcomes included are those consistent with full economic evaluations and cost studies, including measures of resource use (budget impact, cost per patient or cost per case of pre-eclampsia correctly managed) and health outcomes (life-years or QALYs gained). Each step of the review was completed by two health economists and any disagreements were resolved by discussion.

5.1.2 Methods for data extraction and critical appraisal of economic studies

Data extraction was performed using a pre-designed standard data extraction form that was used in the previous DAR. [7] The included economic evaluations were critically appraised using the same checklist that was used in the previous DAR. [7] This was based on criteria in checklists proposed by Drummond and colleagues,[80] Philips and colleagues[81] and the NICE reference case.[82]

5.1.3 Results of the review of economic studies

Starting with an original 1953 potentially relevant references identified in the original and updated searches, we applied a filter for the word 'cost' anywhere in the study report to reduce the number of references to 119. Of the 119 references, twenty-six[7 10 83-106] appeared to provide information about economic studies based on title and abstract screening, and were retrieved for full-text screening (Figure 1). After inspection, 15 references were excluded: 13 of which are conference abstracts,[83-87 89-93 95-97] one is a duplicate of the previous NICE appraisal[88] and the remaining one is a protocol for a study in the clinicaltrials.gov.[94] The eleven published economic studies included in the systematic review[7 98-106 10] are described in further detail in Appendix 7 and critically appraised in Appendix 12. The excluded references and the reason for exclusion are shown in Appendix 3.

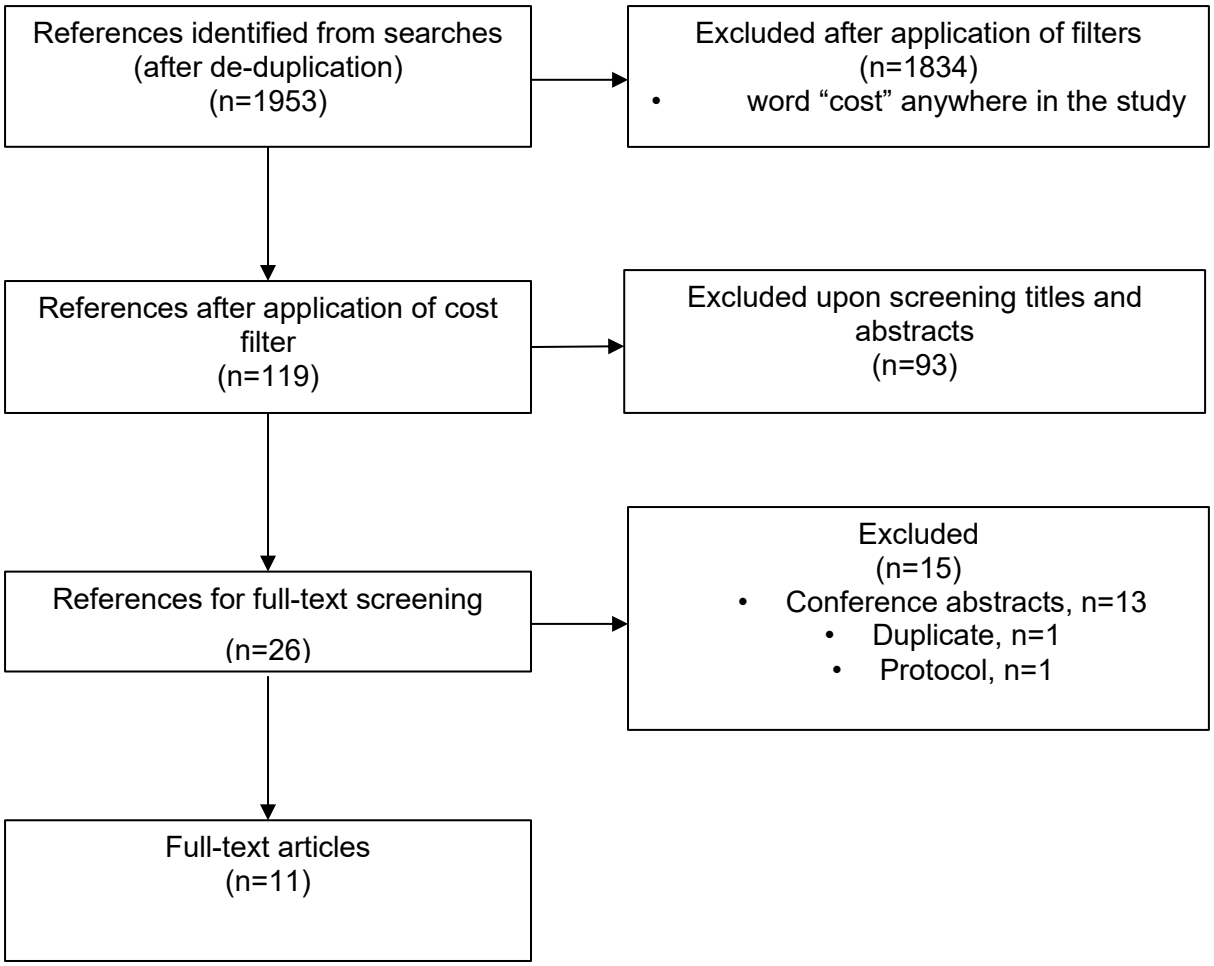

Figure 3 Flow chart for the identification of economic studies

We identified eleven economic evaluations of diagnostic tests that are within the scope of this assessment, i.e. diagnostic tests for pre-eclampsia administered to women between 20 weeks and 36 weeks plus 6 days of gestation. Table 42 provides an overview of the characteristics of the included economic studies and a brief summary of their base-case results. Six of the included studies are evaluations of the Elecsys sFlt-1/PlGF ratio test,[100 101 103 105 106 10] two are evaluations of the Triage PlGF test,[98 99] two assess more than one PlGF test (Elecsys Sflt-1/PlGF ratio test, Triage PlGF test and BRAHMS Kryptor sFlt-1/PlGF ratio test)[7 104] and the other did not report which PlGF test(s) were evaluated.[102] We categorised five studies as cost-effectiveness analyses,[7 99 105 106 10] two as cost analyses,[98 100] one as a budget impact analysis,[101] one as cost-effectiveness and budget impact analysis,[104] one as a cost and budget impact analysis[103] and one as a cost analysis.[102] One study did not use a model;[102] nine used short-term decision trees to model the cost of managing suspected pre-eclampsia according to using a specific diagnostic test combined with usual care compared with usual care,[7 98 100 101 103-106 10] and one study used a decision tree with a Monte Carlo simulation.[99] Only one model measured the effects in QALYs,[7] two considered maternal and

neonatal outcomes,[7 99] and the other nine concentrated on potential savings due to more appropriate management.[7 98 100-106 10]

The studies suggest that including diagnostic tests alongside usual care has the potential to reduce maternal adverse events and reduce the number of women who receive inappropriate treatment (mainly hospitalisation) due to false-positive diagnoses. Six studies[98-100 102 103 106] reported a cost saving within a range of £94 to £2,896 per woman tested due to the introduction of a first PlGF test in addition to usual care versus usual care alone. Five studies[100 101 103 105 106] reported a cost saving between £26 and £607 for women who have received a retest. The study by Myrhaug and colleagues[104] reported £3,710 as the cost per additional correctly identified case of pre-eclampsia.

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Table 42 Characteristics of included economic studies

Study	Duckworth et al. [98]	Duhig et al. [99]	Figueira et al. [100]	Frampton et al. [7]	Frusca et al. [101]
Publication Year	2016	2019	2018	2016	2017
Country	England	UK	Brazil	UK	Italy
Study type	Cost analysis	CE analysis	Cost analysis	CE analysis	Budget impact analysis
Population	Women aged ≥16 years with suspected pre-eclampsia between 20+0 and 35 weeks of gestation with a singleton or twin pregnancy	Women with suspected pre-eclampsia between 20 and 36+6 weeks of gestation with a singleton pregnancy[a]	Women with suspected pre-eclampsia between 24 and 36+6 weeks of gestation	Women with suspected pre-eclampsia between 20 and 36+6 weeks of gestation	Women with suspected pre-eclampsia between 24 and 36+6 weeks of gestation
Intervention(s)	Intervention: Triage PlGF test[b] + management algorithm Comparator: usual care	Intervention: Triage PlGF test + management algorithm Comparator: usual care	Intervention: Elecsys sFlt-1/PlGF ratio test[b] + usual care Comparator: usual care	Interventions: PlGF tests (Triage PlGF test, Elecsys sFlt-1/PlGF ratio test) + usual care Comparator: usual care	Intervention: Elecsys sFlt-1/PlGF ratio test[b] + usual care Comparator: usual care
Source of clinical evidence	PELICAN study	PARROT study	PROGNOSIS study	Systematic review	PROGNOSIS study and clinical experts
Diagnostic cut-offs	<12 pg/mL, 12-100 pg/mL, >100 pg/mL	<12 pg/mL, 12-100 pg/mL, >100 pg/mL	<38, 38-85, >85	Triage PlGF test: <12 pg/mL, 12-100 pg/mL, >100 pg/mL Elecsys sFlt-1/PlGF ratio test: <38, 38-85, >85	<38, 38-85, >85
Repeat test	No	No	Yes, included in the base case (2 weeks after a	No	Yes, included in the base case (2 weeks after a

Study	Duckworth et al. [98]	Duhig et al. [99]	Figueira et al. [100]	Frampton et al. [7]	Frusca et al. [101]
			negative initial test (ratio < 38) if the woman had not been hospitalized and had presented continuing symptoms of pre-eclampsia)		negative initial test (ratio < 38) if the woman had not developed pre-eclampsia, had not been hospitalized and had presented at least one clinical sign of pre-eclampsia)
Model type	Decision tree	Decision tree with Monte Carlo simulation	Decision tree	Decision tree	Decision tree
Cost year	2013/2014	2016/17, except for the cost of test (2017/18)	2016	2014	2015[f]
Intervention effect	6% of women presented with suspected pre-eclampsia prior to 35 weeks' gestation, of which 30% had a final diagnosis of pre-eclampsia. One woman had a false negative test. Nineteen women had a false positive test	PIGF testing alongside clinical management algorithm resulted in an average of 15 fewer maternal adverse events per 1000 women tested compared with current standard care	The introduction of the test reduced the number of women hospitalised by 56%, from 36% to 16%.	For women presenting before 35 weeks, total QALYs for each strategy are similar, with no more than 0.00076 QALYs separating the most clinically effective diagnostic strategy and the least clinically effective diagnostic strategy. For women presenting between 35 and 37 weeks, there is no difference between the strategies in terms of QALYs.	The test can reduce 69.5% of unnecessary woman's hospitalisations before pre-eclampsia onset
Base case results[d]	Cost saving of £635 per woman tested[c]	Cost saving of £149 per woman tested in 55.5% of iterations of the model.	Base case: Cost saving in M'Boi Mirim of £26 per woman and £90 in Einstein	For women presenting before 35 weeks, cost saving of £2896 (Triage PIGF test versus current standard	Over five-years, net cost saving per-woman is equal to £607

Study	Duckworth et al. [98]	Duhig et al. [99]	Figueira et al. [100]	Frampton et al. [7]	Frusca et al. [101]
			No retest scenario: Cost saving in M'Boi Mirim of £94 per woman and £183 in Einstein	care), £2489 (Elecsys sFlt-1/PlGF ratio test versus current standard care) and £408 (Triage PlGF test versus Elecsys sFlt-1/PlGF ratio test) For women presenting between 35 and 37 weeks, cost saving of £365 (Triage PlGF test versus current standard care), £174 (Elecsys sFlt-1/PlGF ratio test versus current standard care) and £191 (Triage PlGF test versus Elecsys sFlt-1/PlGF ratio test)	
Funding source	Tommy's Charity and Alere (San Diego, CA)	National Institute for Health Research, Research for Patient Benefit Programme and National Institute for Health Research Professorship	Roche Diagnostics	Health Technology Assessment programme of the National Institute for Health Research.	Roche Diagnostics

[a] Triage PlGF test is used in women with suspected pre-eclampsia after 20 weeks and prior to 35 weeks of gestation.[22]

[b] Plasma samples were tested by trained laboratory staff at the site where the sample was taken.

[c] There is an inconsistency within the publication: a cost saving of £635 per woman tested is reported in the Results and of £582 is reported in the Abstract.

[d] Figueira and colleagues: converted from Brazilian Real at an exchange rate of 1 Brazilian Real = £0.14, December 2020; Frusca and colleagues, Giardini and colleagues, Hodel and colleagues; Schlembach and colleagues: converted from Euro at an exchange rate of 1 Euro = £0.91, December 2020; Myrhaug and colleagues: converted from Norwegian Krone at an exchange rate of 1 Norwergian Krone = £0.086, December 2020.

[e] Clarification provided after contact from EAG.

Study	Duckworth et al. [98]	Duhig et al. [99]	Figueira et al. [100]	Frampton et al. [7]	Frusca et al. [101]
[g] There is an inconsistency within the publication, chapter 2.7. Sensitivity Analyses reports that this rate was applied to women in the low outpatient setting and Figure 3 reports that this rate was applied to women in both low and intermediate settings. CE, cost-effectiveness; PlGF, placental growth factor; QALYs, quality-adjusted life-years; sFlt-1, soluble FMS-like tyrosine kinase-1; UK, United Kingdom					

Table 43 Characteristics of included economic studies (continued)

Study	Giardini et al.[102]	Hodel et al.[103]	Myrhaug et al.[104]	Ohkuchi and colleagues[10]	Schlembach et al.[105]	Vatish et al.[106]
Publication Year	2019	2019	2020	2021	2018	2016
Country	Italy	Switzerland	Norway	Japan	Germany	UK
Study type	Retrospective study and cost analysis	Cost and budget impact analysis	CE and budget impact analysis	CE analysis	CE analysis	CE analysis
Population	Women with a singleton pregnancy who accessed the emergency room for blood pressure increase after the 20th week of gestation.	Women with suspected pre-eclampsia, defined as the onset of proteinuria and hypertension after 20 weeks of gestation	Women with suspected pre-eclampsia between 20 and 36+6 weeks of gestation	Women with suspected pre-eclampsia from 18 weeks + 0 days gestation to 36 weeks + 6 days gestation in the Japanese cohort of PROGNOSIS	Women with suspected pre-eclampsia between 24 and 36+6 weeks of gestation	Women with suspected pre-eclampsia between 24 and 36+6 weeks of gestation
Intervention(s)	Intervention: PlGF tests (not reported which ones) + usual care Comparator: usual care	Intervention: Elecsys sFlt-1/PlGF ratio test[a]+ usual care Comparator: usual care	Intervention: PlGF tests (Elecsys sFlt-1/PlGF ratio test or Triage PlGF test or BRAHMS Kryptor sFlt-1/PlGF ratio test) + usual care	Intervention: Elecsys sFlt-1/PlGF ratio test[a] + usual care Comparator: usual care	Intervention: Elecsys sFlt-1/PlGF ratio test[a] + usual care Comparator: usual care	Intervention: Elecsys sFlt-1/PlGF ratio test[a] + usual care Comparator: usual care

Study	Giardini et al.[102]	Hodel et al.[103]	Myrhaug et al.[104]	Ohkuchi and colleagues[10]	Schlembach et al.[105]	Vatish et al.[106]
			Comparator: usual care			
Source of clinical evidence	Current study	PROGNOSIS study	INSPIRE study	PROGNOSIS study	PROGNOSIS study	PROGNOSIS study
Diagnostic cut-offs	Not reported	<38, 38-85, >85	NA	≤38 to rule out preeclampsia, > 38 high risk of pre-eclampsia	≤38, >38 and <85 (for gestational weeks 20+0–33+6) OR > 38 and <110 (gestational week 34 onwards), ≥85 (gestational weeks 20+0–33+6) OR ≥110 (gestational week 34 onwards)	<38, 38-85, >85
Repeat test	No	Yes, but only as scenario analyses 1. Inclusion of a 6.5% retest rate for women in low follow up settings[d] 2. Inclusion of a100% retest rate for all women	No	Yes, included as a scenario.	Yes, included in the base case (2 weeks after a negative initial test (ratio < 38) if the woman had not developed pre-eclampsia and had not been hospitalized)	Yes, included in the base case (2 weeks after a negative initial test (ratio < 38) if the woman had presented continuing symptoms of pre-eclampsia)

Study	Giardini et al.[102]	Hodel et al.[103]	Myrhaug et al.[104]	Ohkuchi and colleagues[10]	Schlembach et al.[105]	Vatish et al.[106]
		3. Inclusion of 4 times retesting for all women in intermediate follow up setting				
Model type	No model	Decision tree	Decision tree	Decision tree	Decision tree	Decision tree
Cost year	2016[c]	Cost year not clear; cost sources: 2016, 2018	2020	2020	2017	2014
Intervention effect	The test would have avoided 18% of all hospitalizations, 35% of hospitalizations for blood pressure increase, 43% of outpatient referrals, and 13% of emergency room accesses.	Hospitalization rates were reduced in the test vs. the no-test scenario, with 822 (14%) vs. 1160 (19%) women hospitalized, respectively	For an initial cohort of 6000 women, 777 receiving PlGF test + current standard care vs. 489 receiving care standard care alone were correctly early identified cases of pre-eclampsia.	Introduction of the sFlt-1/PlGF ratio test using a cut-off value of 38 resulted in a reduced hospitalization rate compared with the rate in the no-test scenario (14.4% versus 8.7%).	Intervention: 40.8% of hospitalised women developed pre-eclampsia Comparator: 29.6% of hospitalised women developed pre-eclampsia	20% fewer women being hospitalised compared with usual care
Base case results[b]	Cost saving of £363 per woman	Base case: Cost saving of £313 per woman Retest scenarios: 1. cost saving of £266 per woman 2. cost saving of £186 per woman	Cost per additional correctly identified case of pre-eclampsia of £3,710	Base case: Cost saving of £108 per woman Retest scenario: Cost saving of £49.	Cost saving of £327 per woman	Base case: Cost saving of £344 per woman No retest scenario: Cost saving of £382 per woman

Study	Giardini et al.[102]	Hodel et al.[103]	Myrhaug et al.[104]	Ohkuchi and colleagues[10]	Schlembach et al.[105]	Vatish et al.[106]
		3. cost saving of £97 per woman				
Funding source	No funding[c]	Roche Diagnostics	Norwegian Institute of Public Health	Roche Diagnostics	Roche Diagnostics	Roche Diagnostics

[a] Plasma samples were tested by trained laboratory staff at the site where the sample was taken.

[b] Figueira and colleagues: converted from Brazilian Real at an exchange rate of 1 Brazilian Real = £0.14, December 2020; Frusca and colleagues, Giardini and colleagues, Hodel and colleagues; Schlembach and colleagues: converted from Euro at an exchange rate of 1 Euro = £0.91, December 2020; Myrhaug and colleagues: converted from Norwegian Krone at an exchange rate of 1 Norwergian Krone = £0.086, December 2020; Ohkuchi and colleagues converted from Japanese Yen at an exchange rate of 1 Japanese Yen = £0.0065, May 2021.

[c] Clarification provided after contact from EAG.

[d] There is an inconsistency within the publication, chapter 2.7. Sensitivity Analyses reports that this rate was applied to women in the low outpatient setting and Figure 3 reports that this rate was applied to women in both low and intermediate settings.

CE, cost-effectiveness; PlGF, placental growth factor; QALYs, quality-adjusted life-years; sFlt-1, soluble FMS-like tyrosine kinase-1; UK, United Kingdom

5.1.4 Assessment of the quality and relevance of the economic studies

A summary critical appraisal checklist for quality assessment and relevance of the included studies is shown in Appendix 12. The studies used a similar comparator (usual care without PlGF-based testing) relevant to the current decision problem. All the studies also evaluated a patient population relevant to the current decision problem, except for the studies by Giardini and colleagues[102] and Hodel and colleagues[103] where there are some uncertainties about the patient population as explained above. It's uncertain how relevant the studies conducted for different healthcare systems and settings[10 100-105] are for the UK NHS. One study did not use a model.[94] The remaining ten studies used appropriate models, although Duhig and colleagues[99] did not clearly describe the modelling methodology, structure and assumptions. Moreover, the data inputs were not fully described and justified in four studies.[100 102 105 106] Of the ten published studies, only two based the effectiveness on a systematic review,[7 104] and only one measured the health benefits in QALYs using standardised and validated generic instruments for assessment of quality of life.[7] The authors have described and justified the resource costs used, except for Giardini and colleagues.[102] Most of the studies assessed uncertainty through deterministic and scenario analyses[7 10 98 100 101 103 105 106] but Duhig and colleagues[99] used a probabilistic sensitivity analysis, and Giardini and colleagues[102] and Myrhaug and colleagues[104] did not assess uncertainty at all. Model validation was only reported for the study by Frampton and colleagues.[7]

5.1.5 Methods for review and data extraction of HRQoL studies

The EAG undertook searches to identify data on health-related quality of life (HRQoL) in gestational hypertension, pre-eclampsia and general pregnancy. The aim of these searches was to identify utility values that were suitable for use in the economic model. The following HRQoL measures were eligible for inclusion: EQ-5D (3 or 5-level version), Short Form questionnaire-36 items (SF-36) (using all subscales), Short Form questionnaire-12 items (SF-12), Short Form questionnaire-6 items (SF-6D), Health Utilities Index (HUI) 1, 2 and 3 and 15D questionnaire. All these measures are general preference-based utility measures or can be mapped to the EQ-5D using published algorithms, in line with the NICE reference case.[82] The relevant population is women who are or have been pregnant and who have experienced hypertensive disorders during pregnancy (such as gestational hypertension and/or pre-eclampsia) and their neonates. Only primary research studies were included. Studies assessing specific symptoms of pregnancy or morbidity (such as urinary incontinence or emesis) or studies assessing subpopulations of pregnant women (such as

those with human immunodeficiency virus, thyroid conditions or cancer) that are not directly related to gestational hypertension or pre-eclampsia were excluded.

A sequential approach was used to identify HRQoL studies and all steps were conducted by two health economists, with any disagreements resolved through discussion:

1. Systematic searches of bibliographic databases were conducted for HRQoL data in pregnant women or women with hypertensive disorders of pregnancy.
2. Ad hoc searches were conducted for HRQoL data in pregnant women or women with hypertensive disorders of pregnancy.

The systematic searches were carried out as separate searches in MEDLINE (Ovid), including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Embase (Ovid), and Web of Science for the Science Citation Index Expanded (SCI-EXPANDED) and the Conference Proceedings Citation Index – Science (CPCI-S). A set of focused HRQoL-related terms were used, consistent with the previous Diagnostic Assessment Report,[7] to identify utility values for use in the economic model. The search strategies are detailed in Appendix 1. The inclusion and exclusion criteria for eligibility screening are given in Table 44. The same eligibility criteria were used for screening both titles and abstracts and full-text records, with an exception that reference type was only applied at full-text screening.

Table 44 Inclusion/exclusion criteria for the review of HRQoL studies

Inclusion criteria
Research type
Primary research studies
Population
Women with pre-eclampsia or gestational hypertension;
General pregnancy/post-partum population experiencing any events that could be relevant to HRQoL estimation in pre-eclampsia or gestational hypertension (e.g. mode of delivery, hospitalisation);
Neonates experiencing any events that could be relevant to HRQoL estimation in pre-eclampsia or gestational hypertension.
Outcomes
SF-36, SF-12, SF-6D, EQ-5D, HUI-1, -2 and -3 and 15D
Exclusion criteria
Research type
Cost-effectiveness studies

Population
Conditions not specifically relevant to pre-eclampsia or gestational hypertension (e.g. thyroid disease, human immunodeficiency virus)
Reference type
Conference abstracts, letters, protocols, case reports
Language
Studies not in English language

Data extraction was performed using a pre-designed standard data extraction form that had been used in the previous Diagnostic Assessment Report.[7]

5.1.6 Results of the review of HRQoL studies

The systematic searches identified 133 potentially relevant studies (Figure 4): 125 were identified directly from database searches and a further eight were identified from ad hoc searches. Of the 133 references, 32 were retrieved for full-text screening and five studies[107 108 109 110 111] were included after full text screening. Of the excluded studies, 12 were conference abstracts,[112 113 114 115 116 117 118 119 120 121 122 123] 12 exclusions were based on study design,[124 125 126 127 128 129 130 131 132 133 134 135] two on population[136 137] and one[138] on HRQoL measure. The excluded references and reasons for exclusion are shown in Appendix 3.

The five included studies are described below (Table 45). Only two studies[110 107] reported EQ-5D whilst three[108 109 111] reported SF-36. Of the five studies, none were in the UK and four had European populations.[108 110 107 111] Three had samples sizes greater than 200.[110 107 111]

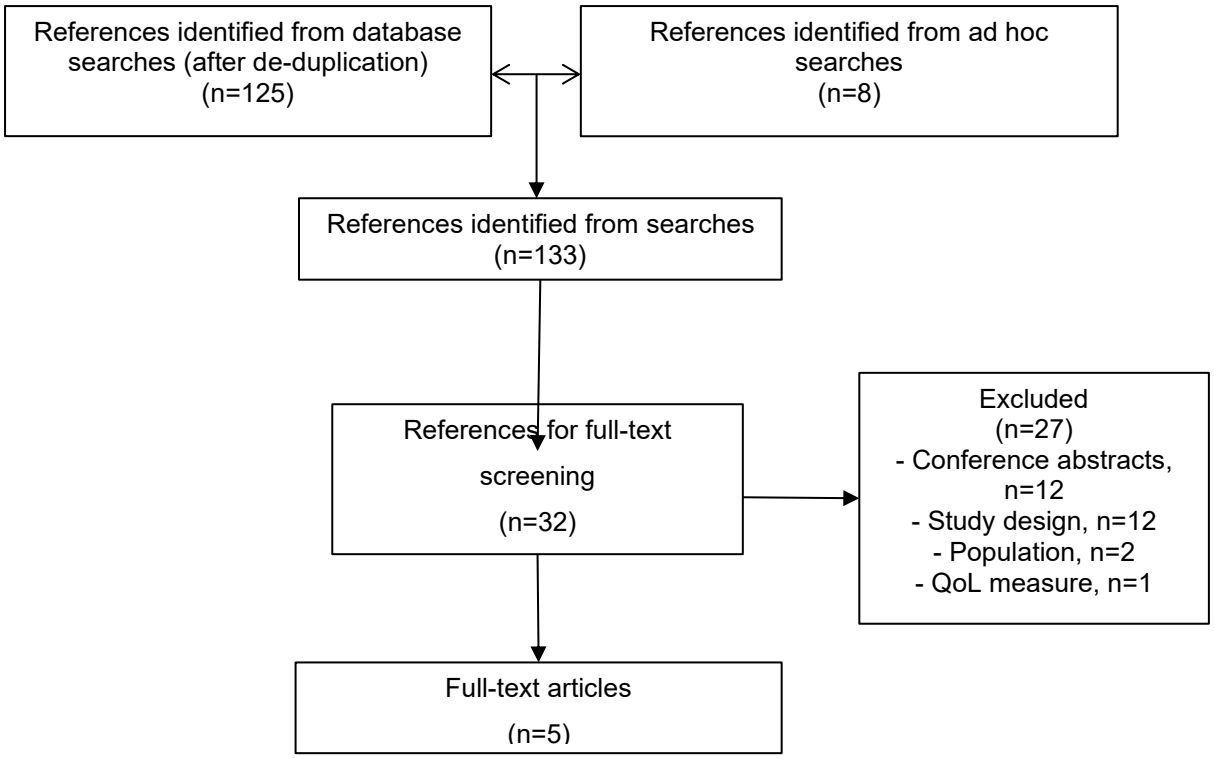


Figure 4 Flow chart for the identification of HRQoL studies

Table 45 Characteristics of included HRQoL studies

First Author, Year	N (total analysed)	Country	Instrument	Health state(s) described
Brusse et al. 2016 [108]	85	The Netherlands	SF-36	6-8 weeks postpartum for normotensive women, women with chronic hypertension, women with pregnancy induced due to hypertension and women with pre-eclampsia (mild or severe)
Cao et al. 2016 [109]	60	China	SF-36	Pregnancy with hypertension with or without music therapy treatment. (between about 26 weeks and 30 weeks of pregnancy)
Morin et al. 2018 [110]	332	France	EQ-5D 3L	Pregnant women between 3rd and 9th month of gestation with no complications, some complications (simple pathological) and multiple complications (complex pathological).
Prick et al. 2015 [111]	1391	The Netherlands	SF-36	Induction of labour and expectant management in women with intra-

				uterine growth restriction (IUGR) and hypertensive disorders (The DIGITAT and HYPITAT trials). Anaemic women after postpartum haemorrhage to red blood cell transfusion or expectant management (The WOMB trial).
Seppänen et al. 2017 [107]	229	Finland	EQ-5D 3L	Pregnant women before acute hospitalization; 6 months postpartum/post discharge from intensive care unit

EQ-5D

Morin and colleagues[110]

Morin and colleagues[110] conducted a prospective cohort study which evaluated the HRQoL of French pregnant women (n=332) with a full-term birth from the first trimester to the 9th month using the EQ-5D-3L questionnaire (French tariff), comparing physiological (no medical complications), simple pathological (occurrence of one or more conditions that did not require home monitoring or hospitalization), or complex pathological pregnancies (occurrence of one or more conditions that did require home monitoring and/or hospitalization). The conditions listed were viral or bacterial infections, breakthrough bleeding, gestational diabetes, cholestasis, thrombocytopenia, preterm labour risk, hypertension, premature rupture of the amniotic sac, delayed intrauterine growth, ultrasound malformation in addition to renal, respiratory, thromboembolic, and psychopathological maternal disorders. High blood pressure was experienced by 8.5% of women with simple pathological pregnancies and 20.7% of women with complex pathological pregnancies, respectively. The EQ-5D values are shown in Table 46.

Table 46 EQ-5D scores reported in Morin and colleagues.

Type of pregnancy		**3rd month**	**4th month**	**5th month**	**6th month**	**7th month**	**8th month**	**9th month**
Physiological	**N**	190	182	200	184	193	197	138
	Mean (SD)	0.75 (0.25)	0.71 (0.26)	0.69 (0.28)	0.58 (0.31)	0.48 (0.3)	0.41 (0.3)	0.38 (0.28)
Simple pathological	**N**	38	40	43	40	38	35	23
	Mean (SD)	0.66 (0.3)	0.7 (0.29)	0.55 (0.3)	0.45 (0.3)	0.29 (0.26)	0.26 (0.33)	0.31 (0.31)
	N	47	44	50	44	49	46	26

Complex pathological	**Mean (SD)**	0.71 (0.3)	0.69 (0.3)	0.63 (0.33)	0.47 (0.32)	0.42 (0.33)	0.26 (0.3)	0.29 (0.27)
Source: Morin et al [110]								
SD, standard deviation								

Morin and colleagues[110] report utility scores at different stages of gestation for women with and without pregnancy complications. Women with pregnancy complications have generally lower utility values than those without. However, utility values for women with simple pathological conditions are generally lower than those for women with complex pathological conditions. This is likely due to the lower baseline utility of women with simple pathological conditions. These results do not meet the NICE reference case since French tariffs were used to obtain EQ-5D utilities. This study reports a maximum utility score of 0.75 during pregnancy, for women in the 3rd month of pregnancy who do not have complications. This value is lower than is reported in other studies, for example, in the study by Seppänen and colleagues[107] the HRQoL was 0.907 for women admitted to the intensive care unit (i.e. at a more severe stage). Furthermore, other studies that evaluated HRQoL during pregnancy also reported higher utility values than Morin and colleagues,[139 140 141] for example a cross-sectional study from the UK reported a utility of 0.81 around the 3rd month of gestation.[140]

Seppänen and colleagues[107]

Seppänen and colleagues[107] conducted a retrospective register-based study to examine HRQoL in pregnant women admitted to the intensive care unit in Finland. Hypertensive complications (pre-eclampsia, eclampsia, hypertension) were the most common cause of admission to intensive care units. Other admission causes included haemorrhage, pregnancy or delivery related complications and non-obstetric causes. Both EQ-5D-3L (Finnish tariff) and EQ-VAS were used to measure HRQoL at baseline (refers to the time preceding the acute hospitalisation) and six months after discharge from the intensive care unit. Women with missing EQ-5D data from baseline or follow-up were excluded. From 229 women with available measurements, 115 were lost to follow-up. The EQ-5D scores from the study and the general population scores are presented in Table 47.

Table 47 EQ-5D scores reported in Seppänen and colleagues

EQ-5D	General population	Baseline (upon admission to ICU)	Follow-up (post-partum)	P value
18-24 years				
N	166	28	13	

score	0.96	0.894	0.940	<0.05*
25-34 years				
N	213	126	73	
score	0.95	0.912	0.954	<0.01*
35-44 years				
N	170	60	28	
score	0.93	0.903	0.926	NS
All				
N	549	214	114	
score	0.946	0.907	0.946	<0.001*

Source: Seppänen et al. [107]

*vs. baseline

NS, non-significant, ICU, intensive care unit

The utility score of the study population upon admission to an intensive care unit during pregnancy is lower (0.907) compared to the general population score (0.946). However, pre-pregnancy utility score of the study population is not reported and may differ from the utility score for the general population. Assuming that the general population characteristics were similar to those in the follow-up group of the study population, these results suggest that HRQoL of women largely recovered by 6 months postpartum (0.946), as was assumed in the previous Diagnostic Assessment Report.[7]

The study by Bijlenga and colleagues [142] used in the previous Diagnostic Assessment Report [7] followed up a cohort of women with hypertensive disorders and measured their HRQoL scores at the final weeks of gestation (between 36 and 41 weeks), at 6 weeks post-partum and at 6 months post-partum. Therefore, we consider the utility values reported by Bijlenga and colleagues preferable to those from *Seppänen and colleagues* since the utility values from Bijlenga and colleagues can be used for different time-points and, thus for different health states of the model [142]. However, none of the HRQoL studies of the previous Diagnostic Assessment Report [7] reported HRQoL scores related with admission to hospital and intensive care units.

SF-36

Brusse and colleagues[108]

Brusse and colleagues[108] conducted a prospective case-control study in the Netherlands that compared the HRQoL of pregnant women with normal blood pressure, chronic

hypertension, pregnancy-induced hypertension, mild pre-eclampsia and severe pre-eclampsia, measured six to eight weeks postpartum. Eighty-five participants received the HRQoL questionnaire and 75 returned it but the authors did not report how missing data were dealt with. Three instruments were used to measure HRQoL: SF-36, Multidimensional Fatigue Inventory and EQ-VAS. The SF-36 scores are reported in Table 48 below. We mapped these scores to EQ-5D-3L utility values using the method developed by Ara and Brazier.[143]

Table 48 SF-36 scores reported in Brusse and colleagues

SF-36, 0-100 (mean, SD)	Normotensive (n=25)	Chronic hypertension (n=8)	Pregnancy induced hypertension (n=6)	Mild pre-eclampsia (n=9)	Severe pre-eclampsia (n=23)
Physical sum score	51.0 (8.6)	52.0 (3.6)	46.3 (9.3)	50.7 (7.1)	47.9 (8.3)
Physical Functioning	87.1 (14.7)	93.0 (7.0)	80.0 (19.0)	95.0 (5.0)	97.0 (10.5)
Role Physical	75.0 (36.9)	90.6 (26.5)	70.8 (33.2)	86.1 (33.3)	64.1 (36.0)
Bodily Pain	74.4 (30.9)	78.5 (29.7)	66.0 (28.5)	74.9 (29.8)	66.3 (30.8)
General Health	84.3 (13.4)	82.0 (10.7)	82.8 (13.9)	79.3 (12.2)	70.4 (14.0)
Mental sum score	50.4 (8.4)	56.5 (6.0)	56.5 (5.3)	55.6 (3.5)	46.2 (10.7)
Vitality	60.2 (19.3)	73.6 (11.3)	65.0 (21.7)	62.2 (16.0)	52.2 (19.2)
Social Functioning	78.5 (19.3)	95.3 (6.5)	89.6 (12.3)	93.1 (12.7)	68.5 (21.6)
Role Emotional	83.3 (31.1)	98.5 (35.4)	94.4 (13.6)	96.3 (11.1)	72.5 (41.0)
Mental Health	78.7 (14.0)	90.5 (8.8)	84.0 (16.0)	88.4 (8.6)	72.7 (15.9)
Mapping to EQ-5D*	0.86	0.94	0.84	0.93	0.85

Source: Brusse et al. [108]
*using Ara and Brazier algorithm [143]
SD, standard deviation

Each population subgroup has a small sample size (n≤25). In addition, the study reports higher EQ-5D scores for women with chronic hypertension and mild pre-eclampsia than normotensive individuals and similar scores for women with pregnancy induced hypertension and severe pre-eclampsia six to eight weeks postpartum. Although previous studies [144] [142] [145] [146] [7] have showed that women almost completely recovered in terms of HRQoL after this time period, it does not seem plausible that women with chronic hypertension or mild pre-

eclampsia have higher utility values than the other subgroups. Therefore, we consider these results to be associated with large uncertainty and we do not use them in our economic model.

Cao and colleagues [109]

Cao and colleagues [109] conducted a prospective cohort study in China and compared the HRQoL of women with pregnancy induced hypertension receiving conventional therapy (spasmolysis with magnesium sulphate, lowering blood pressure with nifedipine and others) (n=30) or a conventional therapy plus music therapy (n=30) for four weeks. The treatment lasted between the 22nd and 30th weeks of gestation. HRQoL was measured with the SF-36 after the treatment and the scores are shown in Table 49. We mapped these scores into EQ-5D-3L using the method developed by Ara and Brazier.[143]

This study presents a utility score (0.72) for pregnant women experiencing hypertensive disorders in the third trimester of gestation. However, it includes a small sample size (n=30) and was conducted in China, in which the standard clinical healthcare is likely to be not generalisable to the UK. Therefore, we do not use these results in our economic model.

Table 49 SF-36 scores reported in Cao and colleagues

SF-36, 0-100	Conventional therapy plus music therapy (n=30)	Conventional therapy (n=30)	P value
Physiological Function	84.5 ±10.6	71.2 ±10.4	<0.05
Physiological Functioning	82.6 ±10.1	72.3 ±9.8	<0.05
Physical Pain	74.5 ±10.4	62.9 ±9.6	<0.05
Overall Health	84.2 ±11.2	70.5 ±11.9	<0.05
Vitality	88.4 ±10.3	74.2 ±10.7	<0.05
Social Functions	74.9 ±9.1	62.9 ±8.3	<0.05
Emotional Functioning	73.3 ±9.4	60.5 ±9.8	<0.05
Mental Health	81.5 ±8.3	72.6 ±8.4	<0.05
Mapping to EQ-5D*	0.84	0.72	NA
Source: Cao et al. [109] *using Ara and Brazier algorithm [143]			

Prick and colleagues[111]

Prick and colleagues[111] used data from three randomized controlled trials to investigate postpartum HRQoL in women after an obstetric complication (n=1391). The DIGITAT and HYPITAT trials compared induction of labour and expectant management in women with intra-uterine growth restriction and hypertensive disorders. The WOMB trial randomized anaemic women after postpartum haemorrhage to red blood cell transfusion or expectant management. The study was set in the Netherlands. The HRQoL-measure SF-36 was completed at six weeks postpartum and its values, along with their mapping into EQ-5D-3L,[143] are shown in Table 50.

Table 50 SF-36 scores reported in Prick et al

SF-36	DIGITAT		HYPITAT		WOMB		Total all studies		Dutch population	Post-partum reference
Component	**N**	**(SD)**	**N**	**(SD)**	**N**	**(SD)**	**N**	**(SD)**	**(SD)**	**(SD)**
Physical functioning	403	86 (18)	528	85 (16)	452	86 (17)	1383	86 (17)	92 (13)	85 (19)
Role-physical	401	57 (42)	528	50 (42)	450	73 (38)	1379	60 (42)	86 (29)	74 (37)
Bodily pain	401	77 (19)	528	54 (25)	456	73 (28)	1385	61 (28)	79 (19)	78 (28)
General health	398	76 (19)	527	78 (17)	454	79 (18)	1379	78 (18)	77 (17)	78 (18)
Vitality	401	57 (18)	527	57 (17)	454	66 (18)	1382	60 (18)	68 (16)	68 (18)
Social functioning	402	75 (25)	528	75 (23)	456	84 (20)	1386	78 (23)	86 (19)	86 (19)
Role-emotional	399	82 (34)	528	83 (33)	452	85 (32)	1379	84 (33)	82 (33)	83 (34)
Mental health	401	79 (16)	527	80 (15)	454	86 (15)	1382	82 (15)	76 (15)	86 (14)
Mapping to EQ-5D*	NA	0.87	NA	0.80	NA	0.88	NA	0.83	0.89	0.89

Source: Prick et al [111]
*using Ara and Brazier algorithm [143]
x, mean; NA, Not applicable; SD, standard deviation

The HYPITAT trial reports utility values for women with hypertensive disorders six weeks postpartum (0.80). The utility values are lower than the general Dutch population and post-

partum reference scores (0.89). We note that the study by Bijlenga and colleagues,[142] used in the previous Diagnostic Assessment Report,[7] evaluated HRQoL in the same population of pregnant women with hypertensive disorders (from the HYPITAT trial). We consider the study by Bijlenga and colleagues,[142] to be preferable to the study by Prick and colleagues[111] as Bijlenga reported the HRQoL scores for different time points (from the final stage of pregnancy to 6 weeks and 6 months post-partum). Furthermore, the study by Bijlenga and colleagues[142] reported the HRQoL scores for the two groups of women in the HYPITAT trial (induction of labour group and expectant management group), while Prick and colleagues[111] study report the results for the whole population of the trial.

5.2 Overview of economic evidence in the company submissions

Four companies - Quidel Ireland, Roche Diagnostics Ltd, Thermo Fisher Scientific and PerkinElmer Health Sciences - participated in the current diagnostic assessment. The companies provided economic evidence, together with evidence on test accuracy. Although all companies reported the costs of their biomarker tests (as described in section 5.4.7.3), they did not provide economic models.

5.3 Overview of the evidence from the systematic review of test accuracy and clinical effectiveness

Table 51 summarises the clinical effectiveness evidence selected to inform the EAG independent economic model. This selection was based on an assessment of the robustness of the available evidence, its relevance to the current decision problem and suitability for prediction of health effects and NHS resource use to inform cost-effectiveness estimates.

The EAG base case analyses for the Triage and Elecsys tests are informed by evidence from the recently published PARROT[9] and INSPIRE[32] RCTs, respectively. These trials were both conducted in the UK and evaluated the addition of PlGF-based tests to standard clinical assessment of women with suspected pre-eclampsia. They report prognostic accuracy of the tests and a range of maternal, fetal and neonatal clinical effectiveness outcomes. This provides a good foundation for 'end-to-end' evaluation of the Triage and Elecsys tests as adjuncts to usual care in UK clinical contexts, reducing the need for assumptions that would be required to link measures of diagnostic/prognostic accuracy to health outcomes and NHS resource use.

We also conduct scenario analyses for the Triage and Elecsys tests using the 'next best' line of evidence from prospective observational comparisons of PlGF-based add-on tests versus

usual care alone: the analysis of MAPPLE/PELICAN cohort studies[16] for the Triage PlGF test; and the PreOS before/after prospective study[34] for the Elecsys sFlt-1/PlGF ratio.

Evidence for the BRAHMS Kryptor sFlt-1/PlGF ratio tests is weaker. Andersen and et al [48] estimated predictive accuracy for the BRAHMS test as an add-on to usual care from retrospective cohort data, but this is only reported in a conference abstract, and is of limited use for economic analysis because of a lack of comparison with usual care. Salahuddin and colleagues[47] reported accuracy for prediction of adverse events within 2 weeks for both the BRAHMS and Elecsys tests by reanalysing frozen samples from the ROPE cohort study.[45] They estimated an identical area under the curve (AUC) for the two tests, using a model that also accounted for systolic blood pressure and proteinuria. We therefore present a simple cost-comparison analysis between BRAHMS and Elecsys, based on an assumption of equal predictive accuracy. We note that this analysis is subject to uncertainty due to the context of the ROPE cohort study[45] (standalone tests in a single US centre) and the study population (women with gestational age outside of 20 – 36-week range).

A cost-effectiveness analysis for the DELFIA Xpress PlGF 1-2-3 test could potentially be informed by the COMPARE study,[30] which compared the performance of three tests (standalone use) – Triage, Elecsys and DELFIA. (see Section 4.1.3). However, it has not been possible to conduct such an analysis in the time available.

Table 51 Test accuracy and clinical effectiveness evidence included in the economic model

Study (type)	Setting (n)	Study period	Source	Gestational age (weeks)	Pregnancy type (n)	Cut-offs considered	
Triage PlGF test							
PARROT (add-on, pragmatic stepped wedge cluster RCT)	11 maternity units in the UK	2016-2017	Duhig 2019[15], 2021[9], 2019[14], 2019[13]	20^{+0} - 36^{+6}	Singleton (1023)	Rule-in: <100 pg/ml and <12 pg/ml for PE required delivery: • within 14 days for <35 weeks • before 37 weeks for 35-36^{+6} GA	
MAPPLE (add-on, prospective cohort)	UK, Germany, Austria and Australia	2014-2016	Sharp 2018[16]	< 35	Singleton (356) or twin (40)	< 12 pg/ml (very low) 12–100 pg/ml (low) > 100 pg/ml (normal)	
PELICAN (standalone, prospective cohort)	UK and Ireland	2011-2012	Duckworth 2016[21]	< 35	Singleton (275) or twin (12)	ROC analysis	
Elecsys sFlt-1/PlGF ratio test							
INSPIRE (add-on, individual parallel group RCT)	A single tertiary referral centre in England	2015-2017	Cerdeira 2019[32]	24^{+0} - 37^{+0}	Singleton (370)	> 38 (rule in PE within 1 week)	≤ 38 (rule out PE within 1 week)
			Cerdeira 2020[33] (Research letter)	24^{+0} - $36^{+6/7}$		≥ 85 (rule in PE within 4 weeks)	
			Cerdeira 2021[31] (CQ	24+0 - 36+6			≤38 (rule out PE within 4

Study (type)	Setting (n)	Study period	Source	Gestational age (weeks)	Pregnancy type (n)	Cut-offs considered	
			response AiC)				weeks)
PreOS (add-on, prospective before/after study)	Five hospitals: four in Germany (n = 162) and one in Austria (n = 47)	Started in July 2012 TBC	Klein 2016[34]	≥ 24	Singleton (204) or twin (5)	≥ 85	< 33
BRAHMS Kryptor sFlt-1/PlGF ratio							
Andersen (standalone, prospective cohort)	Denmark	2017-2019	Andersen 2019[48]	< 35	NR	< 33 pg/ml (rule out PE within 1 and 4 weeks) >85 (rule in PE within 1 and 4 weeks)	
Salahuddin (analysis of frozen samples from ROPE	A single centre in the USA (ROPE)	2009-2010	Salahuddin 2016[47]	36.4 (33.6, 38.0)	Singleton (412)	≥ 85, AUC analysis for BRAHMS Kryptor sFlt-1/PlGF ratio and Roche Elecsys sFlt-1/PlGF ratio for short-term AOs within 2 weeks	
ROPE (standalone, prospective cohort)	A single centre in the USA	2009-2012	Rana 2018[45]	≤37	Singleton (402)	>38 (within 2 weeks), >85 (within 2 weeks)	
DELFIA Xpress PlGF 1-2-3							
COMPARE (standalone, retrospective analysis of samples from PEACHES,[24]	PEACHES - two London academic health science centres; PELICAN-1 and PELICAN-2 -	PEACHES – 2009 – 2017, PELICAN-1 and	McCarthy et al.[30]	24-37	Singleton (396 plasma samples and 244	ROC analysis to rule in delivery within 2 weeks for the cut-offs: - <100 pg/ml for Alere (now Quidel) Triage PlGF - >38 for Roche Elecsys sFlt-1/PlGF ratio	

Study (type)	Setting (n)	Study period	Source	Gestational age (weeks)	Pregnancy type (n)	Cut-offs considered
PELICAN-1[60] and PELICAN-2 [147]	18 maternity units in the UK and Ireland	PELICAN-2 – 2011 - 2013			serum samples)	- an optimally derived cut-off of <150 pg/ml for the PerkinElmer DELFIA Xpress PlGF 1-2-3
AOs, adverse outcomes; AUC, area under the curve; NR, not reported; PE, pre-eclampsia; ROC, receiver operating characteristic						

5.4 External Assessment Group (EAG) independent economic evaluation

5.4.1 Decision problem

The decision problem for this economic evaluation is as stated in Section 2 of this report. This, in turn, reflects the NICE scope for this appraisal[8] (see section 2.1).

5.4.2 Population

The populations considered in the EAG base-case and scenario analyses are summarised in Table 52 below.

In the base-case analysis, the relative effectiveness of Triage and Elecsys PlGF-based testing when used in addition to standard clinical assessment versus standard clinical assessment without PlGF-based testing was estimated from two clinical trials, the PARROT[9] and INSPIRE[32] RCTs (see section 5.1.3 above). We also present a simple cost-comparison for the BRAHMS ratio test based on similar estimates of predictive accuracy of the BRAHMS and Elecsys tests from the Salahuddin case-control study.[47]

Quidel state in their submission to NICE that the Triage PlGF test can be used in women presenting with signs and symptoms of pre-eclampsia prior to 35 weeks of gestation. However, the population in the PARROT trial, which informed the base-case analysis for this test was the same as in the NICE scope,[8] i.e. women with gestational age from 20 weeks up to 36 weeks and 6 days (Duhig 2021[9]).

The population in the base-case analysis for the Elecsys immunoassay sFlt-1/PlGF ratio test (women with gestational age from 24^{+0} to 37^{+0} weeks, as shown in Table 52) is the same as that defined in the Roche's submission for the short-term prediction of pre-eclampsia. This is based on the study population in the INSPIRE RCT.[32]

For the BRAHMS test, the accuracy estimates were derived from the same source as for Triage - the PARROT trial,[9] with the population of women at gestational age of 20 - 36^{+6} (Table 52), which is in line with the population for which this test is suitable >20 weeks of gestation.

Table 52 Populations included in the EAG economic analysis

Intervention	Population		Study	Source
	Gestation age (weeks)	Pregnancy type (%)		
Triage PlGF				
Base case	20 - 36^{+6}	Singleton	PARROT	Duhig 2021[9]
Scenario analysis	<35	Singleton (90%) or twin (10%)	MAPPLE	Sharp 2018[16]
	< 35	Singleton (96%) or twin (4%)	PELICAN	Duckworth 2016[21]
Elecsys immunoassay sFlt-1/PlGF ratio				
Base case	24^{+0} - 37^{+0}	Singleton	INSPIRE	Cerdeira 2019[32]
Scenario analysis	≥ 24	97.5% singleton 2.5% twin	PreOS	Klein 2016[34]
BRAHMS sFlt-1 Kryptor / BRAHMS PlGF plus Kryptor PE ratio test				
Base case	<34	Singleton	ROPE	Salahuddin[47]
NR, not reported				

The effect of changing assumptions about the accuracy of the tests was explored in scenario analyses using data from observational comparisons of PlGF-based tests when used in addition to standard clinical assessment versus standard clinical assessment without PLGF-based testing: MAPPLE/PELICAN[16 21] for Triage, and PreOS[34] for Elecsys and BRAHMS. The participants in the MAPPLE and PELICAN[16 21] studies were women with gestational age at presentation of less than 35 weeks (Table 52), which overlaps with the patient population for which Triage is suitable, i.e. women with gestational age from 20 weeks up to 34 weeks and 6 days. In the scenario for Elecsys, the gestational age was ≥ 24 weeks.

5.4.3 Interventions

The intervention is the use of PlGF-based tests (specified in Table 53) used alongside standard clinical assessment, to help diagnose pre-eclampsia and make subsequent decisions about care.

Table 53 PlGF-based tests included in the EAG economic analysis

Intervention	Intended use	Study
Triage PlGF	As part of the clinical management algorithm shown in Figure 10 (Appendix 8)	Base case: PARROT RCT[9]

	As part of the clinical management algorithm shown in Figure 12 (Appendix 8)	Scenario: MAPPLE[16] (add-on)/ PELICAN[21] (standalone)
Elecsys immunoassay sFlt-1/PlGF ratio	As part of the clinical management algorithm shown in Figure 11 (Appendix 8): • > 38 (elevated risk of developing PE within 1 week[a]) • ≤ 38 (low risk of developing PE within 1 week[a])	Base case: INSPIRE RCT[32]
	• ≥85 - confirm a diagnosis of hypertensive pregnancy disorder • ≤33 - rule out a diagnosis of PE	Scenario: PreOS[34] (add-on)
BRAHMS sFlt-1 Kryptor / BRAHMS PlGF plus Kryptor PE ratio test	>85 for predicting AOs in mothers and babies within 2 weeks	Base case: Salahuddin[47] (standalone)
AOs, adverse outcomes; GA, gestational age [a] Intended use of Elecsys in the INSPIRE trial		

The clinical management algorithms used in the trials for managing suspected pre-eclampsia, which incorporated the result of PlGF-based testing, are shown in Appendix 8. The EAG's clinical advisers advised that the Triage PlGF and Elecsys immunoassay sFlt-1/PlGF tests are currently used in some NHS hospitals for the assessment of suspected pre-eclampsia, but the other two tests are not used.

In the base case, we assume, in accordance with the PARROT[9] and INSPIRE[32] trials, that PlGF-based testing is conducted in all women with suspected pre-eclampsia.

5.4.3.1 Repeat testing

The NICE scope[8] states that, in this appraisal, the interventions (the tests) should be assessed when used once per episode of suspected pre-eclampsia. However, a repeat test can be performed in pregnant women who have had an initial PlGF-based test for suspected pre-eclampsia that was negative, and who have no additional signs or symptoms of possible pre-eclampsia.

Expert clinical advice to the EAG suggests that repeat testing could be considered if the first PlGF-based test result indicated low or intermediate risk of pre-eclampsia. The suggested timing of the subsequent testing with the Elecsys test (as shown in the Manchester NHS Foundation trust and the Newcastle upon Tyne Hospitals NHS Foundation Trust guidelines

in Appendix 9) is two weeks for low risk pre-eclampsia, and one or two weeks intermediate risk. Repeat testing would usually be considered at two weeks after the first test, and the proportion of women undergoing repeat testing could vary between 20% up to 50% depending on local clinical practice protocols. Repeat testing of women at a later gestation would be less likely, although this would depend on local practice.

Repeat testing was reported in just one study included in the systematic review of test accuracy and clinical effectiveness, the prospective observational standalone study PROGNOSIS study (Elecsys sFlt-1/PlGF ratio).[36]

When testing is repeated, it is likely that there is conditional dependence between the first and subsequent tests, that is, the sensitivity (or specificity) of the subsequent test would not be independent of the outcome of the first test.[148] Therefore, the overall sensitivity and specificity of the repeat testing strategy should be calculated taking into account the effect of test covariance. This would require additional evidence on pairwise test results for the first and subsequent tests. Such evidence was not available in clinical effectiveness studies informing this economic evaluation. For this reason we were unable to conduct scenario analyses of repeat testing.

5.4.4 Comparator

The comparator in this economic evaluation no further clinical assessment (beyond assessments already done, such as blood pressure measurement, urinalysis and fetal monitoring) to diagnose pre-eclampsia and inform subsequent decisions about care.

The 2010 NICE guideline on managing hypertension and pre-eclampsia (CG107)[59] was replaced in 2019 by the NICE guideline on Hypertension in pregnancy: diagnosis and management (NG133).[3] The key differences between the CG107[59] and NG133[3] guidelines are discussed below. NICE guideline NG133.[3 6] incorporates the recommendation from the NICE DG23[6] on the use of the Triage PlGF test and the Elecsys immunoassay sFlt-1/PlGF ratio test in addition to standard clinical assessment and subsequent clinical follow-up, to help rule-out pre-eclampsia in women presenting with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation.[3 6] NG133 also includes is the use of online risk assessment tools (fullPIERS and PREP-S) to estimate the risk of adverse events in women diagnosed with pre-eclampsia.

The PARROT and INSPIRE trials, which inform many of the parameters and assumptions in this economic evaluation, were initiated before NG133, and their clinical management algorithms incorporating PlGF testing (shown in Figure 10 and Figure 11, Appendix 8) were based on the previous guideline CG107.[59] Therefore, to be consistent with these trials the modelled costs accrued in the test and comparator arms are based on the CG107 guideline.[59]

We conduct a scenario analysis assuming that gestational hypertension and pre-eclampsia would be managed according to the current NICE guideline NG133.[3] In this scenario, we do not model PlGF testing to rule out pre-eclampsia (as recommended in the NICE DG23[6]) because this appraisal is an update of that guidance.

5.4.5 Key considerations when selecting a model structure

In this section we focus on what we believe are the most important factors that need to be considered when selecting a model structure for the decision problem described above.

As reported in PARROT,[9] one of only two UK RCTs of biomarkers for assessment of women with suspected pre-eclampsia, addition of PlGF testing to standard clinical practice for managing suspected pre-eclampsia did not lead to significantly more cases of preeclampsia being diagnosed but it shortened the time to diagnosis. The trial also reports a reduction in severe maternal adverse events seen with the implementation of revealed PlGF testing, with the largest reduction in the PlGF 12–100 pg/ml group. The authors argue that the improvement in clinical outcomes in this group may have been mediated by the use of the clinical management algorithm which recommends increasing antenatal surveillance and monitoring; this may be particularly important in the group of women with PlGF 12–100 pg/ml who presented with clinical features of gestational hypertension but may also have had sub-clinical multi-organ disease features.

In the INSPIRE RCT,[32] the clinical use of PlGF/sFlt-1 testing enabled more accurate targeting of hospital admission for high-risk women and improvements in antenatal steroid administration prior to delivery to reduce the likelihood of infant respiratory distress syndrome requiring neonatal unit admissions.[32]

It has been shown that there is a correlation between the level of angiogenic biomarkers in women with suspected pre-eclampsia and the time from testing to delivery.[9,47]

Therefore, a candidate model structure should be able to capture clinical risk stratification into low, intermediate and high risk of pre-eclampsia. It should also be able to adequately represent the clinical management algorithms for gestational hypertension and pre-eclampsia (with hypertension stratified by the level of severity), the management of delivery and the risk of maternal and neonatal adverse outcomes.

5.4.6 Description of the decision analytic model

In common with the majority of the studies identified in the cost-effectiveness systematic review (see Section 5.1.3), we used a decision tree model for the economic evaluation of the PlGF-based testing. The decision tree builds on the model reported in the previous DAR[7] which informed NICE DG23.[6]

The model was developed in accordance with the scope of the appraisal issued by NICE.[8] It includes the outcomes identified in the NICE scope[8] (section 2.1) described in sections 5.4.6 and 5.4.7. The costs are evaluated from the perspective of the NHS and Personal Social Services (section 5.4.7.2). Outcomes are expressed as QALYs (section 5.4.7.5). The lifetime time horizon was adopted in the base case with the discount rate of 3.5% applied to both costs and QALYs, in line with the NICE guidance.[149] A shorter time horizon of up to six months post-partum was tested in a scenario analysis.

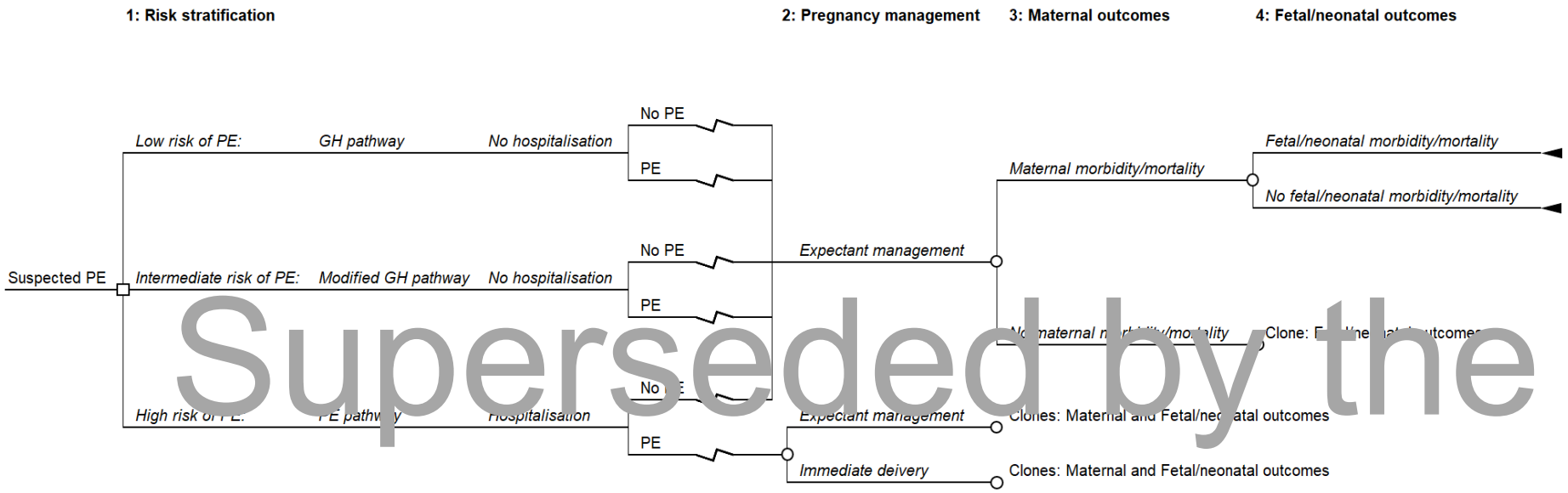
Similar to the model in the previous DAR,[7] which informed NICE DG23,[6] the current model incorporates diagnosis and management of clinical symptoms of suspected pre-eclampsia, timing and mode of delivery, neonatal outcomes and maternal outcomes up to six months post-partum. The model also estimates the long-term impact of complications on quality of life of children and their mothers; longer-term costs of respiratory distress syndrome (RDS) and intraventricular haemorrhage (IVH); and the impact of false positive results on quality-of-life of women who are misdiagnosed (as explained in sections 5.4.7.2 and 5.4.7.5 below).

Figure 5 outlines the model structure, which includes four main components:

- Stratification of women into sub-cohorts depending on the risk of suspected PE (low, intermediate, or high) based on the results of standard clinical assessment with or without PlGF testing
- Pregnancy management (identified as expectant management or immediate delivery based on key symptoms of pre-eclampsia or emergent eclampsia)

- Maternal outcomes (in terms of admission to intensive care, extended hospital stay, and morbidity associated with pre-eclampsia)
- Fetal and neonatal outcomes (in terms of admission to intensive care, extended hospital stay, and morbidity associated with fetal conditions that may be caused by maternal pre-eclampsia and/or with early delivery)

The latter three model components are shown in more detail in Figure 6 and Figure 7 and further described below. They are structurally similar to sub-models used in the previous DAR.[7] As pointed out above, in the base case it is assumed that suspected pre-eclampsia is managed in accordance with the NICE guideline CG107[59] for managing gestational hypertension and pre-eclampsia, which stratifies hypertension into mild, moderate and severe. (NB. this stratification is not shown in the model diagram (Figure 5)). The scenario analysis based on the 2019 update of the NICE guideline (NG133[3]), distinguishes between hypertension and severe hypertension (see section 5.4.7.4 and Appendix 10 for further details on CG107[59] and NG133[3] guidelines).



GH, gestational hypertension; PE, pre-eclampsia

Figure 5 Overview of the economic model structure

5.4.6.1 Risk stratification

The following assumptions are made at the risk stratification phase of the model. The model assumes that every woman has an initial appointment where the clinician assesses the risk of pre-eclampsia (either with or without the use of PlGF testing) and decides on the appropriate initial management pathway. Depending on the outcomes of the clinical assessment, women are either hospitalised or managed in outpatient settings. The risk of admission depends on the risk of pre-eclampsia: women at high risk of pre-eclampsia are admitted and managed as inpatients, while those at low and intermediate risk of pre-eclampsia are managed in an outpatient setting (in accordance with clinical management algorithms incorporating PlGF testing and NICE guidelines for managing gestational hypertension and pre-eclampsia shown in Appendix 9). Admission to hospital is possible at a later stage if symptoms of pre-eclampsia develop, in which case management in an inpatient setting will continue until delivery. Women who have been admitted to hospital but do not develop disease are assumed to be discharged at some point and managed as outpatients up to delivery. The model assumes that severe hypertension in women managed as outpatients can also lead to hospitalisation for up to three days (as explained in section 5.4.7.2 below).

Women whose test result is false positive would be hospitalised, but a decision to initiate delivery would not be driven solely by the test result since delivery is based on standard signs and symptoms related to both mother and fetus. This is supported by the outcomes in the PreOS study[34] where the physician's decision to induce delivery was unchanged for 98.2% of women (114/116) after the sFlt-1/PlGF test.

In the case of false negatives, we assume that women who have disease but have been misdiagnosed are treated in an outpatient setting according to standard of care and their care would be escalated if their clinical signs and symptoms progressed.

5.4.6.2 Delivery management and maternal outcomes

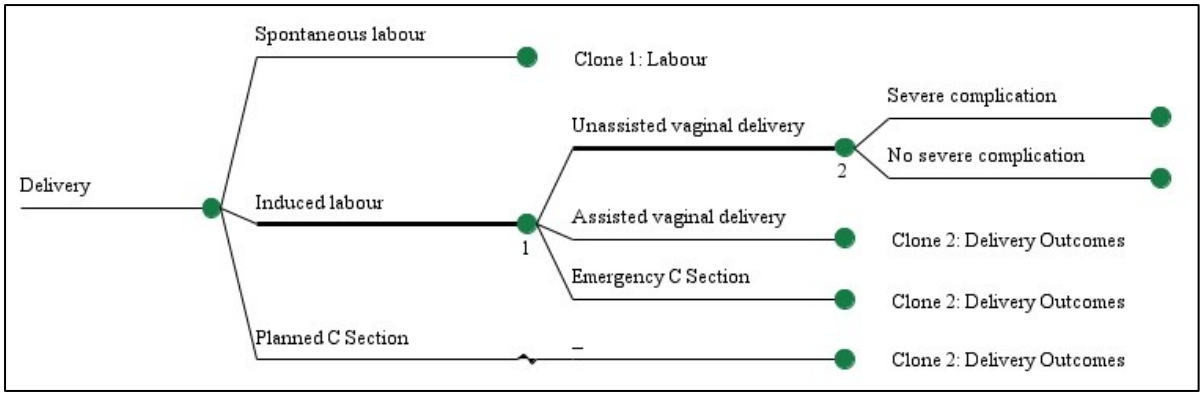


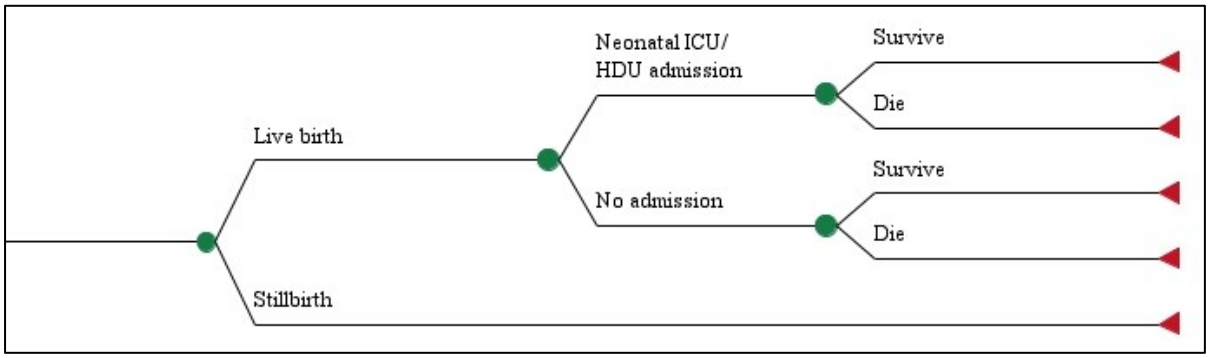
Figure 6 Delivery management and maternal outcomes model sub-tree

Figure 6 shows a sub-tree for the delivery and maternal outcome component of the model. As mentioned previously, this model structure was adopted from the previous DAR.[7] This sub-tree begins with delivery, resulting either from spontaneous labour, induced labour, or planned caesarean section. Spontaneous and induced deliveries are considered separately, because induction of delivery is associated with a higher cost than spontaneous delivery due to the need to administer medication to induce labour and a requirement for maternal monitoring during induction. Each of these modes of delivery may be associated with a risk of conversion to assisted/ instrumental vaginal delivery or to emergency caesarean and the probability of these outcomes may differ according to whether labour was initially spontaneous or induced. Each mode of delivery is also associated with a risk of a severe adverse event associated with the progression of severity of pre-eclampsia during the delivery, which results in convulsions. These adverse events confer both higher maternal risk and admission to intensive or high-dependency care units and a requirement for administration of anti-convulsive therapy. The model assumes that women who do not experience convulsions are transferred to the ward following delivery and those who do not experience any further adverse events have a normal length of stay for the given mode of delivery.

5.4.6.3 Fetal and neonatal outcomes

Figure 7 shows the structure for the fetal and neonatal outcome sub-tree, adopted from the previous DAR.[7] The model takes a simplified approach to assessing fetal and neonatal outcomes, where morbidity in terms of clinical manifestations (such as respiratory distress syndrome) is not modelled directly. Instead, we model fetal or neonatal outcomes that may be associated with increased resource use (i.e. intensive care unit or high-dependency unit). As stated in the previous DAR,[7] this approach was used to ensure tractability of the modelling task, but inevitably it involved some simplification of the clinical practice.

The first branch in this sub-model establishes whether the labour results in a live birth or stillbirth. The following branch relates to admission to neonatal high dependency or intensive care units which is assumed to be related to the risk of pre-eclampsia. Stillbirth and mortality are included in the calculation of costs and QALYs (see sections 5.4.7.4 and 5.4.7.5).



ICU: intensive care unit; HDU: high-dependency unit

Figure 7 Fetal and neonatal outcome sub-tree

5.4.6.4 Estimation of costs

The decision analytic model accounts for the costs incurred starting from the time women present to a maternity hospital with symptoms suggestive of pre-eclampsia. The costs considered in the economic analysis are comprised of:

- The cost of PlGF testing, including the cost of equipment, reagents and consumables, and the cost of staff and associated training
- The cost of managing gestational hypertension and pre-eclampsia from presentation to delivery, including the cost of antihypertensive treatment, and corticosteroids for fetal lung maturation
- Delivery cost, including the cost of magnesium sulphate to reduce the risk of seizure.
- The cost of maternal intensive care and ward stay
- The cost of neonatal unit stay including intensive care (NICU), high dependency (HDU) and special care (SCBU)
- Long-terms costs associated with complications in neonates

These cost components are further described in section 5.4.7.2.

It appears that the costs of managing gestational hypertension and pre-eclampsia are driven by the time to delivery (see Table 57 below) and, therefore, estimated separately for the gestational age of up to 35 weeks and 35-37 weeks of gestation. These costs are also stratified by the level of hypertension (mild or no hypertension, moderate or severe in 2010 NICE guideline CG107;[59] hypertension or severe hypertension in the current NICE guideline NG133[3]) and can be higher in women with pre-eclampsia (as shown in Table 57 below). As explained above, the cost of delivery depends on the mode of delivery and is significantly higher for assisted and emergency deliveries (Table 104). Therefore, such differences were taken into account when estimating the costs accrued in the test and comparator arms (see section 5.4.7.2).

5.4.6.5 Estimation of QALYs

When estimating the total QALYs for the test and comparator arms, we considered the impact of neonatal and maternal morbidity and mortality as outlined below and further described in section 5.4.7.5.

Induced labour, planned caesarean section and admission to an intensive care unit (ICU) are assumed to have an impact on quality of life of the mother, and this is modelled by applying utility decrements associated with delivery (from 3 weeks to 6 months post-partum), emergency and non-emergency caesarean section (from birth to 3 weeks post-partum), and admission to ICU (from admission to 6 weeks post-partum).

The positive test result (including false positives) may be associated with substantial anxiety. To take account of this impact on women's quality of life, we applied a utility decrement for women with false positive results.

For women with false negative results, we assumed that their outpatient care would be escalated if their clinical signs and symptoms progressed. However, negative test results may reassure women and they may not return to hospital in time for effective treatment, which could negatively affect the health of their children born preterm. This is modelled via long-term impact of adverse outcomes in neonates on the quality of life of the mother and baby.

5.4.7 Model parameters

The model parameters include test accuracy, clinical inputs (such as onset of labour, mode of delivery and birth outcomes) and costs (including the costs of testing, hospitalisation, ante-natal management, delivery and the costs of managing complications). Resource use

assumptions for costing diagnostic and management strategies are presented in section 5.4.7.2. Unit costs were taken from UK sources for the most recent available year. Parameters included in the model are discussed in the following sections. An overview of all model parameters and model assumptions is provided in Appendix 10.

5.4.7.1 Parameterisation of the risk stratification phase of the model

The clinical effectiveness study outcomes, as parameterised for risk stratification in the base-case model are shown in Table 103 (Appendix 13) and for scenario analyses in Table 106 (Appendix 14).

Triage PlGF test

The risk stratification in the base-case model for Triage was parameterised, where possible, from the outcomes in the PARROT RCT.[63] In this pragmatic trial, women presenting with suspected preeclampsia were randomized to management by Triage PlGF test in conjunction with standard clinical assessment versus standard clinical assessment alone:

- Women with a serum PlGF concentration of >100 pg/ml followed a care pathway involving outpatient management and routine surveillance unless clinical parameters such as severe hypertension indicated otherwise.
- Women with low PlGF concentrations were advised to increase surveillance with a greater frequency of antenatal care visits and fetal ultrasound scanning.
- Women with very low PlGF were assessed as pre-eclampsia, which included consideration for admission, intensive monitoring, and fetal ultrasound scanning.

The clinical management algorithm used in this trial is shown in Figure 10 (Appendix 8).

In PARROT, the outcomes (including the characteristics of labour and delivery for women with suspected pre-eclampsia, maternal and neonatal outcomes and the use of corticosteroids in both trial arms) were stratified by PlGF level: <12 pg/ml, 12-100 pg/ml and >100 pg/ml (Duhig et al. 2021[63]). Hospitalisation rates for these PlGF categories were not reported, but it was stated that the clinical management algorithm used by clinicians in PARROT (Appendix 8) did not recommend routine admission for women with low or very low PlGF (Duhig 2021[63]). Therefore, in the base-case analysis we assumed that women with PlGF of less than 12 pg/ml would be hospitalised while women with PlGF levels of ≥12 pg/ml would be managed in outpatient settings except those with severe hypertension who can also be admitted for up to three days. The proportion of women with PlGF level of <12 pg/ml in the comparator arm who would be hospitalised within 24 hours was estimated from the

risk ratio for diagnosis within 24 hrs (RR = 1.31) based on Duhig 2019.[8] The impact of uncertainty in the hospitalisation rate was assessed in a one-way sensitivity analysis.

We conducted an additional analysis for the Elecsys PlGF test using data from a comparative study of MAPPLE and PELICAN (Sharp et al 2018[9]). In the analysis reported by Sharp and colleagues,[9] clinical outcomes in women with singleton or twin pregnancies presenting prior to 35 weeks' gestation were compared, where possible, between revealed (MAPPLE) and concealed (PELICAN) cohorts. Data from Sharp[9] are categorised by PlGF concentration: <12 pg/ml (very low), 12–100 pg/ml (low; representing <5th percentile of normal) and >100 pg/ml (normal).

Elecsys immunoassay sFlt-1/PlGF ratio test

The accuracy estimates for predicting the development of preeclampsia within 7 days for the cut-off of 38, and the clinical outcomes from the INSPIRE RCT (including the rates of hospital admissions within 24 hours)[32] were used in the base-case analysis for Elecsys immunoassay sFlt-1/PlGF ratio test. In this pragmatic trial, women presenting with suspected preeclampsia were randomized to management by sFlt-1/PlGF ratio test incorporated into standard clinical care versus standard clinical care alone.

The trial reported the number of women in the reveal and conceal arms who were admitted following clinical assessment (with or without PlGF testing). Treatment decision was based on a clinical management algorithm used in INSPIRE (shown in Figure 11, Appendix 8). The criteria for admission in the reveal arm were a high sFlt-1/PlGF ratio and blood pressure of more than 150/100. Admission was also considered if a woman had a high sFlt-1/PlGF ratio and blood pressure of less than149/99. In the conceal arm, the decision to admit was based on the NICE guideline CG107.[59] The proportion of women who would be managed on Stage 1 clinical pathway (see Figure 11, Appendix 8) was not reported in INSPIRE and, therefore, was approximated by outcomes reported in PreOS (another study of Elecsys). A scenario with an alternative assumption on the proportion of patients managed according to Stage 1 clinical pathway parameterised from PARROT was also conducted.

Outcomes from the PreOS study were used in another scenario analysis where the risk stratification part of the model was parameterised from the number of hospitalised women with the ratio of <33, from 33 to <85 and ≥85 before and after Elecsys test results were revealed (Klein 2016[79]).

BRAHMS sFlt-1 Kryptor / BRAHMS PlGF plus Kryptor PE ratio test

In the cost-comparison between BRAHMS and Elecsys, based on the assumption of equal predictive accuracy of these tests, the clinical effectiveness evidence was the same as for the Elecsys test – the INSPIRE RCT (Cerdeira 2019[32]) in the base-case (section 5.5.1) and PreOS (Klein 2016[79]) in a scenario analysis (section 5.5.2).

5.4.7.2 Resource use and costs

The following sections report resource use and cost parameters used in the model, including costs of PlGF tests, costs of the management of women with suspected pre-eclampsia, costs of delivery and the costs of maternal and/or neonatal morbidity. Resource use assumptions for costing diagnostic tests, management strategies and birth complications are presented in full below. They are based on companies' submissions, the NICE Hypertension in Pregnancy: The Management of Hypertensive Disorders During Pregnancy guideline CG107[59] and expert opinion.

5.4.7.3 Costs associated with PlGF-based tests

In this economic evaluation we assumed there is no cost associated with standard clinical assessment as this is a component of both the intervention and the comparator. We do, however, estimate the incremental cost of the PlGF-based tests. Test costs were estimated from information provided by the test manufacturers to NICE, and from clinical experts and laboratory staff who use the Triage PlGF test and Elecsys sFlt-1/PlGF ratio test in clinical practice. Where information was unavailable for certain cost items, we made reasonable assumptions to inform our cost estimates.

The estimation of the cost of the tests considered the following components:

- Cost of test kit (for Triage PlGF test and BRAHMS Kryptor sFlt-1/PlGF ratio test)
- Charge per reportable test, includes capital, maintenance and equipment costs (for Elecsys sFlt-1/PlGF ratio test)
- Machine costs
- Service charges and maintenance costs
- Equipment (laboratory materials and consumables)
- Staff time for training
- Staff time to perform and analyse test and staff time for quality control
- Phone calls to communicate test results

Time to test results is variable and depends on the hospital/laboratory which runs the test and the workload of these institutions at each moment. Our experts advised that it could be around 4 hours between collecting the blood tests until there is a result. However, the EAG

is not aware of any differences between the PlGF-based tests in terms of time to test results. As this is not likely to have a significant impact on the costs of tests, we have not considered it in our model.

More details on the assumptions used in the estimation of the tests are shown in Appendix 15. The cost components and the total cost of the PlGF tests are shown in Table 54.

Table 54 Cost components and total cost of PlGF tests used in the base case analysis

Cost component	Cost per test		
	Triage [a]	Elecsys [b]	BRAHMS [c]
Cost of test kit	£40		£22
Charge per reportable test [d]		£70	
Machines costs	£0.46		£0.003
Service charges and maintenance costs	£0.64		£0.003
Equipment (laboratory materials and consumables)	£1.92		£21.04
Staff time for training	£0.43	£0.43	£0.43
Staff time to perform and analyse test and staff time for quality control	£2.67	£5.33	£5.33
Phone calls to communicate test results	£3.47	£3.47	£3.47
Total	**£50**	**£79**	**£52**

Source: based on companies' submissions, expert opinion and assumptions
[a] Triage PlGF test.
[b] Elecsys sFlt-1/PlGF ratio test.
[c] BRAHMS Kryptor sFlt-1/PlGF ratio test
[d] Cost per reportable test including capital, maintenance, and equipment costs.

5.4.7.4 Resource use and costs associated with management of suspected pre-eclampsia

Where possible, we used data from PARROT[9] for the Triage PlGF test and data from INSPIRE[32] for the Elecsys sFlt-1/PlGF ratio test. For time to delivery, onset of delivery and mode of delivery parameters, we used data from PARROT[9] for both tests since no information were reported by the studies for the Elecsys sFlt-1/PlGF ratio test. For the remaining missing data, we have made some assumptions based on the inputs used in the previous DAR,[7] discussed below. For the BRAHMS Kryptor sFlt-1/PlGF ratio test, we assumed the same resource use and costs as for Elecsys sFlt-1/PlGF ratio test, with the exception of the cost of the test itself.

Resource use for management of women with suspected pre-eclampsia

The management of women with suspected pre-eclampsia is based on NICE CG107.[59] This guideline defines the management of pre-eclampsia and gestational hypertension and its associated resource use by hypertension category (mild, moderate or severe hypertension).

Table 55 shows the distribution of patients by hypertension category used in the model. The proportion of women with severe hypertension was reported by the RCTs (PARROT[9] and INSPIRE[32]). The authors from INSPIRE also provided some data on the [redacted] as a reply to a question sent by the EAG. We assumed that [redacted]. Then, we apportioned the remaining women for the mild and moderate levels of hypertension for Triage based on data from the study by Duckworth and colleagues.[98]

Table 55 Distribution of model patients by hypertension category

Category of hypertension		Intervention	Comparator	Source
Triage PlGF test				
Mild	PE	15%	15%	Duckworth and colleagues[98]
	No PE	25%	25%	Duckworth and colleagues[98]
Moderate	PE	43%	43%	Duckworth and colleagues[98]
	No PE	33%	33%	Duckworth and colleagues[98]
Severe	PE	42%	42%	PARROT[9]
	No PE	42%	42%	PARROT[9]
Elecsys sFlt-1/PlGF ratio test				
Mild	PE	[redacted]	[redacted]	INSPIRE[32]
	No PE	[redacted]	[redacted]	INSPIRE[32]
Moderate	PE	[redacted]	[redacted]	INSPIRE[32]
	No PE	[redacted]	[redacted]	INSPIRE[32]
Severe	PE	[redacted]	[redacted]	INSPIRE[32]
	No PE	[redacted]	[redacted]	INSPIRE[32]
PE, pre-eclampsia				

Women at high-risk of pre-eclampsia

We assumed that women identified as being at high-risk of pre-eclampsia (based on diagnostic accuracy data) could follow two pathways: expectant management (women <35 weeks of gestation and women >35 weeks of gestation and mild or moderate hypertension) or immediate delivery (women >35 weeks of gestation and severe hypertension). According to CG107,[59] immediate delivery is recommended for women with pre-eclampsia and severe hypertension after 34 weeks of gestation (after a course of corticosteroids has been

completed) and for women with pre-eclampsia and mild or moderate hypertension after 34 weeks of gestation in the presence of any maternal and fetal risk.

In accordance with CG107,[59] all women at high-risk of pre-eclampsia are admitted to hospital. To determine the length of stay for these women, the time to delivery from the PARROT trial[9] were used. Based on clinical guidelines,[59] women are expected to have varying lengths of monitoring according to their disease status and gestational age. Based on that evidence, we used time to delivery estimates from the PARROT trial to determine how long women are managed in each of the NICE CG107 pathways.

Table 56 presents our time to delivery assumptions depending on disease status, gestational age and risk of pre-eclampsia. The main difference between the two pathways in terms of resource use is the length of stay until delivery, i.e. 12 days in the intervention arm and 17 days in the comparator arm for women <36 weeks and 4 days and 8 days in intervention and comparator arms, respectively, for women between 35 and 37 weeks of gestation in expectant management.[9] For women in the immediate delivery pathway, birth occurred within 2 days after admission.[59]

Table 56 Time to delivery assumptions

Population group	Time to delivery			
	Up to 35 week		Between 35-37 weeks	
	Intervention	Comparator	Intervention	Comparator
High risk of pre-eclampsia				
Mild/moderate hypertension	12 days	17 days	4 days	8 days
Severe hypertension [a]			2 days	
Intermediate risk of pre-eclampsia				
Mild/moderate hypertension	26 days	27 days	13 days	11 days
Severe hypertension [a]			2 days	
Low risk of pre-eclampsia				
Mild/moderate hypertension	50 days	50 days	20 days	21 days
Severe hypertension [a]			2 days	

Source: based on PARROT study.[9]

[a] Assumption based on CG107.[59]

The other healthcare resources were assumed to be similar in the intervention and comparator arms and were based on the management of pre-eclampsia recommended in NICE CG107.[59] We assumed that women receive oral labetalol until delivery, in line with the previous Diagnostic Assessment Report.[7] NICE CG107[59] recommends the administration of corticosteroids for fetal lung maturation in women with pre-eclampsia between 24 and 36 weeks of gestation and a likely delivery within 7 days. Based on this, we assumed that all women with high-risk of pre-eclampsia receive corticosteroids for fetal lung maturation. Appendix 10 (Table 99) shows the recommended resource use to manage women at high-risk of pre-eclampsia for each hypertension category.

Women at intermediate- and low-risk of pre-eclampsia

The cost of management of women identified as being at intermediate or low risk of pre-eclampsia (based on predictive accuracy data) was based on the management of gestational hypertension recommended in NICE CG107.[59] We assumed that women at both intermediate and low risk of pre-eclampsia use the same healthcare resources but those at low-risk are managed for a longer period until delivery (
Table 56). The length of stay for women with severe hypertension was informed by the previous DAR.[7] Appendix 10 (Table 100) shows the recommended resource use to manage women at intermediate- and low-risk of pre-eclampsia for each hypertension category.

In a scenario analysis, we assumed that women were managed according to the recommendations of the most recent guideline NG133.[3] The changes in the assumptions were the following:

- Women managed with immediate delivery: women with high-risk of pre-eclampsia, >35 weeks of gestation and severe pre-eclampsia. The rate of severe pre-eclampsia was informed by the two RCTs.[32] [9]
- Women were categorized into two levels of hypertension instead of three: hypertension (<159/109 mmHg) and severe hypertension (>160/110 mmHg).
- For women managed according to the pre-eclampsia pathway, resource use for the hypertension group (<159/109 mmHg) was equal to the resource use for the mild hypertension group (<149/99 mmHg) considered for base case but includes the prescription of oral labetalol.
- For women manged according to the gestational hypertension pathway, resource use for the hypertension group (<159/109 mmHg) was similar to the resource use for the moderate hypertension group (<159/109 mmHg) considered for base case.

According to the previous Diagnostic Assessment Report,[7] the EAG decided not to model aspirin therapy. Clinical experts had previously advised us that during the time period of the model (20+0 until 36+6 weeks of gestation), women at high-risk of pre-eclampsia should have already be receiving aspirin and would not receive a new prescription during this time. Moreover, aspirin has a negligible unit cost which is not likely to impact the overall conclusions of this study.

Costs for managing women with suspected pre-eclampsia

We used the unit costs for resources from the National Schedule of Reference Costs 2018/19 for NHS Trusts and NHS Foundation Trusts,[150] NHS Payment by Results Tariff 2020/21[151] and the 2020 version of drugs and pharmaceutical electronic market information tool (eMIT) national database.[152] Appendix 13 (Table 104) presents the unit costs required for the NICE CG107 pathways.[59]

Payment by Results Tariffs were used for the cost of hospital stay because the data set more closely corresponds to the expected length of stay of the model population. The payment by results tariff assesses stays of 0-5 days and 0-9 days, and provides the costs for additional days.

The EAG assumed that the costs of blood pressure monitoring and dipstick proteinuria testing are included within the cost of a routine outpatient antenatal appointment as the cost for the tests are negligible. Similarly, for women managed in an inpatient setting, the cost of these tests is included within the cost of hospitalisation.

Table 57 shows the total costs incurred to manage women identified as being at high-, intermediate- and low-risk of pre-eclampsia split by hypertension status and gestational age, based on the NICE CG107 pathways[59] and the length of monitoring and resources described above. The total costs were calculated by multiplying the frequency of use of each resource component (as described in Table 99 and Table 100 of Appendix 10) by their unit costs (as presented in Table 104 of Appendix 13) and by the length of time those resources were used (as determined by time to delivery as shown in
Table 56). Hospitalisation costs were not multiplied by the length of management since they already capture the whole period of hospitalisation for each NICE CG107 pathway. Similarly, as fetal assessment and corticosteroids for fetal lung maturation were administered only once on average, its cost is not multiplied by the length of management.

For misdiagnosed patients (false positive and false negatives), we assumed that patients were managed as high-risk or intermediate-/low-risk for half the time to delivery and were managed as low-risk or high-risk, respectively, for the other half. In summary, we used an average of the costs from high- and low-risk groups for false positive patients and an average of the costs from intermediate-/low- and high-risk groups for false negative patients (Table 57).

Table 57 Total costs for managing women with high, intermediate and low risk of pre-eclampsia

Population group		Total cost			
		Up to 35 weeks		Between 35-37 weeks	
		Intervention	Comparator	Intervention	Comparator
High risk of pre-eclampsia					
PE (TP)	Mild hypertension	£3,714.65	£5,765.49	£892.72	£2,072.19
	Moderate hypertension	£3,733.10	£5,790.85	£902.71	£2,086.9
	Severe hypertension	£3,733.10	£5,790.85	£895.61	£895.61
No PE (FP)[a]	Mild hypertension	£2,109.28	£3,134.70	£587.34	£1,180.78
	Moderate hypertension	£2,318.38	£3,347.25	£672.81	£1,272.5
	Severe hypertension	£2,649.21	£3,678.08	£1,067.09	£1,074.69
Intermediate risk of pre-eclampsia					
PE (FN)[b]	Mild hypertension	£2,020.5	£3,049.62	£561.45	£1,143.78
	Moderate hypertension	£2,133.56	£3,170.02	£619.67	£1,196.58
	Severe hypertension	£2,464.39	£3,500.85	£1,013.95	£998.77
No PE (TN)	Mild hypertension	£326.35	£333.75	£230.18	£215.38
	Moderate hypertension	£534.01	£549.19	£336.63	£306.26
	Severe hypertension	£1,195.68[d]	£1,210.86[d]	£1,132.30[d]	£1,101.93[d]
Low risk of pre-eclampsia					
PE (FN)[c]	Mild hypertension	£2,109.28	£3,134.70	£587.34	£1,180.78
	Moderate hypertension	£2,318.38	£3,347.25	£672.81	£1,272.5
	Severe hypertension	£2,649.21	£3,678.08	£1,067.09	£1,074.69
	Mild hypertension	£503.91	£503.91	£281.96	£289.36

No PE (TN)	Moderate hypertension	£903.65	£903.65	£442.91	£458.10
	Severe hypertension	£1,565.32[d]	£1,565.32[d]	£1,238.58[e]	£1,253.76[e]

Time to deliveries based on data from the PARROT study [9].

[a] These were calculated as the average between high-risk and low-risk costs.

[b] These were calculated as the average between intermediate-risk and high-risk costs.

[c] These were calculated as the average between low-risk and high-risk costs.

[d] These were calculated as the moderate hypertension costs plus 3-day hospitalisation costs.

[e] These were calculated as the moderate hypertension costs plus 3-day hospitalisation costs plus fetal assessment costs.

FN, false negative; FP, false positive; PE, pre-eclampsia; TN, true negative; TP, true positive.

Resource use and costs associated with birth

The details of onset of labour (spontaneous, induced or caesarean) and mode of delivery (unassisted, assisted or emergency caesarean section) for women with pre-eclampsia or gestational hypertension come from the PARROT study. [15,9] Appendix 13 (Table 103) reports the probabilities of each type of delivery used in the model.

It was assumed that a proportion of women diagnosed with pre-eclampsia received treatment with intravenous magnesium sulphate at a loading dose of 4g as a bolus over 5-15 min followed by a maintenance dose of 1g per hour for at least 24 hours.[59] The proportion of patients taking magnesium sulphate was sourced from PARROT [9] and is also presented in Appendix 13 (Table 103).

The costs for the different types of deliveries were based on the *National Schedule of Reference Costs 2018/19 for NHS Trusts and NHS Foundation Trusts*[150] and are shown in Appendix 13 (Table 104). The cost of magnesium sulphate were sourced from the *British National Formulary* (accessed March 2021).[153] Administration costs were not modelled given that they were low and were likely to be accounted within the hospitalisation costs.

Resource use and costs associated with maternal and neonatal outcomes

Maternal and neonatal outcomes for the Triage PlGF test were informed by data from the PARROT study[9] and for the Elecsys sFlt-1/PlGF ratio test were informed by data from INSPIRE study[32] when available. For example, length of stay in special care baby units for Elecsys were informed by PARROT[9] since no data from INSPIRE or other studies assessing Elecsys were available. Where no data were available for Elecsys, we assumed there were no difference in outcomes between the intervention and comparator arms. None of the RCTs reported maternal death. [32 9]

The differences in the maternal outcomes were not reported directly by the RCTs, for women with and without pre-eclampsia. We considered that those with pre-eclampsia would have more adverse outcomes than those without. Therefore, we adjusted the proportion of women and babies with complications using a ratio of 3:1 for women with and without pre-eclampsia for the Triage PlGF test and 2:1 for the Elecsys sFlt-1/PlGF ratio test.

Maternal and neonatal outcomes for the Triage PlGF test

Appendix 13 (Table 103) shows the maternal and neonatal outcomes used in the model for the Triage PlGF test. We assumed that 29% of patients who were admitted to the neonatal unit were admitted to intensive care and high-dependency units and the remaining were admitted to the special care baby unit, as reported in the Phoenix study.[154]

Maternal and neonatal outcomes for the Elecsys sFlt-1/PlGF ratio test

The maternal severe/major complications for the Elecsys test were taken from INSPIRE[32] and includes pulmonary oedema, abruption and eclampsia. We assumed that each woman experienced only one of the adverse outcomes. Appendix 13 (Table 103) shows the parameters associated with maternal, fetal and neonatal outcomes used in the model for the Elecsys sFlt-1/PlGF ratio test. INSPIRE[32] reported the number of neonates admitted to the special care baby unit. However, it is not clear to the EAG if this refers to intensive care unit admissions. For the base case, we assumed that special care baby unit admissions were different from intensive care and high-dependency unit admissions. But given that there is some uncertainty regarding this terminology, we used the PARROT estimates as a scenario analysis. Again, we assumed that this corresponds to 71% of babies who were admitted and therefore the remaining 29% were admitted to intensive care and high-dependency units.[154]

Costs associated with maternal and neonatal complications

Mothers who did not experienced major complications were managed with standard post-natal care. The EAG considered that women and babies with severe outcomes were likely to be managed in maternal and neonatal intensive care units, neonatal high-dependency units or neonatal special care units. Therefore, we decided to only model the costs related with admission and stay in critical care units to capture the effects of maternal and neonatal morbidity (Appendix 13, Table 104). The unit cost of stay in neonatal intensive and high dependency care units were calculated as the average of intensive care unit and high dependency unit costs (Appendix 13, Table 104).

Long-term costs

We included the long-term costs associated with complications for neonates. A study by Khan and colleagues[155] estimated the costs for pre-term birth for the first two years of life compared to those born at full-term. For those babies born >37 weeks, all costs were incurred during the initial hospitalisation. We, therefore assumed a follow-up cost of zero for those born >37 weeks (without complications). For those born between 32-36 weeks, there were costs of £1037 (after inflating the costs to the year 2020 using the Hospital and Community Health Service Index[156]). For base case, we used this cost for those neonates with respiratory distress syndrome while we assumed that this cost will be applied to all admitted neonates as a scenario analysis. For the costs of babies born with intraventricular hemorrhage, we assumed the lifetime costs to be the same as for cerebral palsy, as used by Varley-Campbell.[157] Kruse and colleagues[158] estimated lifetime costs for cerebral palsy for the year 2000 in a Danish population. They discounted costs using a discount rate of 5% per annum. We converted the lifetime costs to pounds and inflated the costs to 2020, to give a lifetime cost of £93,251.

In accordance with Varley-Campbell,[157] we assumed that the costs after two years would be the same for those born pre-term without intraventricular haemorrhage and those born full-term.

5.4.7.5 Utilities

Of the five studies in our review of HRQoL studies (5.1.6 *Results of the review of HRQoL studies)* only one study (Seppänen and colleagues)[107] provided better utility estimates, in our judgement, than those used in the previous DAR.[7] The study by Seppänen and colleagues[107] provides evidence for a decrement in utility for women admitted to an intensive care unit due to pregnancy complications.

The studies identified suggest that women largely recovered to pre-pregnancy HRQoL scores by six months post-partum. We model short-term HRQoL outcomes until six months post-partum, and longer-term HRQoL outcomes beyond 6 months (described in more detail below).

Women who were misdiagnosed as high-risk of pre-eclampsia were assumed to be likely to experience anxiety related to the positive result and admission to hospital. We assumed that the utility decrement for these women was similar to that reported by a study by Prosser and colleagues[159] who assessed the HRQoL losses perceived by parents due to a false positive result obtained within a newborn screening programs of metabolic disorders. We used the utility decrement related to hospitalisation of newborns due to false positive results reported

in this study (0.028) in our model to account for women with false positive results. This disutility was applied for the time period between admission and delivery (see Appendix 13, Table 105). We assumed this period was 8 days for the intervention and 12.5 days for the comparator (calculated as the average time to delivery of women before and after 35 weeks). For women managed with immediate delivery, we considered a time to delivery of 2 days. This decrement should be interpreted with caution since the participants in the study by Prosser and colleagues[159] were interviewed 6 months after the resolution of the false positive results and consequently may not have fully captured the stress and anxiety experienced during the waiting period. Moreover, study samples were small and geographically limited. The method used was time-trade off and there were potential biases inherent to the use of parent proxies.

Appendix 13 (Table 105) shows the utility scores used in the EAG economic model for the short-term HRQoL. All of them, except for the decrements for women and babies admitted to an intensive care unit and women with false positive results, were used in the previous DAR.[7] Based on the results from Seppänen and colleagues,[107] we assumed a decrement of 0.039 in HRQoL for women admitted to an intensive care unit. We assumed that after six weeks post-partum women who were admitted to intensive care unit would have the same HRQoL as those women not admitted to the intensive care unit as they are expected to have mostly recovered from adverse effects (as reported in Bijlenga et al.[144]). We assume that the utility decrement would decline in a linear manner over this time period. We also used this disutility for babies admitted to critical care units.

QALYs were calculated by multiplying the utility scores and decrements by the time spent in each health state.

5.4.7.6 Long-term estimation of QALYs in children

QALYs in neonates accrued up to hospital discharge are estimated from perinatal deaths and neonatal unit admissions. Zero QALYs are assumed for miscarriage and stillbirth. When estimating long-term QALYs for babies born alive, we considered the risk of being born preterm, and the risks of respiratory distress syndrome and intraventricular haemorrhage. As the proportion of babies born at different gestational ages was not reported in PARROT,[9] we consider respiratory distress syndrome and intraventricular haemorrhage to be a proxy for preterm birth.

In PARROT,[9] there was a high prevalence of respiratory distress syndrome requiring neonatal unit admission among babies with a PlGF < 12 pg/ml. However, the proportion of babies with RDS was slightly higher in the reveal arm (13.8%) versus conceal arm (12.2%). The proportion of babies reported in PARROT with intraventricular haemorrhage was 1.2% in the reveal arm and 2.5% in the conceal arm. More details on the incidence of these adverse effects per level of risk of pre-eclampsia in Appendix 13 (Table 103). INSPIRE[32] does not report on these outcomes nor any other study that assessed the Elecsys sFlt-1/PlGF ratio test.

Varley-Campbell and colleagues[157] estimated total discounted QALY loss for children for respiratory distress syndrome and intraventricular haemorrhage compared to preterm survivors. They used survival from ONS life tables,[160] used age-related disutilities from Ara and Brazier[161] and discounted at 3.5% per annum. For RDS and IVH they used lower utilities of 0.85 and 0.76 respectively. They considered that those with less severe respiratory distress syndrome and intraventricular haemorrhage would not have a QALY loss and assumed that the proportion with less severe was 44% for RDS and 70% for IVH. Using this assumption, the total discounted QALY loss for respiratory distress syndrome was 0.41 and for intraventricular haemorrhage was 0.91.

We also included the total discounted QALY loss associated with neonate mortality, which was estimated to be 24.7 QALYs. We calculated this by assuming a life expectancy of 80 years, using the age related disutilities from Ara and Brazier[161] and discounting at 3.5% per annum.

5.4.7.7 Long-term estimation of QALYs in mothers

The longer-term HRQoL of mothers of children with and without adverse child outcomes are also taken from Varley-Campbell and colleagues.[157] The estimates are derived assuming the average age at birth of 30 years (as reported in ONS 2015, [160]). Varley-Campbell and colleagues estimated the average discounted QALYs to be 17.42 for mothers whose child survived. For mothers whose child died, they either assumed that that the mother suffered an adverse outcome utility for her remaining lifetime (total QALYs 13.45) or the mother suffers the adverse pregnancy outcome for 10 years and then revert to the utility for no previous adverse pregnancy outcomes (total QALYs 15.94). The utility assumed for mothers with no adverse child outcome was 0.834 and with an adverse child outcome was 0.644.[157] We assume the average lifetime discounted QALYs of 13.45 for in the base case for loss of child, and 15.94 in a scenario analysis. We assumed that there would be a loss of quality of life for mother for children who had respiratory distress syndrome or intraventricular

haemorrhage of two years in the base case (i.e. total QALY of 17.05) and 10 years in a scenario analysis. These estimates are applied after 6 months post-partum.

Appendix 13 (Table 105) shows the long-term QALYs used in the EAG economic model.

5.5 Results of the External Assessment Group (EAG) independent economic evaluation

5.5.1 Base-case analysis

The assumptions made in the base-case analysis are outlined below and further described in Table 101 (Appendix 11):

- The population enters the model after a clinical examination with or without PlGF-based testing.
- Decisions on treatment are driven by the test result and clinical judgement.
- False positive results have an impact on quality-of-life of women who are misdiagnosed.
- Women with pre-eclampsia are at higher risk of major complications.
- New-borns of mothers with pre-eclampsia are at a higher risk of respiratory distress syndrome, intraventricular hemorrhage, and intensive care unit admission.
- Complications in neonates have an impact on quality of life of children and their mothers.
- Respiratory distress syndrome and intraventricular haemorrhage result in longer-term costs.

This section reports the cost-effectiveness results for women presenting for assessment of suspected pre-eclampsia between 20+0 and 36+6 weeks of gestation, using the PlGF-based tests in addition to standard clinical assessment as compared with standard clinical assessment alone.

5.5.1.1 Cost-effectiveness results for the Triage PlGF test

The cost-effectiveness results for Triage PlGF test versus standard clinical assessment are presented in Table 58. In the base case, total costs are £11,305 for the Triage PlGF test and £13,051 for standard clinical assessment. Total QALYs are 17.20 for the Triage PlGF test and 16.99 for standard clinical assessment. The strategy including the test yields a cost reduction of £1,746 and a QALY gain of 0.204. The base case results indicate that using the

Triage PlGF test in the assessment of pre-eclampsia is more effective and less expensive when compared to standard clinical assessment. The breakdown results are presented in Table 59. The main drivers of the base case results are the long-term costs and QALYs. The rate and costs of neonatal care have a large impact in the results as well.

Table 58 Base-case: results for Triage PlGF test

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Standard assessment	£13,051	16.99			
Triage PlGF test	£11,305	17.20	-£1,746	0.204	Dominant
QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio					

Table 59 Base-case: breakdown results for Triage PlGF test

Components	Triage PlGF test	Standard assessment	Incremental
Costs			
First testing	£50	£0	£50
Management	£1,561	£1,791	-£230
Delivery	£3,880	£3,740	£140
Maternal care	£370	£410	-£40
Neonatal care	£3,969	£4,661	-£692
Neonatal care - long term	£1,476	£2,450	-£974
Total	£11,305	£13,051	-£1,746
QALYs			
Management	0.0000	-0.0001	0.0000
Delivery	0.0348	0.0353	-0.0005
Maternal - short term	0.3841	0.3840	0.0000
Neonatal - short term	-0.0007	-0.0007	0.0000
Maternal - long term	17.2887	17.2668	0.0219
Neonatal - long term	-0.5107	-0.6936	0.1829
Total	17.1961	16.9918	0.2043
QALYs, quality-adjusted life-years			

5.5.1.2 Cost-effectiveness results for the Elecsys sFlt-1/PlGF ratio test

The cost-effectiveness results for the Elecsys sFlt-1/PlGF ratio test versus standard clinical assessment are presented in Table 60. In the base case, total costs vary between £10,942

for the Elecsys sFlt-1/PlGF ratio test and £10,321 for standard clinical assessment. Total QALYs vary between 17.03 for the Elecsys sFlt-1/PlGF ratio test and 17.17 for standard clinical assessment. The strategy including the test is more expensive (+£621) and produces less QALYs (-0.140) than standard clinical assessment. The breakdown results are presented in Table 61. The main drivers are again the long-term costs and QALYs and also the costs of neonatal care. For the long-term outcomes (child death, respiratory distress syndrome and intraventricular haemorrhage), it was assumed that there is no difference between the intervention and comparator arms (see section 5.4.7.5). A possible explanation for the incremental costs and QALYs can be the higher prevalence of women with pre-eclampsia and also higher number of women categorised as high-risk of pre-eclampsia in the Elecsys sFlt-1/PlGF ratio test arm, which are more costly and also incur high loss in QALYs.

Table 60 Base-case: results for the Elecsys sFlt-1/PlGF ratio test

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Standard assessment	£10,321	17.17			
Elecsys sFlt-1/PlGF ratio test	£10,942	17.03	£621	-0.140	Dominated
QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio					

Table 61 Base-case: breakdown results for Elecsys sFlt-1/PlGF ratio test

Components	Elecsys sFlt-1/PlGF ratio test	Standard assessment	Incremental
Costs			
First testing	£79	£0	£79
Retesting	£0	£0	£0
Management	£1,185	£1,492	-£308
Delivery	£3,912	£3,751	£161
Maternal care	£299	£344	-£45
Neonatal care	£2,935	£2,679	£256
Neonatal care - long term	£2,532	£2,055	£477
Total:	£10,942	£10,321	£621
QALYs			
Management	-0.0001	-0.0002	0.0001

Components	Elecsys sFlt-1/PlGF ratio test	Standard assessment	Incremental
Delivery	0.0347	0.0353	-0.0006
Maternal - short term	0.3841	0.3841	0.0000
Neonatal - short term	-0.0006	-0.0004	-0.0001
Maternal - long term	17.2630	17.2896	-0.0267
Neonatal - long term	-0.6485	-0.5356	-0.1129
Total:	17.0325	17.1728	-0.1402
QALYs, quality-adjusted life-years			

5.5.1.3 Cost-effectiveness results for BRAHMS Kryptor sFlt-1/PlGF ratio test

The cost-effectiveness results for BRAHMS Kryptor sFlt-1/PlGF ratio test versus standard clinical assessment are presented in Table 62. Those are assumed to be similar to the results for Elecsys sFlt-1/PlGF ratio test, with the only difference being the cost of the test itself which leads to a total cost of £10,915 for the BRAHMS Kryptor sFlt-1/PlGF ratio test. Total QALYs are the same as the ones reported for Elecsys sFlt-1/PlGF ratio test. Therefore, the strategy including the test is more expensive (+£594) and produces less QALYs (-0.14) than standard clinical assessment. The breakdown results are presented in Table 63.

Table 62 Base-case: results for BRAHMS Kryptor sFlt-1/PlGF ratio test

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Standard assessment	£10,321	17.17			
BRAHMS ratio test (ThermoFisher)	£10,915	17.03	£594	-0.14	Dominated
QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio					

Table 63 Base-case: breakdown results for BRAHMS Kryptor sFlt-1/PlGF ratio test

Components	Elecsys sFlt-1/PlGF ratio test	Standard assessment	Incremental
Costs			
First testing	£52	£0	£52
Retesting	£0	£0	£0
Management	£1,185	£1,492	-£308
Delivery	£3,912	£3,751	£161
Maternal care	£299	£344	-£45

Components	Elecsys sFlt-1/PlGF ratio test	Standard assessment	Incremental
Neonatal care	£2,935	£2,679	£256
Neonatal care - long term	£2,532	£2,055	£477
Total:	£10,915	£10,321	£594
QALYs			
Management	-0.0001	-0.0002	0.0001
Delivery	0.0347	0.0353	-0.0006
Maternal - short term	0.3841	0.3841	0.0000
Neonatal - short term	-0.0006	-0.0004	-0.0001
Maternal - long term	17.2630	17.2896	-0.0267
Neonatal - long term	-0.6485	-0.5356	-0.1129
Total:	17.0325	17.1728	-0.1402
QALYs, quality-adjusted life-years			

5.5.2 Sensitivity analyses

This section provides an overview of how uncertainties associated with test diagnostic accuracy, costs and utilities was incorporated into the decision analysis.

5.5.2.1 Scenario analyses

The following scenario analyses were performed:

- **Alternative study sources of test accuracy data:** MAPPLE/PELICAN for Triage and PreOS for Elecsys
    - **Inputs from MAPPLE/PELICAN**: we used inputs from the MAPPLE/PELICAN[16] trials where available (including time to delivery, maternal outcomes and neonatal incidence of respiratory distress syndrome and intraventricular hemorrhage). We applied this scenario to the Triage PlGF test arm only.
    - **Inputs from PreOS**: we used inputs from the PreOS[34] trial where available. We applied this scenario to the Elecsys sFlt-1/PlGF ratio test arm only.
- **Cost of PlGF-based tests**: the EAG explored the uncertainty around the main assumptions of the cost of tests. Here we present the assumptions corresponding to the minimum and maximum cost per test only. These are (1) using the price of test kits only (see Appendix 13) and (2) using the cost reported in Duhig and colleagues[99] for Triage PlGF test (£70), the cost suggested by one of the experts advising EAG for

Elecsys sFlt-1/PlGF ratio test (£110) and an increase of 20% for the BRAHMS Kryptor sFlt-1/PlGF ratio test (£70).

- **Time horizon**: we tested the impact of a shorter time horizon of up to 6 months post-partum, i.e. excluding longer-term costs and outcomes.
- **Management of women with suspected pre-eclampsia**: this scenario explored the management of women with suspected pre-eclampsia following the recommendations stated in NG133.[3]
- **Level of hypertension**: we assumed that 70% of patients in the high-risk of pre-eclampsia group and 30% of patients in the low-risk group has severe hypertension.
- **Gestational age <35 weeks**: the EAG explored the impact of extreme assumptions (0% and 100%) on the proportion of women with a gestational age <35 weeks.
- **Time to delivery**: we used time to delivery estimates from PROGNOSIS[36] for the Elecsys sFlt-1/PlGF ratio test.
- **Immediate delivery**: we assumed that women managed in the immediate delivery pathway have a time to delivery of 24 hours.
- **Neonatal admission to critical care units**: the EAG used the estimates from PARROT[9] for both Triage PlGF test and Elecsys sFlt-1/PlGF ratio test.
- **Long-term costs**: we assumed that the costs of pre-term birth (babies born between 32-37 weeks of gestation) were applied to all babies admitted to critical care units with the exception of babies with intraventricular hemorrhage for which we are using a different cost.
- **QALYs for mothers whose child died**: decrement applied for 10 years
- **QALYs for mothers whose child had complications**: decrement applied for 10 years.
- **Death in neonates**: excluding stillbirth

The model inputs for the scenario analyses are listed in Appendix 14.

Scenario analyses for the Triage PlGF test

The cost-effectiveness results for Triage PlGF test versus standard clinical assessment based on MAPPLE/PELICAN[16] inputs are presented in Table 64. Replacing the estimates from PARROT[9] and using the inputs from MAPPLE/PELICAN[16] (where available) does not change the overall conclusions. Triage PlGF test is less expensive and yields more QALYs when compared to standard clinical assessment.

Table 64 Scenario analysis (MAPPLE/PELICAN): results for Triage PlGF test

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Standard assessment	£12,626	16.79			
Triage PlGF test	£12,254	17.05	-£372	0.26	Dominant
QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio					

The diagnostic strategy including the Triage PlGF test is less expensive and yields more QALYs than the standard clinical assessment in all the scenarios except two – when the time horizon is changed to 6 months post-partum and when stillbirth is excluded (Table 65).

In the first scenario, long-term costs and QALYs are not considered. The Triage PlGF test still shows a cost reduction (-£772) but also produces slightly lower QALYs (-0.0005), although the difference is negligible. This indicates that using Triage PlGF test is likely to reduce severe complications with long-term durations which consequences cannot be captured in a shorter time horizon.

In the second scenario, we excluded the impact of stillbirth when modelling the impact of child death on overall costs and quality of life of mothers. The ICER for this scenario (£91,557 per QALY) is located in the south-west quadrant of the cost-effectiveness plane, which indicates that adding the Triage test to current clinical management would be cost-saving but it would also result in lower QALYs when compared to current clinical management alone.

The other scenarios did not change the results qualitatively, i.e. PlGF testing remains a dominant strategy.

Table 65 Scenario analyses: results for Triage PlGF test

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY) vs. standard assessment
Base case	**-£1,746**	**0.204**	**Dominant**
Time horizon: 6 months post-partum	-£772	-0.0005	£1,698,809
Management of women with suspected PE: NG133	-£1,738	0.204	Dominant
Level of hypertension: stratified by level of risk of PE	-£1,739	0.204	Dominant

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY) vs. standard assessment
Base case	**-£1,746**	**0.204**	**Dominant**
Gestational age <35 weeks: 0%	-£1,680	0.204	Dominant
Gestational age <35 weeks: 100%	-£1,964	0.204	Dominant
Immediate delivery: up to 24 hours	-£1,746	0.204	Dominant
Death in neonates: excluding stillbirth	-£1,652	-0.018	£91,557
Cost of testing: low value	-£1,755	0.204	Dominant
Cost of testing: high value	-£1,725	0.204	Dominant
Long-term costs: cost of pre-term babies applied to all admitted neonates	-£1,756	0.204	Dominant
QALY decrement for mothers whose child died: applied for 10 years	-£1,746	0.1855	Dominant
QALY decrement for mothers whose child had complications: applied for 10 years	-£1,746	0.1776	Dominant
NG133, NICE Guideline 133; PE, pre-eclampsia; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio			

Scenario analyses for Elecsys sFlt-1/PlGF ratio test

The cost-effectiveness results for Elecsys sFlt-1/PlGF ratio test versus standard clinical assessment based on PreOS[34] inputs are presented in Table 66. Using the inputs from PreOS[34] (where available) has a significant impact on the results. In contrast to the base case results, the Elecsys sFlt-1/PlGF ratio test produces lower costs (-£595) than standard clinical assessment. This is mainly driven by savings in the neonatal costs, both short- and long-term, compared to base case. Moreover, the difference in QALYs is negligible as there are no differences between arms related with long-term outcomes. As stated in the previous DAR,[7] given that the utility data, particularly the short-term utility data, have a high degree of uncertainty as a result of being derived from mapping from SF-36, the differences in HRQoL are not likely to be clinically significant.

Table 66 Scenario analysis (PreOS): results for Elecsys sFlt-1/PlGF ratio test

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Standard assessment	£9,378	17.34			
Elecsys sFlt-1/PlGF ratio test	£8,783	17.34	-£595	-0.0006	£1,081,112

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio					

The Elecsys sFlt-1/PlGF ratio test is more expensive and produces fewer QALYs than standard clinical assessment in all the scenarios presented below (Table 67).

Table 67 Scenario analyses: results for Elecsys sFlt-1/PlGF ratio test

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY) vs. standard assessment
Base case	**£621**	**-0.1402**	**Dominated**
Time horizon: 6 months post-partum	£144	-0.0007	Dominated
Management of women with suspected PE: NG133	£686	-0.1402	Dominated
Level of hypertension: stratified by level of risk of PE	£677	-0.1402	Dominated
Gestational age <35 weeks: 0%	£685	-0.1402	Dominated
Gestational age <35 weeks: 100%	£575	-0.1402	Dominated
Time to delivery: based on PROGNOSIS	£620	-0.1403	Dominated
Immediate delivery: up to 24 hours	£621	-0.1402	Dominated
Neonatal admission to critical care units: based on PARROT	£305	-0.1402	Dominated
Death in neonates: excluding stillbirth	£621	-0.0565	Dominated
Cost of testing: low value	£608	-0.1402	Dominated
Cost of testing: high value	£652	-0.1402	Dominated
Long-term costs: cost of pre-term babies applied to all admitted neonates	£655	-0.1402	Dominated
QALY decrement for mothers whose child died: applied for 10 years	£621	-0.1303	Dominated
QALY decrement for mothers whose child had complications: applied for 10 years	£621	-0.1762	Dominated
NG133, NICE Guideline 133; PE, pre-eclampsia; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio			

5.5.2.2 One-way deterministic sensitivity analysis

We produced tornado diagrams for the Triage and the Elecsys tests to illustrate parameters with the greatest sensitivity to variation in estimates. For model parameters such as rates or proportions, the parameter value for the comparator arm was changed by 10% absolute differential value to find lower and upper bounds. If parameter values were the same in both arms, the parameter in the comparator arm was varied by 10%. The same percentage was used to estimate lower and upper bounds for utilities. In the one-way sensitivity analysis for the Triage test, the proportion of women in the comparator arm hospitalised after the first assessment was varied by 20% absolute differential value.

A Tornado diagram of the net monetary benefit of Triage versus standard clinical assessment is shown in Figure 8 and Tornado for Elecsys in Figure 9.

The cost effectiveness results for the Triage test are most sensitive to variation in the decrement due to child death and the incidence of neonatal death. Less influential are parameters such as the length of stay in ICU/HDU, the incidence of RDS and IVH, and the decrement for mothers whose child died.

The variation in the incidence of neonatal death has the most impact on the NMB of Elecsys, followed by the decrement due to child death, and the incidence of RDS and IVH. Variation in the other parameters appear to have no discernible influence on the results.

An one-way sensitivity analysis for the BRAHMS test has not been conducted because the most influential parameters for this test are likely to be the same as those identified in the one-way sensitivity analysis for Elecsys.

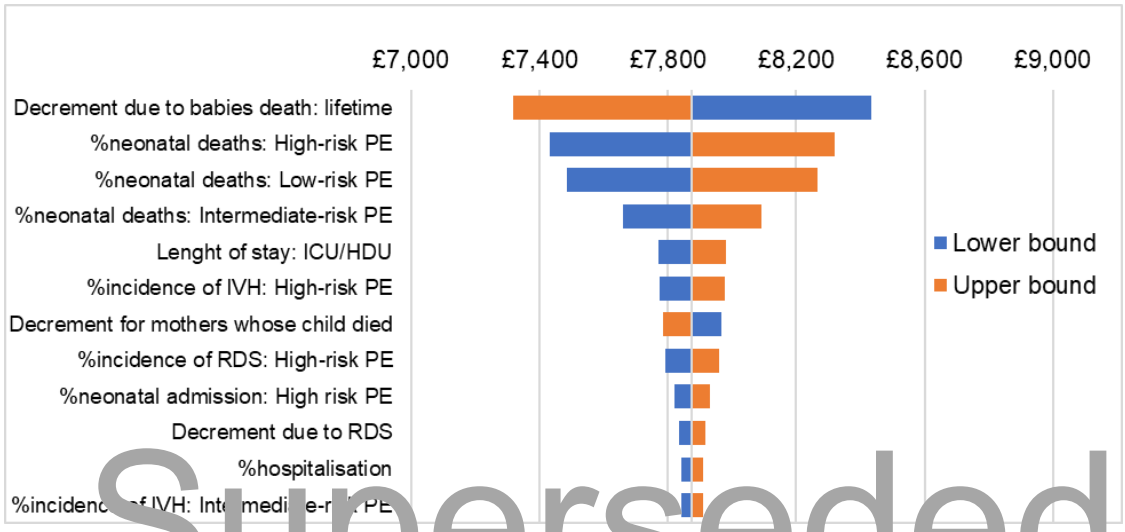


Figure 8 Tornado diagram: Net monetary benefit of Triage PlGF test versus standard clinical assessment

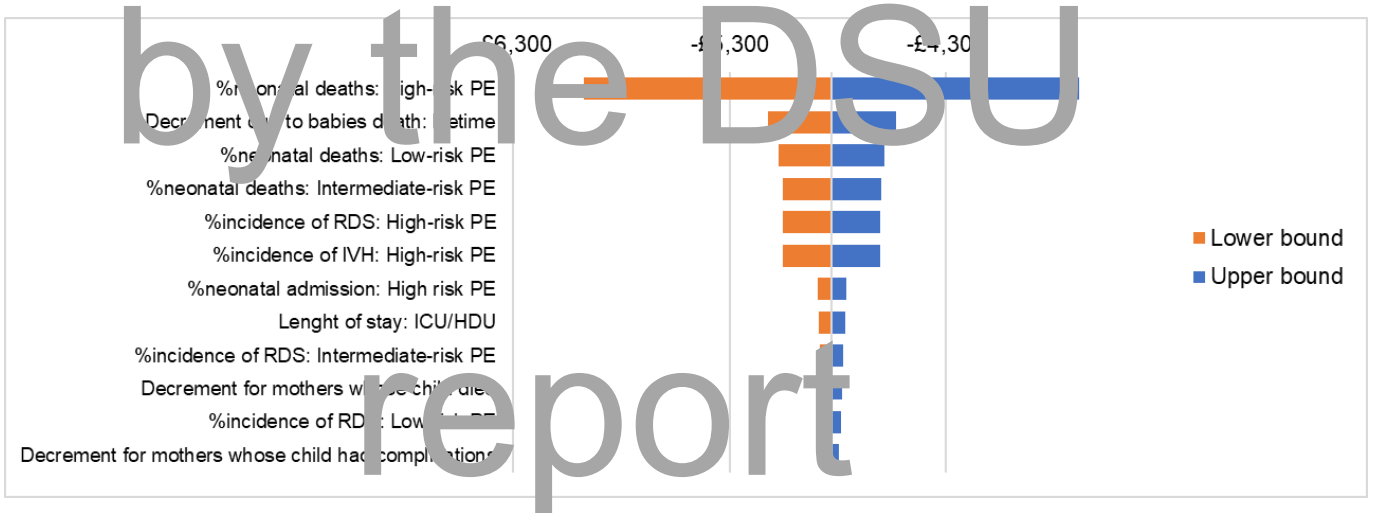


Figure 9 Tornado diagram: Net monetary benefit of Elecsys sFlt-1/PlGF ratio test versus standard clinical assessment

5.5.2.3 Comparison with the results of other economic evaluations

None of the studies in our review of cost-effectiveness searches included long-term costs and QALYs. For the Triage test, Duckworth and colleagues[98] reported a cost saving per woman tested of £635 and Duhig and colleagues[99] reported a cost saving of £149 per woman tested. We estimated a similar saving of £692 per woman tested for the time period to hospital discharge. For the Elecsys test, comparison is more difficult as the studies in our

review used the PROGNOSIS study which reports different results to the INSPIRE study used in our analysis. In particular, the PROGNOSIS study reported a reduction in hospitalisation of 56% for the test arm versus the no test arm (Vatish and colleagues[106]), whereas in the INSPIRE study the hospitalisation rate was higher in the reveal arm (39%) than the non-reveal arm (32%).

6 ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

The practical considerations when conducting the PlGF-based tests highlighted to us by our clinical experts were as follows:

- There are potential implications of adopting new biomarker tests on neonatal unit workload.
- More time for quality assurance per test would be necessary when tests are performed at the point of care.
- Use of different PlGF test platforms in the same maternity unit may cause problems with interpretation of results and the application of appropriate clinical care. Clear protocols would be required to avoid such problems. A standardised interpretation of biomarker concentrations across different tests would be helpful.
- Preference for use of a particular test might depend on existing laboratory facilities, e.g. if the laboratory use the Roche automated analyser system, it is easier to incorporate the Elecsys test than that of another manufacturer.
- Point of care tests (Triage) are not necessarily used at the point of care and samples may be sent to another laboratory for processing.

7 DISCUSSION

7.1 Statement of principal findings

7.1.1 Test accuracy and clinical effectiveness

This update of our previous DAR identified several new studies assessing the diagnostic/prognostic accuracy of PlGF-based tests for suspected pre-eclampsia published in the five-year intervening period. We included a total of 17 studies in this update review of test accuracy and clinical outcomes, compared to just four studies included in the original DAR, suggesting increased scientific and professional interest in the use of PlGF-based testing for suspected pre-eclampsia. Furthermore, we are aware of several relevant on-going

studies whose results, when available, are likely to have significant implications for clinical practice in England and the UK (see Appendix 6).

The research agenda for the clinical use of biomarker tests also appears to be broadening, with recent studies designed to incorporate 'real world' clinical care protocols and to measure longer-term clinical outcomes Thus, we now have a more 'end to end' evidence base for PlGF tests, incorporating test accuracy, effects on care decisions and overall impact on morbidity and mortality. This update DAR, therefore, has drawn upon a more comprehensive, rigorous and certain evidence base than its predecessor.

Most of the published evidence available is on the Triage PlGF test and the Elecsys sFlt-1/PlGF ratio. Notably, the PARROT and INSPIRE randomised trials provide rigorous evidence linking the use of the tests in real world practice settings to a range of clinically relevant maternal, fetal, perinatal and neonatal clinical outcomes. These two studies are of sufficient scientific standard to inform decision making in this appraisal.

The findings of both trials were mixed in terms of the extent to which the interventions evaluated were clinically effective. For example, the Triage PlGF test, used alongside standard clinical management (results revealed), was associated with a marked reduction in time to diagnosis of pre-eclampsia (64%); a lower odds of a maternal adverse outcomes (68%) and a non-statistically significant increase in time to delivery. However, there were no differences between revealed and concealed testing arms for outcomes including rates of pre-term delivery (< 37 weeks), gestation at delivery and perinatal and neonatal outcomes.

There was no statistically significant difference between the trial arms in preeclampsia-related hospital admissions within 24 hours of the test, the primary outcome. However, 100% of participants in the reveal arm admitted were correctly diagnosed with pre-eclampsia, versus 83% in the concealed trial arm. Thus, the authors consider that this test can increase the proportion of high risk patients admitted without influencing the admission rate itself. A post-hoc analysis showed there was no statistically significant difference between the trial arms in the time to the pre-eclampsia diagnosis. There were no statistically significant differences between trial arms for many of the secondary clinical outcome measures. The authors recommend larger studies of the Elecsys test to evaluate its potential in reducing adverse outcomes.

There may be a number of potential explanations for the limited clinical effectiveness impact in the studies of these two tests, one of which might be that the pragmatic 'real world' design

and implementation of these interventions produce the level of effects that would be typically seen in clinical practice (in contrast to greater levels of efficacy expected in a highly protocol driven and patient selective clinical trial).

Despite advancements in the evidence base for the tests, as described above, some notable evidence gaps and uncertainties remain. For example, having recommended the use of the Triage PlGF test and the Elecsys immunoassay sFlt-1/PlGF ratio alongside standard clinical assessment for *ruling out* suspected pre-eclampsia, NICE DG23 recommended further research be done to establish the accuracy of these tests at *ruling-in* pre-eclampsia, specifically on how this affects management decisions on time to delivery and consequent outcomes. The evidence on test performance for ruling-in pre-eclampsia available for this update DAR is limited in both volume and relevance. The PARROT trial assessed test performance for the Triage PlGF <12 pg/mL cut off (rule-in), however, results were only reported for the trial arm in which PlGF test results were concealed from the treating clinician. This information is of only partial relevance to this appraisal. The INSPIRE trial did not report test accuracy at cut off values suggestive of pre-eclampsia diagnosis (i.e. rule-in). We note, however, that PPVs of 0.714 and 0.720 were reported in the revealed and concealed arms of INSPIRE respectively, when a higher cut-off of 85 was applied to predict (rule-in) pre-eclampsia within 4 weeks.

Other research recommendations in NICE DG23 have not been addressed at the current time, including research on the diagnostic accuracy and analytical validity of the DELFIA Xpress PlGF 1-2-3 test and BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio. We identified very limited evidence on both these tests. Similarly, research on the use of repeat PlGF-based testing for suspected pre-eclampsia is lacking, with only one such study included in this review.

7.1.2 Cost-effectiveness

We developed a cost-effectiveness model to assess the cost-effectiveness of PLGF-based tests used alongside standard clinical assessment to help diagnose pre-eclampsia and inform decisions on subsequent care. The model was similar in design to the model which informed NICE's 2016 guidance on PlGF-based testing in suspected pre-eclampsia (DG23).[6] The current model, however, differs from the original[7] by adopting a lifetime time horizon and an assessment of the long-term impact on maternal and neonatal outcomes from PlGF-based testing and associated care.

The base-case analysis of the Triage PlGF test, based on the PARROT trial, estimates that use of this test alongside standard clinical assessment is cost saving compared to standard clinical assessment without PlGF testing, with a saving of £1,746 per woman, including the costs of short- and long-term neonatal care. There was an increase in QALYs of 0.204 per woman, which also accounts for QALY loss in neonates from adverse outcomes related to suspected pre-eclampsia.

The base-case analysis of the Elecsys sFlt-1/PlGF ratio test, based on the INSPIRE trial, suggests that standard clinical assessment without testing dominates use of testing alongside standard clinical assessment (i.e. it is less costly and more effective). However, the results of this analysis are less certain due to lack of relevant data for certain outcomes. For example, the INSPIRE trial did not report clinical outcomes which appear to be key drivers of modelled cost effectiveness (e.g. neonatal death, and incidence of RDS and IVH). As a substitute we therefore used the same estimates for these outcomes from the PARROT trial (the Triage PlGF test) in the model for Elecsys sFlt-1/PlGF ratio test. The model estimates that addition of the Elecsys sFlt-1/PlGF ratio test to standard clinical assessment would increase the cost per woman by £621 and lead to a reduction in QALYs of 0.140.

The cost-effectiveness results for the Triage test are most sensitive to variation in the utility decrement due to child death and incidence of neonatal death. The results for the Elecsys test are driven by the incidence of neonatal death, the utility decrement due to child death, and the incidence of RDS and IVH.

The results of the cost-comparison analysis of the BRAHMS Kryptor sFlt-1/PlGF ratio, based on the assumption of equal predictive accuracy to that of the Elecsys sFlt-1/PlGF ratio test,[47] were the same as for the cost-effectiveness analysis of the Elecsys test, that is, standard clinical assessment alone dominates use of testing alongside standard clinical assessment.

7.2 Strengths and limitations of the assessment

7.2.1 Strengths

Since the previous DAR, more data has been published on the maternal outcomes and neonatal outcomes from RCTs of the Triage and Elecsys PlGF tests (PARROT and INSPIRE). This has enabled the time from assessment to hospital discharge to be modelled from a single source. In addition, we included long-term impact relating to the neonatal adverse outcomes.

Although the clinical effectiveness studies did not report maternal and neonatal outcomes for 20^{+0} – 34^{+6} and 35^{+0} – 37^{+6} subgroups of interest in the NICE scope, a subgroup analysis for the Triage test was possible based on data from the MAPPLE and PELICAN studies, which considered patients with gestational age of less than 35 weeks.

7.2.2 Limitations

It was not possible to meta-analyse the test accuracy and clinical effectiveness studies due to notable heterogeneity in study designs, scope and outcome measures.

A fully incremental cost effectiveness analysis of the four PlGF tests relevant to the decision problem was not possible, due to the lack of data for because of available clinical effectiveness data limitations for the BRAHMS Kryptor sFlt-1/PlGF ratio and the BRAHMS Kryptor sFlt-1/PlGF ratio.

It was not possible to compare the performance of the Triage and Elecsys tetsts directly because the clinical effectiveness evidence for these tests came from different studies. For the BRAHMS test we assumed similar effectiveness as for Elecsys based on Salahuddin et al.[47] and the overall costs for these tests were assumed to be the same except for the cost of testing. This analysis, however, is subject to uncertainty due to the context of the ROPE cohort study[45] which has the same caveats as the analysis for Elecsys.

Where data were not available, it was necessary to make assumptions (see Appendix 13). For example, in the absence of maternal and neonatal outcomes in the INSPIRE study, the outcomes reported in the PARROT trial were used, and in both arms were assumed to be the same as the averages across the intervention and comparator arms in PARROT.

Some studies have suggested that the sFlt-1/PlGF ratio is higher in twins across all gestational ages compared with singleton pregnancies and that different ratio cutoffs may need to be applied.[52-55] This is a caveat of the scenario analyses which used data from the PreOS, MAPPLE and PELICAN trials, because the populations in those trials had women with twin pregnancies, although in small proportions: 2% – 10%.

Structural uncertainty associated with the management of pre-eclampsia has been tested in the scenario analyses where costing was based on the current NICE clinical guideline NG133[3] which replaced the CG107[59] guideline followed in the clinical trials selected for the

economic analysis. However, these scenarios could not capture the impact on costs and quality of life of the mother and their baby of recent changes in NICE recommendations on the timing of delivery, because the clinical evidence used in these scenarios came from (pre-2019) trials where women with suspected pre-eclampsia were managed in accordance with CG107 guideline.[59]

The results of one-way deterministic sensitivity analysis should be considered with caution because, as stated above, assumptions had to be made about clinical outcomes such as death rates and incidence of RDS and IVH in neonates, not reported in INSPIRE, which appear to be among the most influential model parameters. Another caveat of this analysis is that the base-case parameter values were varied within 10-20% (as described in section 5.5.2.2) due to the lack of reported uncertainty estimates.

Although the model was initially designed to perform a probabilistic sensitivity analysis (PSA), such an analysis was not conducted for several reasons. First, it was not clear how uncertainty in the sensitivity and specificity of the diagnostic tests and standard clinical assessment could be introduced into a PSA because our model does not utilise the accuracy estimates directly. Instead, we model the impact of following the clinical management algorithms used in the trials (shown in Appendix 8) on maternal and neonatal costs and HRQoL using maternal and neonatal outcomes stratified by PlGF levels reported in the pivotal RCTs. Secondly, uncertainty around most estimates for maternal and neonatal outcomes used in the model was not reported in the trials, and the lack of such evidence would require additional assumptions about the level of uncertainty in these outcomes. Finally, non-linearity in the model would not be accounted for in a PSA due to the lack of evidence on correlation between the model parameters. For all these reasons, conducting a PSA was deemed to be of limited value.

7.3 Uncertainties

The economic model assesses the PlGF tests based on the PARROT and INSPIRE RCTs. However, there is variability in the population in these groups which influences the model results. The prevalence of pre-eclampsia is higher in the PARROT trial (35%) than in the INSPIRE study (23%). In addition, there is a higher proportion of women with pre-eclampsia in the reveal arm (25%) of the INSPIRE study than the conceal arm (21%), whereas in the PARROT trial the arms are more balanced. It is unclear how the prevalence of pre-eclampsia in these studies differs from clinical practice.

8 CONCLUSIONS

8.1 Implications for service provision

Use of PlGF-based testing alongside standard clinical assessment to help diagnose suspected pre-eclampsia and inform subsequent care decisions, compared to standard clinical assessment alone, can be cost saving for the Triage PlGF test. For the Elecsys test standard clinical assessment alone is less costly and more effective compared to when PlGF based testing is included. The Elecsys results are more uncertain, however, due to limitations in the available evidence base to inform economic modelling.

8.2 Suggested research priorities

Despite an increase in the number of studies included in this update DAR compared to the previous DAR, and the use of well-designed randomised trials to assess longer-term clinically relevant outcomes, some key evidence gaps remain, including:

- Further evidence of the performance of the Triage and Elecsys, tests when used alongside standard clinical assessment to rule-in pre-eclampsia, is required. The current available evidence is of limited volume and relevance to current practice.
- Research on the diagnostic accuracy and analytical validity of the DELFIA Xpress PlGF 1-2-3 test and BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio.
- Research on the use of repeat PlGF-based testing for suspected pre-eclampsia, for all relevant tests, but in particular for the Triage and Elecsys tests given that these are already in use in the NHS (restricted to once per episode of suspected pre-eclampsia).

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10 APPENDICES

Appendix 1. Search strategies

The following search strategies were used to identify evidence for both the review of test accuracy studies and the economic evaluation.

Database searches were carried out from 11-13th November 2020, and the hand-searching of conferences and websites was carried out during the course of the same month. Update searches were run on 18th March 2021.

Searches of the Database of Abstracts of Reviews of Effects (DARE) and the NHS Economic Evaluations Database (NHS EED) were not repeated from the previous DAR as both databases have been closed to new records since March 2015 when the original search was run.

No search filter was used for identifying diagnostic technology accuracy studies. The search was designed to be sensitive and did not limit by any study design type.

Search strategies of two recent reviews were checked and some combined terms were added to describe pre-eclampsia, but no substantial amendments were made to the overall search strategy.[104 162]

Table 68 Search strategies for test accuracy and health economic studies

Database, Host, Years Searched, Date Searched	**Literature Search Strategy**	**Results**
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to November 10, 2020	1 Pre-Eclampsia/ 2 (preeclamp* or "pre eclamp*" or preclamp* or "pre clamp*").tw. 3 (tox?emi* adj5 pregnan*).tw. 4 gestosis.tw. 5 (pregnan* adj3 hypertensi*).tw. 6 (gestation* adj3 hypertensi*).tw. 7 ((maternal or maternity) adj3 hypertens*).tw. 8 Hypertension, Pregnancy-Induced/	First search:1494 Update search: 82

Search limited year 2015 Date searched: 11/11/2020 Update search: 18/03/2021	9 Pregnant Women/ 10 Pregnancy/ 11 Pregnancy Trimester, Second/ or Pregnancy Trimester, Third/ 12 Pregnancy Complications/ or Pregnancy Complications, Cardiovascular/ 13 or/9-12 14 Hypertension/ 15 hypertensi*.tw. 16 14 or 15 17 13 and 16 18 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 17 19 (PlGF and (triage or test* or assay* or immunoassay* or diagnos* or detect* or surveillance or screen* or measur* or analys* or analyz* or determin* or sensitivity or specificity or accuracy or accurate or assessment* or predict* or positive or negative or electrochemiluminescen*)).tw. 20 ("Placenta* growth factor" and (triage or test* or assay* or immunoassay* or diagnos* or detect* or surveillance or screen* or measur* or analys* or analyz* or determin* or sensitivity or specificity or accuracy or accurate or assessment* or predict* or positive or negative or electrochemiluminescen*)).tw. 21 Placenta Growth Factor/ 22 Vascular Endothelial Growth Factor Receptor-1/bl [Blood] 23 ("VEGFR1" or "VEGFR 1").tw. 24 diagnosis/ or early diagnosis/ 25 Diagnostic Tests, Routine/ or Diagnostic Equipment/ or "Diagnostic Techniques, Obstetrical and Gynecological"/ or Diagnostic Services/ 26 Maternal Serum Screening Tests/ 27 Serologic Tests/ 28 Pregnancy Proteins/an, bl [Analysis, Blood]	

	29 Membrane Proteins/bl [Blood] 30 Biological Markers/bl [Blood] 31 "fms-like tyrosine kinase*".tw. 32 (("FLT 1" or "sFLT 1" or "FLT1" or "sFLT1") and (triage or test* or assay* or immunoassay* or diagnos* or detect* or screen* or measur* or analys* or analyz* or determin* or sensitivity or specificity or accuracy or accurate or "prognostic assessment*" or predict* or positive or negative or electrochemiluminescen*)).tw. 33 ("soluble fms-like tyrosine kinase" and (triage or test* or assay* or immunoassay* or diagnos* or detect* or measur* or analys* or analyz* or determin* or sensitivity or specificity or accuracy or accurate or assessment* or predict* or positive or negative or electrochemiluminescen*)).tw. 34 elecsys.af. 35 roche.af. 36 alere.af. 37 quidel.af. 38 delfia.af. 39 perkinelmer.af. 40 brahms.af. 41 kryptor.af. 42 thermo.af. 43 or/19-42 44 18 and 43 45 limit 44 to animals 46 44 not 45 47 limit 46 to yr="2015 -Current" 48 limit 47 to english language	
Embase 1996 to 2020 Week 45 Limited 2015-current	1 preeclampsia/ or "eclampsia and preeclampsia"/ 2 (preeclamp* or "pre eclamp*" or preclamp* or "pre clamp*").tw.	First search: 377

Searched: 13/11/2020 Update search: 18/03/2021	3 (tox?emi* adj5 pregnan*).tw. 4 gestosis.tw. 5 (pregnan* adj3 hypertensi*).tw. 6 (gestation* adj3 hypertensi*).tw. 7 ((maternal or maternity) adj3 hypertens*).tw. 8 maternal hypertension/ 9 pregnancy toxemia/ 10 Pregnancy/ 11 Pregnancy complication/ 12 Pregnancy disorder/ 13 Pregnant woman/ 14 or/10-13 15 Essential hypertension/ or hypertension/ 16 hypertensi*.tw. 17 15 or 16 18 14 and 17 19 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 18 20 (PlGF and (triage or alere or quidel)).af. 21 (Triage and MeterPro).af. 22 ((Elecsys or roche) and ("sFlt-1" or "sFlt1" or VEGFR1 or "VEGFR-1" or PlGF or "sFlt-1/PlGF" or "sFlt1/PlGF" or "soluble FMS-like tyrosine kinase-1")).af. 23 (PlGF and (Delfia or PerkinElmer)).af. 24 ((BRAHMS or Kryptor or Thermo) and (PlGF or "sFlt-1" or "sFlt1" or "sFlt-1/PlGF" or VEGFR1 or "VEGFR-1" or "soluble FMS-like tyrosine kinase-1")).af. 25 or/20-24 26 19 and 25 27 preeclampsia/di, pc [Diagnosis, Prevention] 28 "eclampsia and preeclampsia"/di, pc [Diagnosis, Prevention] 29 27 or 28 30 (test* or triage or assay* or immunoassay* or electrochemiluminescen* or detect* or surveillance	Update search: 10

	or screen* or measur* or analys* or analyz* or determin* or sensitivity or specificity or accuracy or accurate or predict*).tw. 31 ("sFlt-1" or "sFlt1" or VEGFR1 or "VEGFR-1" or PlGF or "sFlt-1/PlGF" or "soluble FMS-like tyrosine kinase-1").tw. 32 placental growth factor/ 33 protein tyrosine kinase/ 34 vasculotropin receptor 1/ 35 or/31-34 36 29 and 30 and 35 37 (pre?eclamp* and diagnos* and test*).ti. 38 (pre?eclamp* and diagnos* and assay*).ti. 39 (pre?eclamp* and diagnos* and immunoassay*).ti. 40 (pre?eclamp* and diagnos* and electrochemiluminescen*).ti,ab. 41 or/37-40 42 26 or 36 or 41 43 limit 42 to english language 44 limit 43 to yr="2015 -Current"	
Cochrane Library (CDSR and CENTRAL) Searched: 13/11/2020 Update search: 18/03/2021	#1 MeSH descriptor: [Pre-Eclampsia] this term only 966 #2 ((preeclamp* or pre-eclamp* or preclamp* or pre-clamp*)):ti,ab,kw 3457 #3 (pre near eclamp*):ti,ab,kw 1859 #4 (tox?emia near pregnan*):ti,ab,kw 50 #5 (gestosis):ti,ab,kw 24 #6 (pregnan* near hypertensi*):ti,ab,kw 1881 #7 (gestation near hypertensi*):ti,ab,kw 99 #8 (matern* near hypertensi*):ti,ab,kw 792 #9 MeSH descriptor: [Hypertension, Pregnancy-Induced] explode all trees 1134 #10 MeSH descriptor: [Pregnancy] explode all trees 21918	Cochrane reviews: 5 Trials: 141 Update search: Reviews: 0 Trials: 6

	#11 MeSH descriptor: [Pregnancy Trimester, Second] this term only 675 #12 MeSH descriptor: [Pregnancy Trimester, Third] this term only 631 #13 MeSH descriptor: [Pregnancy Complications] this term only 1682 #14 MeSH descriptor: [Pregnancy Complications, Cardiovascular] this term only 333 #15 MeSH descriptor: [Pregnant Women] this term only 268 #16 #10 or #11 or #12 or #13 or #14 or #15 22027 #17 MeSH descriptor: [Hypertension] this term only 17565 #18 (hypertensi*):ti,ab,kw 64372 #19 #17 or #18 64372 #20 #16 and #19 916 #21 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #20 4915 #22 ((PlGF and (triage or alere))):ti,ab,kw1 #23 (("placental growth factor" and (triage or alere or quidel))):ti,ab,kw 3 #24 (((Elecsys or roche) and ("sFlt-1" or "sFlt1" or VEGFR1 or "VEGFR-1" or PlGF or "sFlt-1/PlGF" or "SFlt1/PlGF" or "soluble FMS-like tyrosine kinase-1"))):ti,ab,kw 5 #25 ((PlGF and (Delfia or PerkinElmer))):ti,ab,kw 2 #26 (((BRAHMS or Kryptor or Thermo) and (PlGF or "sFlt-1" or "sFlt1" or "sFlt-1/PlGF" or "SFlt1/PlGF" or VEGFR1 or "VEGFR-1" or "soluble FMS-like tyrosine kinase-1"))):ti,ab,kw 0 #27 #22 or #23 or #24 or #25 or #26 10 #28 #21 and #27 6	

	#29 MeSH descriptor: [Pre-Eclampsia] explode all trees and with qualifier(s): [diagnosis - DI] 79 #30 ((test* or triage or assay* or immunoassay* or electrochemiluminescen* or detect* or surveillance or screen* or measur* or analys* or analyz* or determin* or sensitivity or specificity or accuracy or accurate or predict*)):ti,ab,kw 1024389 #31 (("sFlt-1" or "sFlt1" or VEGFR1 or "VEGFR-1" or PlGF or "sFlt-1/PlGF" or "soluble FMS-like tyrosine kinase-1")):ti,ab,kw 513 #32 #30 and #31 448 #33 MeSH descriptor: [Diagnostic Techniques, Obstetrical and Gynecological] explode all trees 2701 #34 #32 and #33 9 #35 #21 and #32 116 #36 ((preeclamp* or pre-eclamp* or "pre eclamp") and (diagnos* and test*)):ti 1 #37 ((preeclamp* or pre-eclamp* or "pre eclamp") and (diagnos* and assay*)):ti,ab 12 #38 (((preeclamp* or pre-eclamp* or "pre eclamp") and (diagnos* and immunoassay*))):ti,ab,kw 6 #39 (((preeclamp* or pre-eclamp* or "pre eclamp") and (diagnos* and electrochemiluminescen*))):ti,ab,kw 0 #40 ((PlGF or "placental growth factor")):ti,ab,kw 277 #41 #21 and #30 and #40 111 #42 #28 or #29 or #34 or #35 or #36 or #37 or #38 or #39 or #41 with Cochrane Library publication date Between Jan 2015 and Nov 2020 146	

Web of Science Indexes=SCI-EXPANDED, CPCI-S Timespan=2015-2020 Searched: 13/11/2020 Update search: 18/03/2021	#1 14,370 (TS=(preeclamp* or "pre eclamp*" or "pre-eclamp*" or preclamp* or "pre clamp*" or "pre-clamp*")) #2 27 (TS=(tox?emia NEAR pregnan*)) #3 16 (TS=(gestosis)) #4 5,312 (TS=(pregnan* NEAR hypertensi*)) #5 523 (TS=(gestation NEAR hypertensi*)) #6 345 (TS=("maternal hypertensi*")) #7 27 (TS=(maternity NEAR hypertensi*)) #8 16,932 #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 #9 24 (TS=(PlGF and (triage or alere))) #10 25 (TS=(("placenta* growth factor") and (triage or alere or quidel))) #11 32 (TS=((Elecsys or roche) and ("sFlt-1" or "sFlt1" or VEGFR1 or "VEGFR-1" or PlGF or "sFlt-1/PlGF" or"SFlt1/PlGF" or "soluble FMS-like tyrosine kinase-1"))) #12 5 (TS=(PlGF and (Delfia or PerkinElmer))) #13 12 (TS=((BRAHMS or Kryptor or Thermo) and (PlGF or "sFlt-1" or "sFlt1" or "sFlt-1/PlGF" or "SFlt1/PlGF" or VEGFR1 or "VEGFR-1" or "soluble FMS-like tyrosine kinase-1"))) #14 58 #13 OR #12 OR #11 OR #10 OR #9 #15 54 #14 AND #8 #16 73,011 (TS=(diagnos* NEAR (test* or assay* or immunoassay* or electrochemiluminescen*))) #17 264 #16 AND #8 #18 289 (#17 or #15) AND LANGUAGE: (English)	First search: 289 Update search: 78
INAHTA database FROM 2015 TO 2020 Searched:	(((ELECSYS OR ROCHE OR ALERE OR QUIDEL OR DELFIA OR PERKINELMER OR BRAHMS OR KRYPTOR OR THERMO) OR ("soluble fms-like tyrosine kinase" and (triage or test* or assay* or immunoassay* or diagnos* or detect* or measur* or	First search: 2 Update search:

13/11/2020 Update search: 18/03/2021	analys* or analyz* or determin* or sensitivity or specificity or accuracy or accurate or assessment* or predict* or positive or negative or electrochemiluminescen*)) OR (("FLT 1" or "sFLT 1" or "FLT1" or "sFLT1") and (triage or test* or assay* or immunoassay* or diagnos* or detect* or screen* or measur* or analys* or analyz* or determin* or sensitivity or specificity or accuracy or accurate or "prognostic assessment*" or predict* or positive or negative or electrochemiluminescen*)) OR ("fms-like tyrosine kinase*") OR ("Serologic Tests"[mhe]) OR ("Maternal Serum Screening Tests"[mhe]) OR ("Diagnostic Services"[mhe]) OR ("Diagnostic Techniques, Obstetrical and Gynecological"[mhe]) OR ("Diagnostic Equipment"[mhe]) OR ("Diagnostic Tests, Routine"[mhe]) OR ("Diagnosis"[mh]) OR ("Early Diagnosis"[mh]) OR (vegfr) OR ((Vascular Endothelial Growth Factor Receptor-1)[mh]) OR (Vascular Endothelial Growth Factor Receptor-1) OR ("Placenta* growth factor" AND (triage or test* or assay* or immunoassay* or diagnos* or detect* or surveillance or screen* or measur* or analys* or analyz* or determin* or sensitivity or specificity or accuracy or accurate or assessment* or predict* or positive or negative or electrochemiluminescen*)) OR (PlGF AND (triage or test* or assay* or immunoassay* or diagnos* or detect* or surveillance or screen* or measur* or analys* or analyz* or determin* or sensitivity or specificity or accuracy or accurate or assessment* or predict* or positive or negative or electrochemiluminescen*))) AND ((pregnan* AND hypertensi*) OR (gestosis) OR ((Hypertension, Pregnancy-Induced)[mh]) OR (((maternal or maternity) AND hypertensi*)) OR ((gestation AND hypertensi*)) OR ((pregnan* and (toxaemia or toxemia))) OR ((preeclamp* or "pre-	0

	eclamp*" or "pre eclamp*")) OR ("Eclampsia"[mhe]))) FROM 2015 TO 2020	
Epistemonikos Title search only. 2015-2020 Searched: 13/11/2020 Update search: 18/03/2021	title:(pre-eclampsia OR preeclampsia OR ((maternal OR maternity OR pregnan* OR gestation*) AND (hypertens*))) AND title:(plgf OR "placenta* growth factor" OR "sFlt-1" OR "sFlt1" OR PlGF OR "sFlt-1/PlGF" OR "SFlt1/PlGF" OR "soluble FMS-like tyrosine kinase-1" OR VEGFR1 OR "VEGFR-1" OR diagnos* OR elecsys OR roche OR triage OR alere OR quidel OR delfia OR perkinelmer OR brahms OR kryptor OR thermo) 37 results Filter: publication year 2015-2020 22 results	First search: 22 Update search: 41
PROSPERO Searched: 18/11/2020	#1 MeSH DESCRIPTOR Pre-Eclampsia EXPLODE ALL TREES #2 preeclamp* or "pre eclamp*" or preclamp* or "pre clamp*" #3 gestosis #4 (hypertensi* or toxemi* or toxaemi*) AND (pregnan* or gestation* or maternal or maternity) #5 #1 OR #2 OR #3 OR #4 #6 MeSH DESCRIPTOR Placenta Growth Factor EXPLODE ALL TREES #7 "placenta growth factor" or "placental growth factor" or PlGF #8 SFLT1 or flt1 or "sflt 1" or "flt 1" or vegfr1 or "vegfr 1" #9 MeSH DESCRIPTOR Serologic Tests EXPLODE ALL TREES #10 MeSH DESCRIPTOR Diagnosis EXPLODE ALL TREES #11 MeSH DESCRIPTOR Early Diagnosis EXPLODE ALL TREES	27

	#12 MeSH DESCRIPTOR Diagnostic Tests, Routine EXPLODE ALL TREES #13 MeSH DESCRIPTOR Diagnostic Techniques, Obstetrical and Gynecological EXPLODE ALL TREES #14 MeSH DESCRIPTOR Diagnostic Equipment EXPLODE ALL TREES #15 MeSH DESCRIPTOR Diagnostic Services EXPLODE ALL TREES #16 triage or test* or assay* or immunoassay* or diagnos* or detect* or surveillance or screen* or measur* or analys* or analyz* or determin* or sensitivity or specificity or accuracy or accurate or assessment* or predict* or positive or negative or electrochemiluminescen* #17 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 #18 #5 AND #17 #19 #6 OR #7 OR #8 #20 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 #21 #5 AND #19 AND #20	
ClinicalTrials.Gov Searched: 13/11/2020 Update search: 18/03/2021	"placental growth factor" OR PlGF OR SFLT1 | Pre-Eclampsia	First search: 58 Update search: 4
BePartofResearch	Pre-eclampsia or PlGF or sFlt-1	First search: 3 (1 relevant)

		Update search: 8 (1 relevant)
Named conferences (as listed in section 3.1) Searched: November 2020	Conferences from 2016 up to 2020 (where possible) were hand-searched. Keywords: pre-eclampsia, hypertension, toxaemia, toxemia, gestosis, placenta growth factor, PlGF, SFLT Where conferences had sessions on pre-eclampsia specifically, and/or clinical trials specifically, only those sessions were hand-searched.	58
Named websites (as listed in section 3.1) Searched: November 2020	Keywords: pre-eclampsia, hypertension, toxaemia, toxemia, gestosis, placenta growth factor, PlGF, SFLT	0

Appendix 2. Study selection worksheet for the systematic review of test accuracy and clinical effectiveness

Research type: Research of any study design, published in English [a]	Yes ↓ next question	Unclear ↓ next question	No → EXCLUDE
Population: People presenting with suspected pre-eclampsia between 20 weeks and 36 weeks + 6 days	Yes ↓ next question	Unclear ↓ next question	No → EXCLUDE
Population decision rule: if a study includes a population with mixed suspected conditions (e.g. people suspected to have pre-eclampsia and/or fetal growth restriction), include study if there is a relevant subgroup analysis of participants with suspected pre-eclampsia only and/or ≥ 70% of the study population had suspected pre-eclampsia. Otherwise, exclude study.			
Index test (intervention): Use of any of the following, alongside standard clinical assessment: • Triage PlGF test • Elecsys immunoassay sFlt-1/PlGF ratio • DELFIA Xpress PlGF 1-2-3 test with or without the DELFIA Xpress sFlt-1 test • BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio	Yes ↓ next question	Unclear ↓ next question	No → EXCLUDE
Comparator/reference standard: Standard clinical assessment alone (i.e. blood pressure measurement, urinalysis and fetal monitoring)	Yes ↓ next question	Unclear ↓ next question	No → EXCLUDE
Outcomes: Any one or more of: • Diagnostic accuracy[b] • Concordance between tests • Prognostic accuracy • Time to test result • Impact of test result on clinical decision making • Test failure rate • Time to diagnosis • Proportion of people diagnosed with pre-eclampsia • Time to onset of pre-eclampsia and/or eclampsia • Proportion of people returned to less intensive follow-up	Yes ↓ next question	Unclear ↓ next question	No → EXCLUDE

• Number of people admitted to hospital / Length of in-patient hospital stay • Time to delivery • Gestation at diagnosis of pre-eclampsia • Use of antihypertensive drugs • Maternal morbidity and mortality [c] • Foetal morbidity and mortality [c] • Neonatal morbidity and mortality • Health related quality of life			
FINAL DECISION	**INCLUDE**	**UNCLEAR**	**EXCLUDE**

[a] if study is a relevant systematic review and/or meta-analysis, exclude the reference and mark it as 'SR' in Endnote custom field 8

[b] sensitivity, specificity, predictive values (+ or -), and/or likelihood ratios (+ or -) reported or calculable

[c] **Examples of relevant morbidity outcomes**

Maternal

Biochemical abnormalities
Disseminated intravascular coagulation/thrombosis
Eclampsia
Emergency caesarean for compromised baby
Haematological abnormalities
HELLP syndrome
Liver failure
Renal failure
Severe hypertension
Stroke

Fetal/neonatal

Breathing difficulties
Chronic lung disease
Gestational age at delivery
Growth at delivery
Intracranial haemorrhage
Late onset infection
Necrotising enterocolitis
Neonatal length of stay
Neonatal resuscitation
Preschool developmental delays
Weight at delivery (very low = <1500g)

Appendix 3. Tables of excluded studies with rationale

Table 69 References excluded from the test accuracy review at full-text screening

Reference	Exclusion reason: first reason identified
Adami 2020[163]	(9) Insufficient information (no response received to author enquiries)
Adami 2020[83]	(7) No relevant outcomes
Adami 2019[164]	(9) Insufficient information (no response received to author enquiries)
Andersen 2015[165]	(3) Ineligible population
Andersen 2016[166]	(3) Ineligible population
Andrietti 2017[167]	(3) Ineligible population
Andrietti 2016[168]	(3) Ineligible population
Bahlmann 2016[169]	(7) No relevant outcomes
Bednarek-Jedrzejek 2019[170]	(6) Ineligible comparator/reference standard
Birdir 2018[171]	(3) Ineligible population
Black 2019[73]	(3) Ineligible population
Black 2019[72]	(3) Ineligible population
Black 2020[74]	(3) Ineligible population
Caillon 2018[172]	(3) Ineligible population
Cetin 2017[173]	(3) Ineligible population
Chaiworapongsa 2016[174]	(3) Ineligible population
Chang 2017[175]	(3) Ineligible population
Cheng 2018[176]	(6) Ineligible comparator/reference standard
Cheng 2018[177]	(3) Ineligible population
Choi 2020[178]	(3) Ineligible population
Ciobanu 2019[179]	(3) Ineligible population
Contino 2018[180]	(8) Conference abstract with insufficient information
Dröge 2015[65]	(3) Ineligible population
Dröge 2021[181]	(9) Insufficient information (no response received to author enquiries)
Duhig 2020[182]	(1) Not primary diagnostic research
Enengl 2020[183]	(3) Ineligible population
Evers 2018[184]	(3) Ineligible population
Frenna 2017[185]	(3) Ineligible population
Gaccioli 2018[186]	(3) Ineligible population
Giardini 2019[102]	(6) Ineligible comparator/reference standard
Giardini 2020[187]	(3) Ineligible population
Giblin 2020[71]	(1) Not primary diagnostic research
Gomez-Roig 2015[188]	(3) Ineligible population
Graupner 2018[189]	(3) Ineligible population
Griffin 2018[190]	(1) Not primary diagnostic research
Heimberger 2020[191]	(3) Ineligible population
Herraiz 2018[192]	(3) Ineligible population
Herraiz 2018[193]	(3) Ineligible population
Hirashima 2018[194]	(5) Ineligible test (i.e. not listed in protocol)
Hoffmann 2017[195]	(7) No relevant outcomes
Honigberg 2016[196]	(3) Ineligible population
Huhn 2018[197]	(3) Ineligible population
Jadli 2019[198]	(3) Ineligible population
Karge 2020[199]	(3) Ineligible population
Karge 2021[200]	(3) Ineligible population
Lind Malte 2018[201]	(6) Ineligible comparator/reference standard
Lou 2019[202]	(3) Ineligible population
Lubis 2020[203]	(3) Ineligible population
Lubis 2019[204]	(3) Ineligible population
MacDonald 2018[205]	(3) Ineligible population

Reference	Exclusion reason: first reason identified
Mathur 2016[206]	(3) Ineligible population
Menke 2016[207]	(2) Non-English language
Mihalceanu 2015[208]	(3) Ineligible population
Mueller 2020[209]	(9) Insufficient information (no response received to author enquiries)
Nagalla 2018[210]	(8) Conference abstract with insufficient information
Nagalla 2020[211]	(3) Ineligible population
Navaratnam 2019[212]	(3) Ineligible population
Navaratnam 2019[213]	(3) Ineligible population
Neuman 2020[214]	(3) Ineligible population
Neuman 2021[215]	(3) Ineligible population
Nguyen 2018[216]	(3) Ineligible population
Niemczyk 2016[217]	(1) Not primary diagnostic research
Palmer 2017[218]	(3) Ineligible population
Palmer 2019[219]	(9) Insufficient information (no response received to author enquiries)
Parchem 2019[69]	(6) Ineligible comparator/reference standard
Parchem 2020[220]	(6) Ineligible comparator/reference standard
Perales 2017[221]	(3) Ineligible population
Perdigao 2019[222]	(6) Ineligible comparator/reference standard
Perry 2020[68]	(3) Ineligible population
Pluddemann 2020[223]	(1) Not primary diagnostic research
Raia-Barjat 2019[224]	(3) Ineligible population
Rana 2017[225]	(1) Not primary diagnostic research
Ratnik 2020[226]	(3) Ineligible population
Ratnik 2016[227]	(3) Ineligible population
Roche 2019[228]	(9) Insufficient information (no response received to author enquiries)
Rodriguez-Almarez 2018[229]	(3) Ineligible population
Rolfo 2015[230]	(3) Ineligible population
Rowson 2019[231]	(4) Ineligible biomarker(s) (i.e. not PlGF, sFlt-1 or ratio)
Sa 2020[232]	(7) No relevant outcomes
Sabria 2018[233]	(3) Ineligible population
Sabria 2018[234]	(7) No relevant outcomes
Saleh 2020[235]	(3) Ineligible population
Saleh 2018[236]	(3) Ineligible population
Saleh 2018[237]	(6) Ineligible comparator/reference standard
Saleh 2017[238]	(6) Ineligible comparator/reference standard
Saleh 2015[239]	(6) Ineligible comparator/reference standard
Saleh 2016[240]	(6) Ineligible comparator/reference standard
Saleh 2016[241]	(6) Ineligible comparator/reference standard
Saleh 2017[242]	(3) Ineligible population
Saleh 2016[243]	(6) Ineligible comparator/reference standard
Sarween 2017[244]	(3) Ineligible population
Sebastian 2019[245]	(3) Ineligible population
Simon 2020[76]	(3) Ineligible population
Simon 2020[246]	(3) Ineligible population
Slomski 2019[247]	(1) Not primary diagnostic research
Smith 2016[248]	(3) Ineligible population
Sovio 2017[249]	(3) Ineligible population
Stepan 2016[77]	(3) Ineligible population
Stolz 2018[250]	(3) Ineligible population
Suresh 2020[251]	(1) Not primary diagnostic research
Tan 2017[252]	(3) Ineligible population
Tardif 2018[253]	(3) Ineligible population
ThermoFisher 2020[254]	(3) Ineligible population
[redacted]	(3) Ineligible population

Reference	Exclusion reason: first reason identified
Torchin 2019[256]	(3) Ineligible population
Tsiakkas 2016[257]	(3) Ineligible population
Tsiakkas 2016[258]	(3) Ineligible population
Tsiakkas 2016[259]	(3) Ineligible population
Valino 2016[260]	(3) Ineligible population
Valino 2016[261]	(3) Ineligible population
Van Helden 2015[262]	(3) Ineligible population
Vatish 2017[263]	(1) Not primary diagnostic research
Verlohren 2018[264]	(1) Not primary diagnostic research
Verlohren 2017[265]	(9) Insufficient information (no response received to author enquiries)
Villalain 2020[266]	(6) Ineligible comparator/reference standard
Widmer 2015[267]	(3) Ineligible population
Wiles 2021[268]	(3) Ineligible population
Zeisler 2016[269]	(1) Not primary diagnostic research
Zeisler 2016[41]	(6) Ineligible comparator/reference standard

Table 70 References excluded studies from the cost effectiveness review

Study	Reason for exclusion
Adami et al., 2020	Conference abstract
Brennecke, 2019	Conference abstract
Cordioli et al., 2017	Conference abstract
Duhig et al., 2019a	Conference abstract
Duva et al., 2017	Conference abstract
Frampton et al., 2016b	Protocol
Garay et al., 2019a	Conference abstract
Garay et al., 2019b	Conference abstract
Garay et al., 2019c	Conference abstract
Ho et al., 2019	Conference abstract
Hodel et al., 2020	Conference abstract
Clinicaltrials.gov, 2017	Protocol
Paolini et al., 2016	Conference abstract
Paolini et al., 2017	Conference abstract
Speranza et al., 2018	Conference abstract

Table 71 References excluded from the Quality of life review

Study	Reason for exclusion
Aviram et al. 2017	Conference abstract
Crnogorac et al. 2015	Conference abstract
Die-Mostic et al. 2018	Conference abstract
Drost et al. 2015	Study design
Einav and Leone 2019	Study design
Feldhaus et al. 2016	Study design
Goodman et al. 2017	Study design
Hersh et al. 2020	Conference abstract
Hersh et al. 2019	Conference abstract
Hersh et al. 2019	Study design
Lagerweij et al. 2020	Study design
Lai et al. 2016	Conference abstract
Machado et al. 2020	QoL measure
McLaren et al. 2017	Study design
Memirie et al. 2019	Study design
Merrill et al. 2016	Conference abstract
Mone et al. 2018	Study design
Rincon et al. 2017	Conference abstract
Sahrakorpi et al. 2017	Population
Saito et al. 2020	Conference abstract
Savitsky et al. 2017	Conference abstract
Savitsky et al. 2017	Conference abstract
Speranza et al. 2017	Conference abstract
Waugh et al. 2017	Study design
Werner et al. 2015	Study design
Bai et al 2018	Population
Lagadec et al 2016	Study design

Appendix 4. Concordance studies

Table 72 Predictive concordance studies

Study	Tests compared				Comments
	Triage PlGF	Elecsys ratio	BRAHMS Kryptor ratio	Delfia Xpress	
Black 2019 [72] PlGF, sFlt-1		● [a]	●	●	Screening at 19-22 weeks for developing PE and other adverse outcomes in a normal pregnancy population. Tests were comparable in predictive capability but using test cut-offs not relevant to the current review.
Black 2019 [73] PlGF, sFlt-1, sFlt-1/PlGF ratio		● [a]	●	●	Testing at 19-22 weeks in a normal pregnancy population. Correlational analyses of biomarker measurements among tests; no PE prediction.
Black 2019 [74] PlGF, sFlt-1		● [a]	●	●	Screening at 19^{+0} to 24^{+6} weeks for PE development in a normal pregnancy population. Tests were comparable in predictive capability but based on a PE screening cut-off not relevant to the current review.
Burke 2016 [75] PlGF	●	●			Study on women with PlGF measurements after 20 weeks GA from 22 cohorts with normal pregnancies or PE and related conditions. Aim was to develop a strategy for cross-test data pooling; not PE prediction.
Cheng 2019 [70] PlGF, sFlt-1, sFlt-1 ratio		●	●	●	Normal pregnancies, 20-39 weeks GA, Chinese population. There were notable inter-test differences in sensitivity and cross-reactivity to PlGF and sFlt-1 isoforms between the tests, meaning that rule-in and rule-out cut-offs for PE prediction are test-specific.
Giblin 2020 [71] PlGF	●	●		●	Women with suspected PE before 35 weeks GA
McCarthy 2019 [30] PlGF, sFlt-1/PlGF ratio	●	●		●	Women with suspected PE or suspected SGA before 35 weeks and between 35 and 36^{+6} weeks GA. Test cut-offs were relevant to the current review. The Alere, Roche and Perkin Elmer tests

					differed in sensitivity and specificity for predicting delivery within 2 weeks but overall AUCs were similar and the authors concluded the tests had similar predictive ability.
Salahuddin 2016 [47]		●	●		
Simon 2020 [76]		●	●		
Stepan 2016 [77]	●	●			
Stepan 2019 [78]		●	●		
AUC: area under the receiver-operator characteristics curve; GA: gestational age [a] used Roche cobas e-411; not specified as Elecsys test					

Appendix 5. Standalone test studies: description of study characteristics and summary of results

Appendix 5.1 Baseline characteristics of participants in the standalone test studies

Table 73 Characteristics of the participants in the Triage standalone test studies

Population characteristic	**PELICAN**[18 21] ***20+0 to 34+6***	**PELICAN**[18 21] ***35+0 to 36+6***	**PEACHES validation cohort**[24] ***No pre-existing disease***	**PEACHES validation cohort**[24] ***Chronic hypertension***	**PEACHES validation cohort**[24] ***Chronic kidney disease***	**PETRA**[25 27] ***20+0 to 35+0***	[redacted]
Variance measure	Median (quartiles)		Median (IQR)			Median (IQR)	
Age, years	31.2 (26.8–35.6)	32.4[a]	31.2 (26.5 to 35.3)	33.5 (30.7 to 36.6)	32.7 (29.2 to 38.2)	[redacted]	[redacted]
Gestational age, weeks	31.1 (28.0–33.4)	35.9[a]	35.9 (32.5 to 37.9)	34.1 (27.9 to 37.0)	33.4 (30.6 to 36.6)	[redacted]	[redacted]
Parity, n (%)	Not reported	Not reported	0: 275 (60.3)	0: 36 (38.3)	0: 14 (48.2)	[redacted]	[redacted]
BMI, kg/m^2, median (IQR)	28.6 (24.2–33.6)	28.63[a]	27.7 (23.6 to 31.6)	31.1 (26.7 to 36.8)	26.3 (23.7 to 30.3)	[redacted]	[redacted]
Ethnicity, n (%)	White: 187 (65)	White: 88 (64)	White: 313 (68.6)	White: 59 (62.8) Black: 26 (27.7)	White: 21 (72.4) Black: 8 (27..6)	[redacted]	[redacted]

Population characteristic	**PELICAN**[18 21] ***20^{+0} to 34^{+6}***	**PELICAN**[18 21] ***35^{+0} to 36^{+6}***	**PEACHES validation cohort**[24] ***No pre-existing disease***	**PEACHES validation cohort**[24] ***Chronic hypertension***	**PEACHES validation cohort**[24] ***Chronic kidney disease***	**PETRA**[25 27] ***20^{+0} to 35^{+0}***	[redacted]
			Black: 80 (17.5) Asian: 36 (7.9) Other: 27 (5.9)	Asian: 5 (5.3) Other: 4 (4.3)	Asian: 0 Other: 0	[redacted]	[redacted]
Smoking status, n (%)	Smoker: 58 (19) Quit during pregnancy: 34 (12)	Smoker: 21 (15) Quit during pregnancy: 13 (10)	Never: 324 (72.3) Ex-smoker: 80 (17.9) Current: 44 (9.8)	Never: 72 (79.1) Ex-smoker: 13 (14.3) Current: 6 (6.6)	Never: 22 (75.9) Ex-smoker: 5 (17.2) Current: 2 (6.9)	[redacted]	[redacted]
[a]quartiles not reported for this subgroup in PELICAN							

Table 74 Characteristics of the participants in the Elecsys standalone test studies

Population characteristic	PROGNOSIS [36-42]	PROGNOSIS Asia[43]	ROPE[45]	Baltajian 2016[46]	Saleh 2016[54] No pre-eclampsia	Saleh 2016[54] Pre-eclampsia	Wang 2021[11] Pre-eclampsia negative	Wang 2021[11] Pre-eclampsia positive
Variance measure	Median (IQR)	Median (IQR)	Median (Q1, Q3)	Median (Q1, Q3)	Mean (±SD)		Median (25^{th}-75^{th} percentile)	
Age, years	31 (27 – 36)	33 (29–36)	33 (29, 36)	33 (30, 36)	32 ±6	32 ±5	33 (29–36)	34 (31–37)
Gestational age, weeks	31.6 (27.6 – 34.4)	31.6 (27.2–34.6)	34.00 (30.71, 35.86)	33 (31, 35)	31 ±5	30 ±4	29 (24–33)	30 (25–32)
Parity, n (%)	Not reported	Not reported	0: 226 (56.22)	0: 57 (57.0)	Not reported	Not reported	0: 108 (74.0) ≥1: 38 (26.0)	0: 30 (612) ≥1: 19 (38.8)
BMI, kg/m^2, median (IQR)	26.3 (22.4 – 31.2)	22.9 (20.5–26.2)	32.12 (27.97, 37.09)	31.6 (28.5, 37.3)	Not reported	Not reported	23.6 (21.2–25.9)	23.2 (20.7–28.1)
Ethnicity, n (%)	Asian: 54 (5.1) Black: 61 (5.8) Caucasian: 860 (81.9) Other: 75 (7.1)	Asian: 699 (99.9) White: 1 (0.1)	White/Caucasian: 270 (67.16) Black/African American: 73 (18.16) Asian: 29 (7.21) Other: 30 (7.46)	White/Caucasian: 55 (55.0) Black/African American: 17 (17.0) Asian: 6 (6.0) Other/unknown: 22 (22.0)	Not reported	Not reported	Not reported	Not reported
Smoking status, n (%)	Current: 152 (14.5)	Current: 11 (1.6)	Current: 23 (5.75) Never: 251 (62.75)	Current smoker: 1 (1.0)	Not reported	Not reported	Not reported	Not reported

Population characteristic	PROGNOSIS [36-42]	PROGNOSIS Asia[43]	ROPE[45]	Baltajian 2016[46]	Saleh 2016[54] No pre-eclampsia	Saleh 2016[54] Pre-eclampsia	Wang 2021[11] Pre-eclampsia negative	Wang 2021[11] Pre-eclampsia positive
	Past: 216 (20.6)	Past: 60 (8.6)	Past/Quit before pregnancy: 111 (27.75) Quit early in pregnancy: 11 (2.75) Unknown: 4 (1.00)					

Table 75 Characteristics of the participants in the BRAHMS Kryptor standalone test study

Population characteristic	Salahuddin 2016[47]
Variance measure	Median (Q1, Q3)
Age, years	32 (28, 35)
Gestational age, weeks	36.4 (33.6, 38.0)
Parity, n (%)	0: 232 (56.3)
BMI, kg/m^2, median (IQR)	32.6 (29.2, 37.0)
Ethnicity, n (%)	White: 280 (68.0) Black: 61 (14.8) Asian/Pacific Islander: 27 (6.6) Other: 44 (10.7)
Smoking status, n (%)	Smoker: 34 (8.3)

Table 76 Characteristics of the participants in the DELFIA Xpress standalone test study

Population characteristic	COMPARE[30] GA <35+0 weeks	COMPARE[30] GA 35+0 to 36+6 weeks
Variance measure	Median (IQR)	
Age, years	33.4 (29.5–36.8)	32.2 (27.9–35.6)
Gestational age, weeks	27.9 (20.0–32.0)	36.0 (35.7–36.5)
Parity, n (%)	0: 155 (47)	0: 34 (49)
BMI, kg/m^2, median (IQR)	24.5 (21.5–30.5)	22.8 (20.8–26.4)
Ethnicity, n (%)	White: 151 (46) Black: 89 (27) Asian: 24 (7) Other: 63 (19)	White: 39 (57) Black: 8 (12) Asian: 11 (16) Other: 11 (16)
Smoking status, n (%)	Currently smoking: 14 (4) Quit smoking: 35 (11) Never smoked: 278 (85)	Currently smoking: 6 (9) Quit smoking: 11 (16) Never smoked: 52 (75)

Appendix 5.2 Prognostic characteristics of participants in the standalone test studies

Prognostic characteristics relating to reasons for suspected pre-eclampsia are reported in the Table X and Table X below, one for standalone studies using the Triage test and one for standalone studies using the Elecsys test. Neither Salahuddin 2016[47] for the BRAHMS Kryptor test nor COMPARE[30], the only study with data for the DELFIA Xpress test, reported reasons for suspected pre-eclampsia and are not included in the tables.

The studies report differing aspects of medical history relevant to pre-eclampsia and this too is not consistent across the studies, although PROGNOSIS [36-42] and PROGNOSIS Asia[44] did not report this. Below are listed the most widely reported risk factors.

- Previous pre-eclampsia, range 7% to 20%, (Baltajian 2016[46], COMPARE[30], PELICAN[18 21], ROPE[45], Salahuddin 2016[47]) NB PELICAN[18 21] additionally reports previous pre-eclampsia requiring delivery and PEACHES[24] reports previous pre-eclampsia at <34 weeks and at ≥34 weeks.
- Chronic hypertension, range 8% to 44%, (Baltajian 2016[46], COMPARE[30], PEACHES[24], PELICAN[18 21], ROPE[45], Salahuddin 2016[47], Saleh 2016[54], Wang 2021[11]) NB PETRA[25 27] reports both history of chronic hypertension and current chronic hypertension.
- Pre-existing diabetes, range 2% to 11%, (Baltajian 2016[46], COMPARE[30], PEACHES[24], PELICAN[18 21], PETRA[25 27], ROPE[45], Salahuddin 2016[47], Wang 2021[11])
- Systemic lupus erythematosus/antiphospholipid syndrome, range 2% to 5% (COMPARE[30], PEACHES[24], PELICAN[18 21])
- Renal disease, range 3% to 33%, (COMPARE[30], PELICAN[18 21], PETRA[25 27])

Wang 2021[11] additionally reports hypothyroidism or hyperthyroidism, polycystic ovary syndrome, and antiphospholipid syndrome. Saleh 2016[54] additionally reports PCE, use of anti-hypertensives and pre-existing proteinuria. PETRA[25 27] additionally reports gestational hypertension and gestational diabetes. Therefore, relevant medical history is quite heterogeneous. All studies, except Wang 2021[11], reported blood pressure levels and almost half of the studies reported either proteinuria levels or the presence of proteinuria.

Table 77 Prognostic characteristics of participants in the Triage standalone test studies

Prognostic characteristic	PELICAN[18 21] *20+0 to 34+6*	PELICAN[18 21] *35+0 to 36+6*	PEACHES validation cohort[24] *No pre-existing disease*	PEACHES validation cohort[24] *Chronic hypertension*	PEACHES validation cohort[24] *Chronic kidney disease*	PETRA[25 27] *20+0 to 35+0*	[redacted]
Variance measure	Median (quartiles)		Median (IQR)			Median (IQR)	
New-onset hypertension, n (%)	154 (54)	21 (15)	342 (75.0)	22 (23.4)	16 (55.1)	[redacted]	[redacted]
Worsening of existing hypertension, n (%)	56 (20)	21 (15)	45 (98.7)	58 (61.7)	6 (20.7)	[redacted]	[redacted]
New-onset proteinuria, n (%)	160 (56)	85 (62)	260 (57.0)	46 (48.9)	18 (62.1)	[redacted]	[redacted]
Aggravation of pre-existing proteinuria, n (%)	Not reported	Not reported	Not reported	Not reported	Not reported	[redacted]	[redacted]

Prognostic characteristic	PELICAN[18 21] *20+0 to 34+6*	PELICAN[18 21] *35+0 to 36+6*	PEACHES validation cohort[24] *No pre-existing disease*	PEACHES validation cohort[24] *Chronic hypertension*	PEACHES validation cohort[24] *Chronic kidney disease*	PETRA[25 27] *20+0 to 35+0*	[redacted]
New onset of protein in urine, n (%)	Not reported	Not reported	Not reported	Not reported	Not reported	[redacted]	[redacted]
Epigastric or right upper-quadrant pain, n (%)	Not reported	Not reported	27 (5.9)	6 (22.2)	2 (6.9)	[redacted]	[redacted]
Visual disturbances, n (%)	Not reported	Not reported	157 (34.4)[d]	30 (31.9)[d]	8 (27.6)[d]	[redacted]	[redacted]
Headache, n (%)	Not reported	Not reported				[redacted]	[redacted]
Sudden weight gain, n (%)	Not reported	Not reported	Not reported	Not reported	Not reported	[redacted][a]	[redacted]
Abnormal blood test results, n (%)	Not reported	Not reported	Not reported	Not reported	Not reported	[redacted][b]	[redacted]

Prognostic characteristic	PELICAN[18 21] *20+0 to 34+6*	PELICAN[18 21] *35+0 to 36+6*	PEACHES validation cohort[24] *No pre-existing disease*	PEACHES validation cohort[24] *Chronic hypertension*	PEACHES validation cohort[24] *Chronic kidney disease*	PETRA[25 27] *20+0 to 35+0*	[redacted]
Suspected fetal growth restriction, n (%)	Not reported	Not reported	27 (5.9)	2 (2.1)	0	[redacted][c]	[redacted]
Abnormal uterine Doppler ultrasound, n (%)	Not reported	Not reported	Not reported	Not reported	Not reported	[redacted]	[redacted]

[a]Study refers to 'excessive' weight gain rather than sudden weight gain

[b]Study refers to 'unexplained lab results' rather than abnormal blood test results

[c]Study refers to 'abnormal fetal growth' rather than suspected fetal growth restriction

[d]Study groups headaches and visual disturbance together

Table 78 Prognostic characteristics of participants in the Elecsys standalone test studies

Prognostic characteristic	PROGNOSIS [36-42]	PROGNOSIS Asia[43]	Wang 2021[ref] Pre-eclampsia negative	Wang 2021[ref] Pre-eclampsia positive
Variance measure	Median (IQR)	Median (IQR)	Median (25th–75th percentile)	
New-onset hypertension, n (%)	Not reported	363 (51.9)	71/147 (48.3)[a]	30/49 (61.2)[a]
Worsening of existing hypertension, n (%)	145 (13.8)	65 (9.3)		
New onset of elevated blood pressure, n (%)	310 (29.5)	Not reported	Not reported	Not reported
New-onset proteinuria, n (%)	Not reported	193 (27.6)	51 (34.7)[b]	16 (32.7)[b]
Aggravation of pre-existing proteinuria, n (%)	12 (1.1)	4 (0.6)		
New onset of protein in urine, n (%)	386 (36.8)	Not reported	Not reported	Not reported
Epigastric or right upper-quadrant pain, n (%)	79 (7.5)	Not reported	Not reported	Not reported

Prognostic characteristic	PROGNOSIS [36-42]	PROGNOSIS Asia[43]	Wang 2021[ref] Pre-eclampsia negative	Wang 2021[ref] Pre-eclampsia positive
Visual disturbances, n (%)	118 (11.2)	3 (0.4)	Not reported	Not reported
Headache, n (%)	314 (29.9)	Not reported	Not reported	Not reported
Excessive edema, n (%)	126 (12.0)	Not reported	Not reported	Not reported
New onset edema, n (%)	Not reported	Not reported	28 (19.0)	11 (22.4)
Severe swelling of face, hands or feet, n (%)	140 (13.3)	Not reported	Not reported	Not reported
Sudden weight gain, n (%)	99 (9.4)	Not reported	Not reported	Not reported
Abnormal blood test results, n (%)	Low platelets: 71 (6.8) Elevated liver transaminases: 39 (3.7)	Not reported	Not reported	Not reported
Suspected fetal growth restriction, n (%)	155 (14.8)[c]	188 (26.9)	18 (12.2)	5 (10.2)

Prognostic characteristic	PROGNOSIS [36-42]	PROGNOSIS Asia[43]	Wang 2021[ref] Pre-eclampsia negative	Wang 2021[ref] Pre-eclampsia positive
Abnormal uterine perfusion, n (%)	220 (21.0)	Not reported	Not reported	Not reported
Partial HELLP syndrome, n (%)	Not reported	16 (2.3)	Not reported	Not reported

NB. ROPE[45], Saleh 2016[54] and Baltajian 2016[46] do not report reasons for suspected PE and are not included in this table

[a]Includes aggravation/worsening of existing hypertension

[b]Includes aggravation/worsening of existing proteinuria

[c]PROGNOSIS study refers to IUGR rather than FGR

Appendix 5.3 Test accuracy results from the standalone test studies

Table 79 Accuracy outcomes reported in standalone studies, by test

Test	Study identifier	Prediction of pre-eclampsia (PE)	Prediction of delivery	Adverse outcomes
Triage PlGF test	PELICAN[22 270] (PEACHES[24] I)	• PE within any time	• Within 2 weeks • PE requiring delivery within 2 weeks • Preterm PE requiring delivery within 2 weeks • Any preterm delivery • Within 2 weeks due to pre-eclampsia or superimposed pre-eclampsia	
	PETRA[25-27]	• Pre-eclampsia within any time	• Within 1 and 2 weeks • PE requiring delivery within 1 and 2 weeks • Preterm PE requiring delivery within 1 and 2 weeks • Any preterm delivery	
Elecsys sFlt-1/PlGF ratio	PROGNOSIS[39 41 67]	• Pre-eclampsia within 1, 2, 3 and 4 weeks • Re-testing to rule in/out pre-eclampsia		
	PROGNOSIS Asia[43]	• Pre-eclampsia within 1 and 4 weeks	• PE requiring delivery within 1 and 4 weeks	
	ROPE 2018[45]	• Pre-eclampsia with severe features within 2 weeks	• Within 2 weeks • Indicated delivery within 2 weeks	
	Baltajian 2016[46]		• Indicated delivery within 2 weeks	
	Wang[11]	• Pre-eclampsia within 4 weeks		
	Saleh 2016[54]	• Pre-eclampsia at inclusion • Final diagnosis of pre-eclampsia		• Adverse outcomes
BRAHMS Kryptor sFlt-	Salahuddin 2016[47]			• Severe maternal morbidity

Test	Study identifier	Prediction of pre-eclampsia (PE)	Prediction of delivery	Adverse outcomes
1/PlGF ratio (also includes data for Elecsys)				
DELFIA Xpress test (also data for Triage and Elecsys tests	McCarthy 2019[30]		Within 14 days: • secondary to suspected PE • secondary to suspected PE or delivery by 37 weeks' gestation • in women with confirmed pre-eclampsia	

Table 80 Prediction of pre-eclampsia by specific time point

Time point (author emphasis)	Cut-off	Total (n)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Prevalence % (95% CI)
PROGNOSIS, [39] *Roche Elecsys ratio, result concealed, 24^{+0} to 36^{+6} weeks – development cohort*							
Within 1 week (rule out)	≤38	500	0.882 (0.725-0.967)	0.800 (0.761-0.836)	NR	0.989 (0.973-0.997)	NR
Within 4 weeks (rule in)	>38	500	0.746 (0.625-0.845)	0.831 (0.793-0.865)	0.407 (0.319-0.499)	NR	13.4 (NR)
PROGNOSIS, [36 39] *Roche Elecsys ratio, result concealed, 24^{+0} to 36^{+6} weeks – validation cohort*							
Within 1 week (rule out)	≤38	550	0.800 (0.519-0.957)	0.783 (0.746-0.817)	0.094 (0.049-0.158)	0.993 (0.979-0.999)	2.7 (NR)
Within 2 weeks (rule out)	≤38	550	0.780 (0.624-0.894)	0.811 (0.775-0.844)	0.250 (0.178-0.334)	0.979 (0.960-0.999)	7.5 (5.4-10.0 [a])
Within 3 weeks (rule out)	≤38	550	0.700 (0.568-0.812)	0,824 (0.788-0.857)	0.328 (0.248-0.417)	0.957 (0.933-0.975)	10.9 (8.4-13.8 [a])
Within 4 weeks (rule in)	>38	550	0.662 (0.540-0.770)	0.831 (0.794-0.863)	0.367 (0.284-0.457)	0.943 (0.917-0.963)	12.9 (NR)
PROGNOSIS, [39 67] *Roche Elecsys ratio, result concealed, 24^{+0} to 36^{+6} weeks – combined cohorts*							
Within 1 week (rule out)	≤38	1050	0.857 (0.728-0.941)	0.791 (0.765-0.816)	0.167 (0.123-0.219)	0.991 (0.982-0.996)	2.7 (1.5-4.5 [a])
Within 4 weeks (rule in)	>38	1050	0.703 (0.619-0.778)	0.831 (0.805-0.855)	0.386 (0.326-0.450)	0.949 (0.931-0.963)	
PROGNOSIS Asia, [43] [b] *Roche Elecsys ratio, result concealed, 20^{+0} to 36^{+6} weeks*							
Within 1 week (rule out)	≤38	700	0.765 (0.588-0.893)	0.821 (0.790-0.850)	0.179 (0.121-0.252)	0.986 (0.972-0.994)	4.86 [c]
Within 4 weeks (NR)	>38	700	0.620 (0.497-0.732)	0.839 (0.808-0.867)	0.303 (0.230-0.305)	0.951 (0.930-0.968)	10.14 [c]
Wang et al. [11] *Roche Elecsys ratio, result concealed, 20 to 36 weeks (Chinese population)*							
Within 4 weeks (NR)	38	196	0.400 [c]	0.834 [c]	0.167 [c]	0.944 [c]	7.7 (0.5-1.1 [a])

NPV: negative predictive value; NR: not reported; PPV: positive predictive value
Wang et al.[11] commented that the sensitivity, specificity, and PPV were much lower with their cohort (Chinese population) compared to other studies, suggesting that ethnicity may be a confounding factor for the application of the sFlt-1/PlGF ratio.
a calculated by reviewer
b an analysis of a Japanese subgroup of the PROGNOSIS Asia population[10] gave similar findings (data not reproduced here).
c confidence interval not reported

Table 81 Prediction of pre-eclampsia at any time

Time point	Cut-off	Total (n)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Prevalence % (95% CI)
PETRA, [a 26] *Triage test, result concealed, 20^{+0} to 35^{+0} weeks*							
Any time	≤100 pg/mL	753	0.757 (NR)	0.688 (NR)	0.859 (NR)	0.530 (NR)	NR [b]
PELICAN, [22] *Triage test, result concealed, 20^{+0} to 34^{+6} weeks, prediction of preterm PE (<35 weeks)*							
Any time	≤100 pg/mL	287	0.900 (0.832-0.947)	0.653 (0.575-0.725)	0.651 (0.573-0.723)	0.901 (0.833-0.948)	41.81 (36.04-47.75 [c])

NPV: negative predictive value; NR: not reported; PPV: positive predictive value
[a] an abstract by Woelkers 2016[28] reported slightly different data values (not reproduced here)
[b] overall PE prevalence reported by Barton 2020[26] (71.4%) but would vary with outcome and has not been reported separately for this outcome.
[c] calculated by reviewer

Table 82 Prediction of pre-eclampsia at inclusion versus final diagnosis

Time point	Cut-off	Total (n)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Prevalence % (95% CI)
Saleh et al, [54] *Roche Elecsys ratio, result concealed*							
At study inclusion	>85	107	0.900 (0.801-0.964) [a]	0.930 (0.817-0.986) [a]	0.950 (0.862-0.982) [a]	0.880 (0.765-0.938) [a]	58.0 [b]
At final diagnosis	>85	107	0.910 [c]	0.980 [c]	0.980 [c]	0.830 [c]	NR

NPV: negative predictive value; NR: not reported; PPV: positive predictive value
[a] 95% CI calculated by reviewer
[b] calculated by reviewer
[c] 95% CI not reported

Table 83 Prediction of pre-eclampsia with severe features

Time point	Cut-off	Total (n)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Prevalence % (95% CI)
ROPE,[45] Roche Elecsys ratio, result concealed, <36^{+6} weeks (lower limit not reported)							
Within 2 weeks	>38	402	0.909 [a]	0.798 [a]	0.469 [a]	0.978 [a]	16.42 [a,b]
	>85	402	0.621 [a]	0.917 [a]	0.594 [a]	0.925 [a]	16.42 [a,b]
ROPE,[45] Roche Elecsys ratio, result concealed, <34 weeks (lower limit not reported)							
Within 2 weeks	>38	199	0.935 [a]	0.850 [a]	0.652 [a]	0.977 [a]	23.12 [a,b]
	>85	199	0.696 [a]	0.928 [a]	0.744 [a]	0.910 [a]	23.12 [a,b]
ROPE,[45] Roche Elecsys ratio, result concealed, <36^{+6} weeks (lower limit not reported) --- Admitted patients only							
Within 2 weeks	>38	167	0.915 [a]	0.639 [a]	0.581 [a]	0.932 [a]	35.33 [a,b]
	>85	167	0.627 [a]	0.796 [a]	0.627 [a]	0.796 [a]	35.33 [a,b]
ROPE,[45] Roche Elecsys ratio, result concealed, <34 weeks (lower limit not reported) --- Admitted patients only							
Within 2 weeks	>38	97	0.932 [a]	0.717 [a]	0.732 [a]	0.927 [a]	45.36 [a,b]
	>85	97	0.682 [a]	0.830 [a]	0.769 [a]	0.759 [a]	45.36 [a,b]

NPV: negative predictive value; NR: not reported; PPV: positive predictive value
[a] confidence interval not reported
[b] prevalence calculated by reviewer

Table 84 Prediction of delivery by time point

Time point	Cut-off pg/mL	Total (n)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Prevalence % (95% CI)
PETRA, [a] *Triage test, result concealed, 20+0 to 35+0 weeks*							
Within 1 week	≤100	[redacted]	0.925 [redacted]	0.622 [redacted]	0.675 [redacted]	0.907 [redacted]	[redacted] [b]
Within 2 weeks	≤100	[redacted]	0.905 [redacted]	0.685 [redacted]	0.766 [redacted]	0.864 [redacted] [b]	[redacted] [b,c]
PELICAN, [22] *Triage test, result concealed, 20+0 to 34+6 weeks*							
Within 2 weeks	≥100	287	0.940 (0.865-0.980)	0.569 (0.498-0.638)	0.470 (0.392-0.549)	0.959 (0.906-0.986)	28.92 (23.74-34.54) [b]
ROPE, [45] *Roche Elecsys ratio, result concealed, <36+6 weeks (lower limit not reported; median gestational age 34 weeks; IQR 30.7 to 35.9)*							
Within 2 weeks	>38	402	0.586 [d]	0.876 [d]	0.773 [d]	0.745 [d]	42.04 [b,d]
	>85	402	0.349 [d]	0.957 [d]	0.855 [d]	0.670 [d]	42.04 [b,d]
ROPE, [45] *Roche Elecsys ratio, result concealed, <34 weeks (lower limit not reported)*							
Within 2 weeks	>38	199	0.763 [d]	0.850 [d]	0.682 [d]	0.895 [d]	29.65 [b,d]
	>85	199	0.593 [d]	0.943 [d]	0.814 [d]	0.846 [d]	29.65 [b,d]

NPV: negative predictive value; NR: not reported; PPV: positive predictive value; TP: true positives; TN: true negatives.
[a] sources: Sibai 2015,[27] Barton 2020[26] NB Sibai is the 2015 Alere company submission - data are academic in confidence so to be redacted from HTA report
[b] calculated by reviewer
[c] overall PE prevalence reported by Barton 2020[26] (not reported separately by outcome) was 71.4%
[d] confidence interval not reported

Table 85 Prediction of indicated delivery within 2 weeks

Cut-off pg/mL	Total (n)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Prevalence % (95% CI)
ROPE, [45] *Roche Elecsys ratio, result concealed, <36+6 weeks (lower limit not reported; median gestational age 34 weeks; IQR 30.7 to 35.9)*						
>38	402	0.620 [a]	0.846 [a]	0.688 [a]	0.803 [a]	35.32 [a,b]
>85	402	0.387 [a]	0.946 [a]	0.797 [a]	0.739 [a]	35.32 [a,b]
ROPE, [45] *Roche Elecsys ratio, result concealed, <34 weeks (lower limit not reported)*						
>38	199	0.857 [a]	0.840 [a]	0.636 [a]		24.62 [a,b]
>85	199	0.673 [a]	0.933 [a]	0.767 [a]		24.62 [a,b]
Baltajian et al., [46] Roche Elecsys ratio, result concealed, <37 weeks (lower limit not reported; median gestational age 33 weeks; IQR 31 to 35)						
≥85	100	0.60 (0.49-0.71)	0.84 (0.70-0.98)	0.91 (0.83-0.99)	NR	NR

NPV: negative predictive value; NR: not reported; PPV: positive predictive value; [a] confidence interval not reported [b] prevalence calculated by reviewer

Table 86 Prediction of PE requiring delivery by time point

Time point	Cut-off	Total (n)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Prevalence % (95% CI)
PETRA, [25] Triage test, result concealed, 20+0 to 35+0 weeks							
Within 1 week	≤100 pg/mL	753	0.939 (NR)	0.588 (NR)	0.616 (NR)	0.932 (NR)	NR [a]
Within 2 weeks	≤100 pg/mL	753	0.925 (NR)	0.638 (NR)	0.698 (NR)	0.903 (NR)	NR [a]
PELICAN, [22] Triage test, result concealed, 20+0 to 34+6 weeks							
Within 2 weeks	≥100 pg/mL	287	0.940 (0.865-0.980)	0.569 (0.498-0.638)	0.470 (0.392-0.549)	0.959 (0.906-0.986)	28.92 (23.74-34.54) [b]
	<12 pg/mL	287	0.63 (0.51-0.74)	0.90 (0.85-0.94)	0.70 (0.57-0.80)	0.87 (0.82-0.91)	26.48 (21.47-31.99) [b]
PELICAN, [22] [270] Triage test, result concealed, 35+0 to 36+6 weeks							
Within 2 weeks	<12 pg/mL	137	0.22 (0.13-0.34)	0.91 (0.82-0.97)	0.71 (0.48-0.89)	0.55 (0.46-0.64)	48.91 (40.27-57.58) [b]
PROGNOSIS Asia, [43] [c] Roche Elecsys ratio, result concealed, 20+0 to 36+6 weeks							
Within 1 week	≤38	695	1.000 (0.692-1.000)	0.804 (0.773-0.833)	0.069 (0.034-0.124)	1.000 (0.993-1.000)	1.44 [b]
Within 4 weeks	≤38	695	0.698 (0.557-0.817)	0.833 (0.802-0.861)	0.257 (0.188-0.336)	0.971 (0.953-0.983)	7.63 [b]

NPV: negative predictive value; NR: not reported; PPV: positive predictive value
[a] overall PE prevalence reported by Barton 2020[26] (71.4%) but would vary with outcome and has not been reported separately for this outcome.
[b] calculated by reviewer
[c] an analysis of a Japanese subgroup of the PROGNOSIS Asia population[10] gave similar findings (data not reproduced here).

In the PELICAN study, Duckworth et al.[21] reported that for women presenting between 20^{+0} and $34^{+6/7}$ weeks of gestation the AUC for PIGF <12 pg/mL for predicting pre-eclampsia requiring delivery in 14 days was 0.87 (95% CI 0.83-0.92). Duckworth et al.[21] also noted that excluding twin pregnancies altered the PIGF test performance by less than 1%; however, 96% of women in the study had a singleton pregnancy.

Table 87 Prediction of preterm PE requiring delivery by time point

Time point	Cut-off	Total (n)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Prevalence % (95% CI)
PETRA, [a] *Triage test, result concealed, 20^{+0} to 35^{+0} weeks*							
Within 1 week	≤100 pg/mL	753	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] [b]
Within 2 weeks	≤100 pg/mL	753	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] [b]
Any preterm delivery	≤100 pg/mL	[redacted]	0.817	0.853	0.935	0.645	[redacted] [b,c]
	<12 pg/mL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] [b,c]
PELICAN, [22] *Triage test, result concealed, 20^{+0} to 34^{+6} weeks*							
Within 2 weeks	≥100 pg/mL	287	0.960 (0.888-0.992)	0.557 (0.487-0.625)	0.434 (0.357-0.513)	0.975 (0.929-0.995)	26.13 (21.15-31-62) [b]
Any preterm delivery	<12 pg/mL	287	0.439 (0.358-0.523)	0.971 (0.928-0.992)	0.942 (0.858-0.984)	0.619 (0.551-0.684)	51.57 (45.62-57.48) [b]

NPV: negative predictive value; NR: not reported; PPV: positive predictive value

[a] sources: Sibai 2015,[27] Barton 2020[26] NB Sibai is the 2015 Alere company submission - data are academic in confidence so to be redacted from HTA report

[b] calculated by reviewer

[c] overall PE prevalence reported by Barton 2020[26] (not reported separately by outcome) was 71.4%

Table 88 Prediction of delivery within 2 weeks due to pre-eclampsia or superimposed pre-eclampsia

Cut-off pg/mL	TP (n)	TN (n)	FP (n)	FN (n)	Total (n)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)	Prevalence % (95% CI)
PEACHES (PELICAN),[24] Triage test, result concealed, 20+0 to 36+6 weeks - No pre-existing disease												
<5th [a] centile	9	111	25	3	123	0.874 (0.794-0.931)	0.548 (0.474-0.621)	0.517 (0.44-0.594)	0.887 (0.814-0.938)	1.93 (1.62-2.30)	0.23 (0.14-0.39)	9.76 [c]
>85 [b]	45	86	20	4	155	0.918 (0.804-0.977)	0.811 (0.724-0.881)	0.692 (0.566-0.801)	0.956 (0/890-0.988)	4.87 (3.25-7.29)	0.10 (0.04-0.26)	31.61 [c]
PEACHES (PELICAN),[24] Triage test, result concealed, 20+0 to 36+6 weeks - Chronic hypertension												
<5th [a] centile	10	42	17	1	70	0.909 (0.587-0.998)	0.712 (0.579-0.822)	0.370 (0.194-0.576)	0.977 (0.877-0.999)	3.16 (2.03-4.91)	0.13 (0.02-0.83)	15.71 [c]
>85 [b]	5	33	8	0	46	1.000 (0.478-1.000)	0.805 (0.651-0.912)	0.385 (0.139-0.684)	1.000 (0.894-1.000)	5.13 (2.75-9.54)	0 (0-0)	10.87 [c]
PEACHES (PELICAN),[24] Triage test, result concealed, 20+0 to 36+6 weeks - Chronic kidney disease												
<5th [a] centile	5	12	3	3	23	0.625 (0.245-0.915)	0.750 (0.476-0.927)	0.556 (0.212-0.863)	0.800 (0.519-0.957)	2.50 (0.92-6.82)	0.50 (0.20-1.28)	34.78 [c]
>85 [b]	9	41	10	1	61	0.900 (0.555-0.997)	0.804 (0.669-0.902)	0.474 (0.244-0.711)	0.976 (0.874-0.999)	4.59 (2.54-8.30)	0.12 (0.02-0.80)	14.75 [c]
PEACHES (PELICAN),[24] Triage test, result concealed, 20+0 to 36+6 weeks - Chronic hypertension or chronic kidney disease												
<5th centile	15	54	20	4	93	0.789 (0.544-0.939)	0.720 (0.604-0.818)	0.417 (0.255-0.592)	0.931 (0.833-0.981)	2.82 (1.83-4.34)	0.29 (0.12-0.71)	9.76 [c]

NPV: negative predictive value; NR: not reported; PPV: positive predictive value
The PEACHES study involves analysis of the patients from the PELICAN study cohort
[a] 5th centile for gestational age, longitudinal cohort
[b] validation cohort (publication Supplementary Table S11)
[c] calculated by reviewer

Table 89 Prediction of delivery within 2 weeks secondary to suspected PE by test and sample type

Sample type	Cut-off	Total (n)	Sensitivity (95% CI)	Specificity (95% CI)	PPV[b] (95% CI)	NPV[b] (95% CI)	Prevalence %[c] (95% CI)
McCarthy et al,[30] Triage test, result concealed, <35 weeks gestation							
Plasma[a]	<100 pg/mL	305	0.808 (0.606–0.934)	0.796 (0.744–0.841)	0.411 (0.341–0.485)	0.959 (0.914–0.981)	8.52
McCarthy et al,[30] DELFIA Xpress test, result concealed, <35 weeks gestation							
Plasma	<150 pg/mL	305	0.846 (0.651–0.956)	0.799 (0.747–0.845)	0.427 (0.359–0.498)	0.967 (0.923–0.986)	8.52
Serum	<150 pg/mL	198	0.875 (0.676–0.973)	0.770 (0.700–0.830)	0.402 (0.330–0.478)	0.972 (0.924–0.990)	12.12
McCarthy et al,[30] Elecsys sFlt-1/PlGF ratio result concealed, <35 weeks gestation							
Plasma	>38	305	0.731 (0.522–0.884)	0.932 (0.896–0.959)	0.654 (0.536–0.756)	0.951 (0.912–0.974)	8.52
Serum	>38	198	0.750 (0.533–0.902)	0.902 (0.848–0.942)	0.575 (0.449–0.692)	0.953 (0.911–0.976)	12.12

NPV: negative predictive value; NR: not reported; PPV: positive predictive value.
[a] no serum samples available for the Triage test
[b] calculated by reviewer
[c] paper states an assumption of 15% prevalence for PPV

Table 90 Prediction of delivery within 2 weeks or delivery by 37 weeks gestation by test and sample type

Sample type	Cut-off	Total (n)	Sensitivity (95% CI)	Specificity (95% CI)	PPV[b] (95% CI)	NPV[b] (95% CI)	Prevalence %[c] (95% CI)
McCarthy et al,[30] Triage test, result concealed, <37 weeks gestation							
Plasma[a]	<100 pg/mL	396	0.795 (0.635-0.907)	0.728 (0.679-0.774)	0.340 (0.290-0.395)	0.953.(0.915-0.974)	9.85
McCarthy et al,[30] DELFIA Xpress test, result concealed, <37 weeks gestation							
Plasma	<150 pg/mL	398	0.821 (0.665-0.925)	0.739 (0.691-0.784)	0.357 (0.307-0.411)	0.959 (0.922-0.979)	9.85
Serum	<150 pg/mL	244	0.893 (0.672-0.936)	0.716 (0.650-0.777)	0.341 (0.285-0.402)	0.961 (0.921-0.981)	14.75
McCarthy et al,[30] Elecsys sFlt-1/PlGF ratio result concealed, <37 weeks gestation							
Plasma	>38	396	0.641 (0.472-0.788)	0.894 (0.857-0.924)	0.515 (0.421-0.609)	0.934 (0.903-0.956)	9.85
Serum	>38	244	0.639 (0.462-0.792)	0.861 (0.806-0.905)	0.447 (0.348-0.551)	0.931 (0.897-0.954)	14.75

NPV: negative predictive value; NR: not reported; PPV: positive predictive value.
[a] no serum samples available for the Triage test
[b] calculated by reviewer
[c] paper states an assumption of 15% prevalence for PPV and NPV.

Table 91 Prediction of delivery within 2 weeks secondary to suspected PE or delivery by 37 weeks gestation by test and sample type

Sample type	Cut-off	Total (n)[b]	Sensitivity (95% CI)	Specificity (95% CI)	PPV[c] (95% CI)	NPV[c] (95% CI)	Prevalence %[d] (95% CI)
McCarthy et al,[30] Triage test, result concealed, 35 to 36^{+6} weeks gestation							
Plasma[a]	<100 pg/mL	91	0.769 (0.462-0.950)	0.514 (0.393-0.633)	0.218 (0.160-0.290)	0.927 (0.820-0.972)	15.29
McCarthy et al,[30] DELFIA Xpress test, result concealed, 35 to 36^{+6} weeks gestation							
Plasma	<150 pg/mL	91	0.769 (0.462-0.950)	0.569 (0.447-0.686)	0.240 (0.175-0.320)	0.933 (0.836-0.975)	15.29
Serum	<150 pg/mL	46	0.750 (0.428-0.945)	0.455 (0.281-0.636)	0.195 (0.134, 0.276)	0.912 (0.783-0.967)	26.67
McCarthy et al,[30] Elecsys sFlt-1/PlGF ratio result concealed, 35 to 36^{+6} weeks gestation							
Plasma	>38	91	0.462 (0.192-0.749)	0.764 (0.649-0.856)	0.256 (0.144-0.415)	0.889 (0.827-0.931)	15.29
Serum	>38	46	0.417 (0.152-0.723)	0.667 (0.482-0.820)	0.181 (0.088-0.335)	0.866 (0.791-0.917)	26.67

NPV: negative predictive value; NR: not reported; PPV: positive predictive value.
[a] no serum samples available for the Triage test
[b] total numbers reported in paper (91 for plasma and 46 for serum respectively) differ from sum of reported individual cells (85 and 45)
[c] calculated by reviewer
[d] paper states an assumption of 15% prevalence for PPV and NPV.

Table 92 Prediction of delivery within 2 weeks in women with confirmed pre-eclampsia by test and sample type

Sample type	Cut-off	Total (n)[b]	Sensitivity (95% CI)	Specificity (95% CI)	PPV[c] (95% CI)	NPV[c] (95% CI)	Prevalence %[d] (95% CI)
McCarthy et al,[30] Triage test, result concealed, <35 weeks gestation							
Plasma[a]	<100 pg/mL	305	0.875 (0.617-0.984)	0.875[b] (0.617-0.984)	0.411 (0.344-0.481)	0.872 (0.906-0.992)	5.25
McCarthy et al,[30] DELFIA Xpress test, result concealed, <35 weeks gestation							
Plasma	<150 pg/mL	305	0.938 (0.698-0.998)	0.782 (0.730-0.828)	0.431 (0.371-0.494)	0.986 (0.914-0.998)	5.25
Serum	<150 pg/mL	198	0.875 (0.617-0.984)	0.742 (0.672-0.804)	0.374 (0.305-0.449)	0.971 (0.902-0.992)	8.08
McCarthy et al,[30] Elecsys sFlt-1/PlGF ratio result concealed, <35 weeks gestation							
Plasma	>38	305	0.813 (0.544-0.960)	0.913 (0.875-0.943)	0.624 (0.516-0.721)	0.965 (0.909-0.987)	5.25
Serum	>38	198	0.813 (0.544-0.960)	0.879 (0.823-0.923)	0.543 (0.429-0.652)	0.964 (0.905-0.987)	8.08

NPV: negative predictive value; NR: not reported; PPV: positive predictive value.
[a] no serum samples available for the Triage test
[b] potential reporting error reviewer calculates as 77.85% (95% CI: 72.62% to 82.51%)
[c] calculated by reviewer
[d] paper states an assumption of 15% prevalence for PPV and NPV.

Other test accuracy predictions

Salahuddin et al.[47] reported the predictive accuracy of the BRAHMS Kryptor sFlt-1/PlGF ratio, when used as a standalone test in a model adding systolic blood pressure and proteinuria, for short-term adverse outcomes occurring within 2 weeks (comprising a specified range of maternal and fetal adverse outcomes). Among women with suspected pre-eclampsia presenting from 20^{+0} to 33^{+6} weeks, at a cut-off of 85 the positive predictive value for adverse outcomes within 2 weeks was 0.710 (95% CI 0.550-0.870) and the negative predictive value was 0.848 (95% CI 0.769-0.927). Salahuddin et al.[47] compared the area under the curve (AUC) for the BRAHMS Kryptor sFlt-1/PlGF ratio and the Roche Elecsys sFlt-1/PlGF ratio when both tests were modelled in addition to systolic blood pressure and proteinuria and they obtained an identical AUC for both tests (0.89; 95% CI 0.82-0.95).

Saleh et al,[54] reported the accuracy of the Roche Elecsys sFlt-1/PlGF ratio test at a test cut-off of $\geq$85 to predict adverse outcomes defined as the occurrence of one or more complication(s) of pre-eclampsia within two weeks after blood sampling with a PPV of 0.950 and an NPV of 0.810.

Appendix 6. Ongoing studies

Table 93 Potentially relevant ongoing studies of PlGF test accuracy and impact clinical outcomes

Study and identifier	Objective	Completion date
Triage PlGF assay		
PARROT-Ireland NCT02881073	RCT to assess the impact of knowledge of PlGF levels (concealed vs revealed arms) on maternal and neonatal outcomes. There will be a cost-effectiveness analysis.	April 2019; results not yet reported
Elecsys PlGF assay		
[redacted]	[redacted]	November 2021; intention to publish January 2022
Elecsys sFlt-1/PlGF ratio		
[redacted]	[redacted]	November 2021; intention to publish January 2022
[redacted]	[redacted]	June 2023
BRAHMS Kryptor PlGF assay and sFlt-1/PlGF ratio		
No ongoing studies additional to PRAECIS[254] and REPORTS[255] were identified.		
DELFIA sFlt-1 and PlGF assays		
[redacted]	[redacted]	Q1 2021

[redacted]	[redacted]	
Test not reported		
PRECOG NCT03289611	RCT to assess whether implementing results of sFlt-1/PlGF ratio test (usual care vs measure ratio) improves perinatal care and reduces costs. Outcomes include hospitalisation, maternal and fetal morbidity, time to delivery, mode of delivery and costs.	November 2021
EuroPE study NCT03231657	RCT to evaluate the incorporation of the sFLT-1/PlGF ratio (routine clinical practice vs incorporate ratio) in the diagnosis of preeclampsia for improvement of maternal and perinatal outcomes.	February 2021
Fernández Oliva 2019 #69 Conference abstract	Evaluation of sFlt-1/PlGF ratio in the diagnosis and classification of preeclampsia	Expected to complete in 2 years (from 2019)

Appendix 7. Systematic review of economic evaluations of PlGF-based tests

Triage PlGF test

Duckworth and colleagues [98]

Duckworth and colleagues reported a cost analysis assessing the use of the Triage PlGF test plus a management algorithm compared with usual care for women with suspected pre-eclampsia prior to 35 weeks of gestation, based on the PELICAN prospective observational cohort study (see section 4.1.1).[270] All women were managed according to the 2010 NICE guideline on the Management of Hypertension in Pregnancy,[59] but for the intervention arm, measurement of PlGF alongside blood pressure and proteinuria were used to risk stratify women. A decision tree was developed to assess the budget impact of introducing PlGF testing as a diagnostic adjunct compared with usual care. Using the proportions derived from the study data, the authors calculated (i) the number of women who would be tested for pre-eclampsia using PlGF; (ii) the number of women who fall into each of the three PlGF categories; (iii) the number of women who would eventually have a diagnosis of pre-eclampsia or not in each of the resulting branches; and (iv) the number of women with no, mild to moderate or severe hypertension in each of the resulting branches. The parameters used to calculate the number of women in each branch are shown in Table 94. In the PlGF plus management algorithm arm, women were divided into three different PlGF test thresholds:<12 pg/ml PlGF; PlGF 12-100 pg/ml; or PlGF >100 pg/ml and into three different groups of hypertension: normotensive or mild hypertension; moderate hypertension; or severe hypertension for a total of nine groups.

Table 94 Population parameters reported in Duckworth and colleagues.[98]

Diagnosis per 1000 women	Percentage	Source
Suspected pre-eclampsia	20%	Clinical expert
Suspected pre-eclampsia < 35 weeks	6%	Clinical expert
Disease incidence		
Incidence of pre-eclampsia	1.8%	
Percentage with moderate hypertension in women diagnosed with pre-eclampsia	68%	Anumba et al (2010) [271]
Percentage with severe hypertension in women diagnosed with pre-eclampsia	8%	Anumba et al (2010) [271]
Percentage with moderate hypertension in women not diagnosed with pre-eclampsia	55%	Anumba et al (2010) [271]

Percentage with severe hypertension in women not diagnosed with pre-eclampsia	4%	Anumba et al (2010) [271]
PlGF test characteristics (<35 weeks predictive for the next two weeks)		
Sensitivity PlGF>100pg/ml	96%	Chappell et al (2013)[270]
Specificity PlGF>100pg/ml	55%	Chappell et al (2013)[270]
Sensitivity PlGF<12pg/ml	63%	Chappell et al (2013)[270]
Specificity PlGF<12pg/ml	90%	Chappell et al (2013)[270]
Source: [98]		

Health care resource use was based on the treatment algorithm used at that time and the 2010 NICE Hypertension in Pregnancy Guideline.[59] Cost parameters (cost year 2013/2014) are included for hospital admissions, outpatient appointments, additional specialised ultrasound and day unit costs (not admitted). The cost of the PlGF test was assumed to be £50, however no details of what this included were reported. Follow-up with the authors clarified that the cost of the test was provided by Alere and only includes the cost of the testing kit. The model did not include the option of a retest. The cost of routine diagnostic tests (such as serum transaminases, urinary protein estimation) and medication were not included on the basis that they represent a small percentage of the total costs of care and reliable data were not available. As clinicians were not aware of PlGF concentrations, it was assumed that on average women present at 31 weeks' gestation for the PlGF test and that all women have two weeks of costs. Plasma samples were tested for PlGF by trained laboratory staff at the point of care.

Of 1,000 women in the model, 60 presented with suspected pre-eclampsia prior to 35 weeks' gestation and 18 (30%) had a final diagnosis of pre-eclampsia. One woman with a final diagnosis of pre-eclampsia had a PlGF concentration greater than 100 pg/ml (false negative). Nineteen women without pre-eclampsia had a PlGF concentration below 100 pg/ml PlGF threshold (false positives) and hence were managed using the PlGF algorithm even though they did not have a final diagnosis related to pre-eclampsia.

The mean cost saving associated with the PlGF test alongside the management algorithm for each woman tested was £635 (95% CI -£1454 to -£4). We note that there is an

inconsistency within the publication because different results are reported in the Abstract and in the Results section: a cost saving of £635 per woman is reported in the Results section and of £582 in the Abstract. Sensitivity analyses were conducted varying pre-eclampsia incidence rates, health care resource use and the cost of PlGF test. Results were most sensitive to changes to cost of admission to the inpatient ward.

Duhig and colleagues [99]

Duhig and colleagues reported the cost-effectiveness of comparing the Triage PlGF test alongside a clinical management algorithm with usual care for women with suspected pre-eclampsia between 20 and 36 weeks' gestation and a singleton pregnancy, based on a within trial analysis of the PARROT trial.[15] We note that the Triage PlGF test is recommended to be used in women with suspected pre-eclampsia after 20 weeks and prior to 35 weeks of gestation.[22] Women in the usual care arm were managed according to 2010 NICE guideline on Management of Hypertension in Pregnancy.[59] For the intervention arm, low values of PlGF indicated higher risk of pre-eclampsia. PlGF concentration of >100 pg/ml followed a care pathway involving outpatient management and routine surveillance unless clinical parameters such as severe hypertension indicated otherwise. Those with low PlGF concentrations (12-100 pg/ml) were advised to increase surveillance with a greater frequency of antenatal care visits and fetal ultrasound scanning. Those with very low PlGF concentrations (<12 pg/ml) were assessed as 'pre-eclampsia', with consideration for admission, intensive monitoring, and fetal ultrasound scanning.

A decision tree with a Monte Carlo simulation was constructed to calculate the probability that PlGF testing is cost saving compared with usual care. The model did not include the option of a retest. Costs were taken from NHS reference costs 2016/17.[272] The cost of each PlGF test was estimated at £70 (prices from 2017/2018), although details of what this includes were not reported. Follow-up with the authors clarified that the cost of the test was provided by the manufacturer and that staff training costs and additional laboratory processing costs over and above the cost of the test itself were not included. Maternal resource use included maternity outpatient appointments, antenatal hospital admission and hospital admission associated with delivery (both standard and intensive care admissions). Infant resource use included routine care and admission to a neonatal unit (special care, high-dependency and intensive care). Resource use was taken from the PARROT trial.[15]

Among participants of the PARROT study, 236 (23.5%) had a PlGF <12 pg/ml, 385 (38.3%) a PlGF 12–100 pg/ml, and 384 (38.2%) had a PlGF > 100 pg/ml. PlGF testing alongside a clinical management algorithm resulted in an average of 15 fewer maternal adverse events

per 1000 women tested compared with usual care. There is a total cost-saving of £149 per patient tested. Sensitivity analyses were conducted varying the cost of the test between £50 and £200.

Elecsys sFlt-1/PlGF ratio test

Vatish and colleagues [106]

Vatish and colleagues [106] assessed the introduction of the Elecsys sFlt-1/PlGF ratio test into UK clinical practice for women with suspected pre-eclampsia between 24+0 and 36+6 weeks of gestation. The authors developed a decision tree to model the progression of women with suspected pre-eclampsia through a management pathway determined by their assessed risk of developing pre-eclampsia and the consequent decision to hospitalise or to manage the pregnancy in an outpatient setting. The study focused on determining the potential cost savings associated with improved diagnostic performance achieved using the sFlt-1/PlGF ratio test in addition to usual care when compared to usual care alone.

The paper does not report what is included in the usual care arm or the criteria that would lead to diagnosis of pre-eclampsia in this arm. The sFlt-1/PlGF ratio threshold values adopted in the study were: ≤38 for low risk (to rule out pre-eclampsia), >38 and <85 for intermediate risk or ≥85 suggesting high risk of developing pre-eclampsia. Test accuracy parameters such as sensitivity and specificity were not reported by Vatish and colleagues.[106] The model assumes that all women who initially test negative (ratio<38) and continue with symptoms of pre-eclampsia (including epigastric pain, severe oedema and headache, confirmed hypertension or proteinuria, one of the criteria for HELLP syndrome, intrauterine growth restriction, or abnormal uterine perfusion) will receive a second sFlt-1/PlGF ratio test two weeks after the initial test, however the proportion of women who received a second test was not reported. Management of women with pre-eclampsia was based on a consensus statement[273] and the 2010 NICE guideline,[59] in which women could be directed to an outpatient setting (low-and intermediate intensity management) or to an inpatient setting (high-intensity management). The percentage of women with a given test threshold and the percentage of women hospitalised, with and without receiving the test, were based on data from the PROGNOSIS study[39] and are reported in Table 95 below. It was assumed that women with a ratio<38 were hospitalised if their blood pressure was higher than 160/110mmHg, as recommended by NICE guidelines.[59]

Table 95 Hospitalisation rates and distribution of women by test threshold

	Distribution by test threshold	Hospitalisation rate
Usual care alone	NA	36%
Elecsys sFlt-1/PlGF ratio test in addition to usual care		
≤38	76.1%	1.7%
>38 and <85	10.7%	55.4%
≥85	13.2%	64.8%
Source: Vatish and colleagues [106] NA, Not applicable		

Resource use assumptions were informed by the 2010 NICE guidelines for the management of women with hypertension in pregnancy[59] and the cost data were derived from UK sources. Costs and frequency of use for all relevant resources seem to be included, except for corticosteroid therapy. The unit cost of the ratio test was estimated at £65, however details of what this includes were not reported.

The introduction of the sFlt-1/PlGF test in addition to usual care was estimated to provide fewer false positive results and a total cost saving of £344 per patient versus usual care alone. Scenario analyses were conducted on inpatient length of stay, proportion of women admitted to hospital based on the value of the test ratio and the assumption of no retest. For the scenario without repeat testing, the cost saving per patient increased to £382. The main driver of costs was the proportion of women hospitalised. All the scenarios remained cost saving except for the scenario in which admission rates to hospital were increased to 10% for women with a ratio<38.

Figueira and colleagues,[100] Frusca and colleagues,[101] Hodel and colleagues,[103] Ohkuchi and colleagues[10]*and Schlembach and colleagues[105]*

The descriptions of the studies by Figueira and colleagues,[100] Frusca and colleagues,[101] Hodel and colleagues,[103] Ohkuchi and colleagues[10] and Schlembach and colleagues,[105] have been described more briefly as they used the same model structure as Vatish and colleagues[106] above. The study population, clinical inputs and the interventions in comparison were also the same as in Vatish and colleagues,[106] except for the study by Schlembach and colleagues in which the clinical inputs were based on data for the subgroup of German women in the PROGNOSIS study[39] and the study by Ohkuchi and colleagues[10] in which the clinical inputs were based on data from a subgroup of Japanese women in the

PROGNOSIS study. None of the five economic studies reported any details of what was included in the PlGF testing costs.

Figueira and colleagues[100] evaluated the Elecsys sFlt-1/PlGF ratio test for a Brazilian hospital perspective. They reported treatment costs associated with hospitalisation (bed costs and physician / nurse costs), outpatient appointments, anti-hypertensive medications, regular testing, the cost of preventing complications and the cost of treating complications (cost of unplanned re-attendance of women at hospital and cost of neonatal intensive care), sourced from two Brazilian hospitals – one public and one private hospital. In the public hospital, where documented data was lacking, conservative assumptions based on clinical advice were used. The outpatient management costs, and frequency of resource use were not clearly described in the study. The out-of-pocket cost of the ratio test was R$347.30 (£49; at an exchange rate of 1 Brazilian Real = £0.14, December 2020).

The introduction of the sFlt-1/PlGF ratio test in addition to usual care reduced the number of women hospitalised unnecessarily by 56%, and there was an expected cost saving per patient in the public hospital of R$185.06 (£26) and of R$635.84 (£90) in the private setting. Deterministic sensitivity analyses were performed varying costs, hospitalisation rates and exclusion of retest. The results were most sensitive to hospitalisation rates and costs. For the scenario of no retest, the cost saving per patient increased to R$661.00 (£94) in the public hospital and to R$1,287.26 (£183) in the private hospital. The authors of the study were contacted and provided some additional details on the standard care and costs of testing. The standard care arm, based on Brazilian and international guidelines, included increased systolic (≥140 mmHg) and diastolic pressure (≥90 mmHg) in a previously normotensive pregnant patient, associated with proteinuria (≥300 mg protein in 24h urine samples). Protein was measured by urinary creatinine ratio (mg / dL) ≥0.3 or a result of a reagent strip equal to ≥1, when other methods were not available. The final cost of the sFlt-1/PlGF ratio test included staff and training costs, validations, logistics, sample preparation, reporting, among others.

Frusca and colleagues[101] evaluated the Elecsys sFlt-1/PlGF ratio test for an Italian healthcare payer perspective by conducting a budget impact analysis. They described what was included in the usual care arm (measurement of blood pressure, urine analysis, ultrasound evaluation of fetal growth and Doppler sonography, evaluation of full blood count, creatinine, lactate dehydrogenase test and aspartate aminotransferase) although they did not report the thresholds to rule out pre-eclampsia in this arm. They estimated the proportion of women with a test ratio < 38 who are hospitalised (5%) by clinical expert opinion; and

reported the proportion of women who received a second test, based on the study of Vatish and colleagues,[106] although this proportion was not reported by Vatish et al.[106] The resource use assumptions were informed by national and international guidelines for the management of women with hypertension in pregnancy[59 274-276] and validated by Italian clinical experts. The cost data were derived from Italian sources. Hospitalisation costs, emergency admission costs and neonatal intensive care unit costs were reported, while the costs for lab and diagnostic tests, outpatient appointments and anti-hypertensive medication were not. The unit cost of the ratio test was €50 (£45; at an exchange rate of 1 Euro = £0.91, December 2020). The frequency of use of resources was not clearly reported. The introduction of sFlt-1/PlGF ratio test in addition to usual care reduced unnecessary hospitalisations before the onset of pre-eclampsia by 69.5% versus usual care alone. Over five years, the cost savings for a cohort of 49,455 women were around €159 million (£144 million). The input parameters were varied by 20% as part of the deterministic sensitivity analysis, which suggested that the model results were most sensitive to changes in the costs of hospitalisation. The results of the sensitivity analysis showed that the cost savings over five years ranged between €497 (£450) and €773 (£700) per patient. Follow-up with authors clarified that the test cost included costs of reagents, calibrators, controls, consumables, instruments, staff and laboratory.

The study from Hodel and colleagues[103] evaluated the Elecsys sFlt-1/PlGF ratio test for a Swiss healthcare perspective. They modelled women with suspected pre-eclampsia after 20 weeks of gestation. However, it is unclear whether the study population corresponds exactly to the current decision problem (women between 20+0 and 36+6 weeks of gestation). They derived the cost data for the outpatient setting from the official Swiss tariff list and from two Swiss hospitals for the inpatient setting. The clinical management for women in the outpatient setting was based on guidance from two Swiss clinical experts (authors of the Hodel et al. paper) and resource use in the inpatient setting was based on the PROGNOSIS study,[39] as described by the Swiss Diagnosis Resource Group codes. The unit cost of the ratio test, including the material, instrument and labour costs, was €141 (£128). The introduction of the test in addition to usual care reduced overall hospitalisation rates from 19% to 14% versus usual care alone and resulted in a total cost saving of €346 (£313) per patient. Hodel and colleagues[103] did not include a retest as part of the base case, but they have explored repeated testing in three scenarios: (1) retest rate of 6.5% for women in the low outpatient setting, based on data from the PreOS study[79] (there is an inconsistency within the publication, because Figure 3 reports that this rate was applied to women in both low and intermediate settings[103]); (2) retest rate of 100%, i.e. all woman retested; and (3) all intermediate follow up women retested four times. These scenarios provided cost savings of

€294 (£266), €205 (£186) and €107 (£97) per patient, respectively. A scenario excluding birth costs and deterministic sensitivity analysis (varying hospitalisation rates and costs and also test costs) were also conducted. Increasing the hospitalization cost by 20% resulted in the greatest saving (€547 [£495]) and increasing hospitalisation rates of women with a sFlt-1/PlGF ratio of ≤38 by 100% resulted in the lowest saving (€89 [£81]).

Schlembach and colleagues[105] evaluated the Elecsys sFlt-1/PlGF ratio test for a German healthcare perspective. They applied a slightly different range of test ratio thresholds than the other studies: ≤38 (to rule out pre-eclampsia), >38 and <85 (for gestational weeks 20+0–33+6) or > 38 and <110 (gestational week 34 onwards) and ≥85 (gestational weeks 20+0–33+6) or ≥110 (gestational week 34 onwards). Additionally, Schlembach and colleagues[105] reported the proportion of women who received a second test, extracted from the PreOS study.[79] The Schlembach and colleagues' study uses clinical data for the subgroup of German women in the PROGNOSIS study, so the clinical inputs differ from those in Table 95 for Vatish and colleagues (see Table 96 below). Schlembach and colleagues[105] derived unit costs from official German sources, including costs associated with the ratio test (€80 [£72]), hospitalisations, outpatient appointments, anti-hypertensive medication, regular testing costs, the cost of preventing complications and the cost of treating complications. A quarterly fee (€115 [£105]) covering all routine examinations was multiplied by the average number of quarters (1.2) and applied to all women irrespective of whether they were hospitalized or not. The cost of hospitalization was based on the Diagnosis Resource Group codes. The introduction of the ratio test in addition to usual care reduced the number of false positive results and consequently provided cost savings of €361 (£327) per patient. Both deterministic sensitivity analyses (varying inpatient length of stay, hospitalisation costs and proportion of women hospitalised based on the value of the ratio) and scenario analyses (retesting for every woman irrespective of whether she developed pre-eclampsia and irrespective of the initial test result) were conducted. Increasing the hospitalization cost by 20% resulted in the greatest saving (€449 [£407]) and introducing a re-test for all women resulted in the lowest saving (€257 [£233]).

Table 96: Hospitalisation rates and distribution of women by test threshold

	Distribution by test threshold	Hospitalisation rate
Usual care alone	NA	44.6%
Elecsys sFlt-1/PlGF ratio test in addition to usual care		
≤38[a]	64.2%	1.5%
>38 and <85 OR >38 and <110[a]	16.2%	57.6%

≥85 OR ≥110[a]	19.6%	70.0%
Source: Schlembach and colleagues [105] [a] The range of test ratio thresholds was: ≤38 (to rule out pre-eclampsia), >38 and <85 (for gestational weeks 20+0–33+6) or > 38 and <110 (gestational week 34 onwards) and ≥85 (gestational weeks 20+0–33+6) or ≥110 (gestational week 34 onwards) NA, Not applicable		

Ohkuchi and colleagues[10] evaluated the Elecsys sFlt-1/PlGF ratio test for a Japanese healthcare perspective. They used clinical data for the subgroup of Japanese women in the PROGNOSIS study. The inclusion criteria for the Japanese cohort were being a pregnant woman ⩾18 years of age who presented with suspected preeclampsia from 18 weeks + 0 days gestation to 36 weeks + 6 days gestation. They derived unit costs from official Japanese sources, including costs associated with the ratio test (9000 JPY [£59, at an exchange rate of 1 JPY = £0.0065, May 2021]), outpatient appointments, inpatient hospitalisation and intensive care costs. Introduction of the sFlt-1/PlGF ratio test using a cut-off value of 38 resulted in a reduced hospitalization rate compared with the rate in the no-test scenario (14.4% versus 8.7%). The reduction in the rate of hospitalizations led to an estimated 16 373 JPY [£108] reduction in healthcare costs per patient. The authors conducted sensitivity analyses. Those sensitivity analyses that had the greatest impact on the model results were increasing the hospitalization rate for women with sFlt-1/PlGF ratio ≤38 to 4% (cost saving per woman 6782 JPY [£45]) and an increase in the hospitalization rate in the no-test scenario to the overall hospitalization rate in PROGNOSIS Asia (cost saving per woman 69,482 JPY [£457]).

Other PlGF tests

Frampton and colleagues [7]

The study by Frampton and colleagues[7] is the previous Diagnostic Assessment Report produced for NICE for PlGF tests for suspected pre-eclampsia. Its goal was to evaluate the accuracy and cost-effectiveness of biomarker tests (Triage PlGF test, Elecsys sFlt-1/PlGF ratio test, DELFIA Xpress PlGF test and BRAHMS Kryptor sFlt-1/PlGF ratio test) in addition to usual care for women presenting with suspected pre-eclampsia between 20 weeks and 36+6 weeks of gestation. Only the Triage PlGF test and the Elecsys sFlt-1/PlGF ratio test were assessed in the economic analysis because no evidence of diagnostic test accuracy was identified for the two other tests.

A decision tree model was constructed with a time horizon corresponding to the duration of pre-birth and immediate postpartum monitoring. The model incorporates four main structural components – risk stratification of women with suspected pre-eclampsia, pre-eclampsia management, maternal outcomes and fetal and neonatal outcomes. Parameter inputs for diagnostic test accuracy and quality of life were derived from systematic reviews. Other clinical inputs were sourced from the PELICAN study[270] where possible, otherwise clinical advice and/or information from targeted searches were used. Resource use parameters were informed by the 2010 NICE guidelines for the management of women with hypertension in pregnancy,[59] the PELICAN study[270] and clinical expert opinion. Cost data (cost year 2014) were collected from official UK sources. The unit costs of the tests were provided by the manufacturers; however they are confidential and details of what costs were included were not reported.

Results were presented for two subgroups – women presenting before 35 weeks and women presenting between 35 and 37 weeks. As previously mentioned, the Triage PlGF test is recommended for women with suspected pre-eclampsia after 20 weeks and prior to 35 weeks of gestation.[22] The total QALY estimates were similar between arms both for women presenting before 35 weeks (increment of no more than 0.00076 QALYs) and for women between 35 and 37 weeks of gestation (no increment in QALYs). Use of the biomarker tests in addition to usual care provided estimated cost savings of £2,896 (Triage PlGF test) and £2,489 (Elecsys sFlt-1 to PlGF ratio test) versus usual care alone for women presenting before 35 weeks. For women presenting between 35 and 37 weeks, Triage PlGF test and Elecsys sFlt-1 to PlGF ratio test in addition to usual care provided a cost saving of £365 and £174 versus usual care alone, respectively. Test sensitivity and specificity, disease prevalence, costs and other model parameters associated with a high degree of uncertainty were varied in deterministic sensitivity analyses. Also, three assumptions were changed in scenario analyses: alternative management pathways, the place where PlGF tests were processed and analysed and the use of a PlGF test as a replacement for quantitative proteinuria testing. The length of neonatal intensive care unit stay was the most influential parameter. Women with multiple pregnancies were not excluded from the study, however there was limited data to assume that the results are relevant to multiple pregnancies.

Giardini and colleagues[102]

Giardini and colleagues[102] report a retrospective study that assessed the clinical and economic impact of the introduction of a PlGF test in Italian clinical practice to manage pregnant women who accessed the emergency room due to increased blood pressure after the 20th week of gestation. The authors clarified, after contact from the EAG, that included

women had a suspected hypertensive disorder, especially pre-eclampsia. It is, however, unclear whether the study population corresponds exactly to the current decision problem (women between 20+0 and 36+6 weeks of gestation) since the authors clarified that women after 36+6 weeks of gestation were also included.

Data on the subsequent emergency room attendance, hospitalisations and outpatient management (obstetric day service) were collected in the study for the entire population and two subgroups. The subgroups were (1) women without a significant blood pressure increase, i.e. women who had not developed clinical complications, and (2) women with significant blood pressure increase, i.e. followed by clinical complication such as pre-eclampsia and/or fetal growth restriction. Two clinical experts further assessed whether the introduction of a PlGF test in clinical practice would have avoided the use of any of the previous healthcare services (Table 97 below). The authors did not mention which PlGF test(s) has been used and did not report any other information related to them (cut off values, predictive accuracy, testing costs).

Table 97: Avoidable percentage of healthcare services due to PlGF test

Health care services	Avoidable percentage
Emergency room access	
Not significant blood pressure increase	18%
Significant blood pressure increase	4%
All	13%
Hospital admission	
Not significant blood pressure increase	19%
Significant blood pressure increase	15%
All	18%
Obstetric Day Service access	
Not significant blood pressure increase	68%
Significant blood pressure increase	22%
All	43%
Source: Giardini and colleagues [102]	

The parameter inputs and sources of resource use assumptions and costs were not reported. The costs included were the direct healthcare costs associated with emergency room attendance, hospitalisations and obstetric day service. The unit cost of the ratio test was about €60 (£54). The use and cost of healthcare services were estimated by the bootstrap method with 1,000 iterations.

The total cost of managing women with increased blood pressure was €2,634 (£2,385) per patient. The introduction of a PlGF test provided an estimated cost saving of €401 (£363) per patient versus usual care. Giardini and colleagues[102] did not report any sensitivity or scenario analyses.

Myrhaug and colleagues[104]

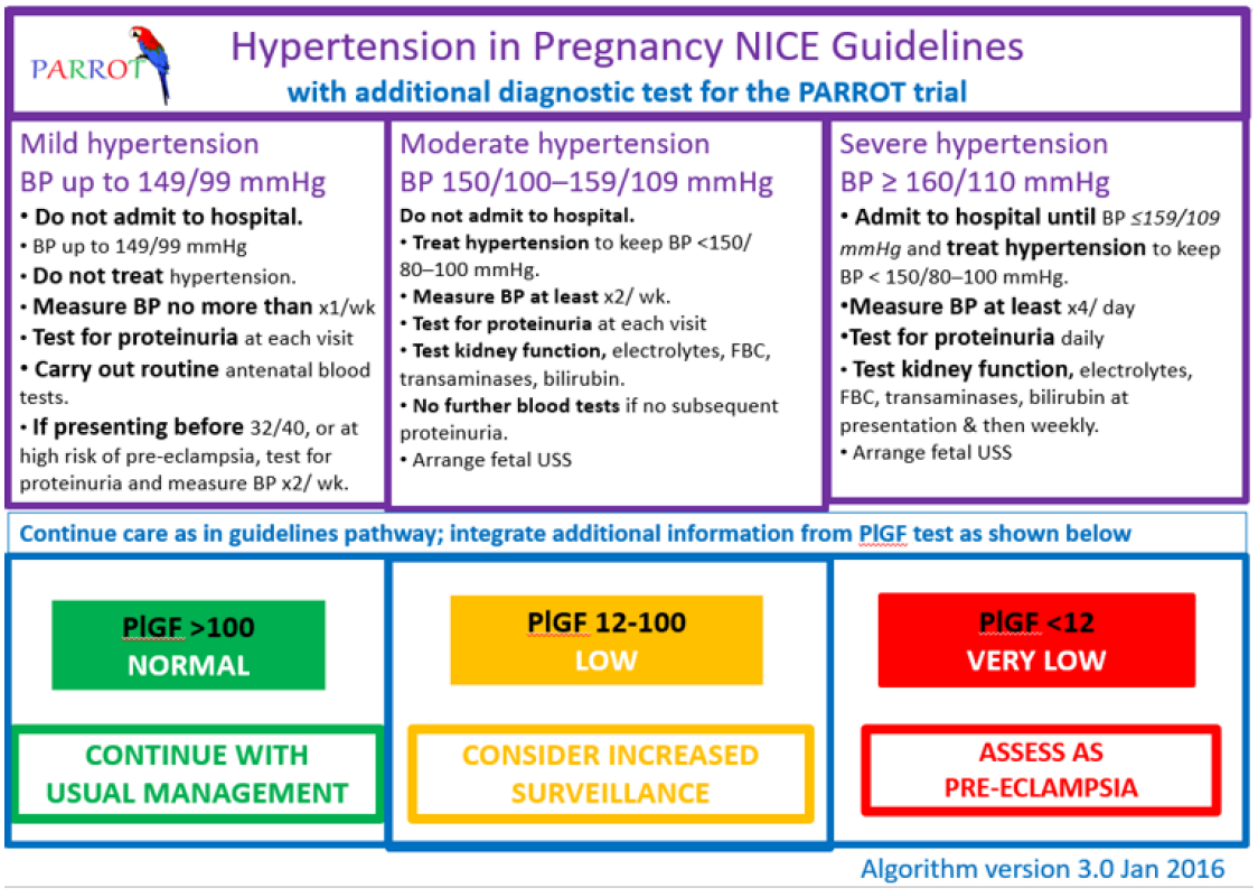
Myrhaug and colleagues[104] reported a cost effectiveness and budget impact analyses of PlGF tests, as part of a wider assessment of safety, effectiveness and health service utilisation. The population was pregnant women with suspected pre-eclampsia in the 2nd or 3rd trimester (week 20 to 36 (+6 days)). A decision tree model was constructed which contained two possible management options: intensive management requiring admission to the hospital and less intensive follow-up on an outpatient basis. Transition probabilities for admission and preeclampsia rates were derived from the INSPIRE study by Cerdeira and colleagues.[32] Hospitalised women were assigned inpatient management costs, depending on whether the diagnosis of pre-eclampsia was confirmed or not. The authors derived most cost estimates from the Norwegian Diagnosis Resource Group database (ISF 2020). Initial assessment costs were assumed to be equal for both strategies, with the cost of PlGF testing added in the strategy including testing. The estimated cost of performing a single test is 1,252 NOK (£108; at an exchange rate of 1 Norwergian Krone =£0.086, December 2020), ranging from 4 NOK (£85) to 1,510 NOK (£129). We note that there is an inconsistency within the publication because a different test cost is reported in Table 11 – 1,247 NOK (£107). All costs include laboratory personnel time, testing kits as well as calibrators and controls. The calculated estimate assumed that each laboratory processed at least 500 tests annually, performing testing 5 times per week, with a variable number of individual tests performed. Capital costs of investment in testing instruments were not included, as many such instruments were already in use in the laboratories. Costs of taking blood samples were not separately accounted for, as these costs are included in the cost estimate for the initial appointment in an outpatient specialist clinic. In the health economic analysis, the authors did not make distinctions between PlGF and sFlt-1/PlGF ratio tests and therefore assumed that they were equally effective, which might not be the case. The sensitivity and specificity of sFlt-1/PlGF ratio, taken from INSPIRE, were 0.85 and 0.87, respectively. Retesting was not included.

Table 98 Transition probabilities by Myrhaug and colleagues[104]

	Usual care alone	PlGF tests in addition to usual care
Hospitalisation rates	26.1%	32.3%
Pre-eclampsia	31.3%	40.0%
No pre-eclampsia	68.7%	60.0%
Outpatient management	73.9%	67.7%
Pre-eclampsia	2.2%	0.01%
No pre-eclampsia	97.8%	99.9%
Source: Myrhaug and colleagues [104]		

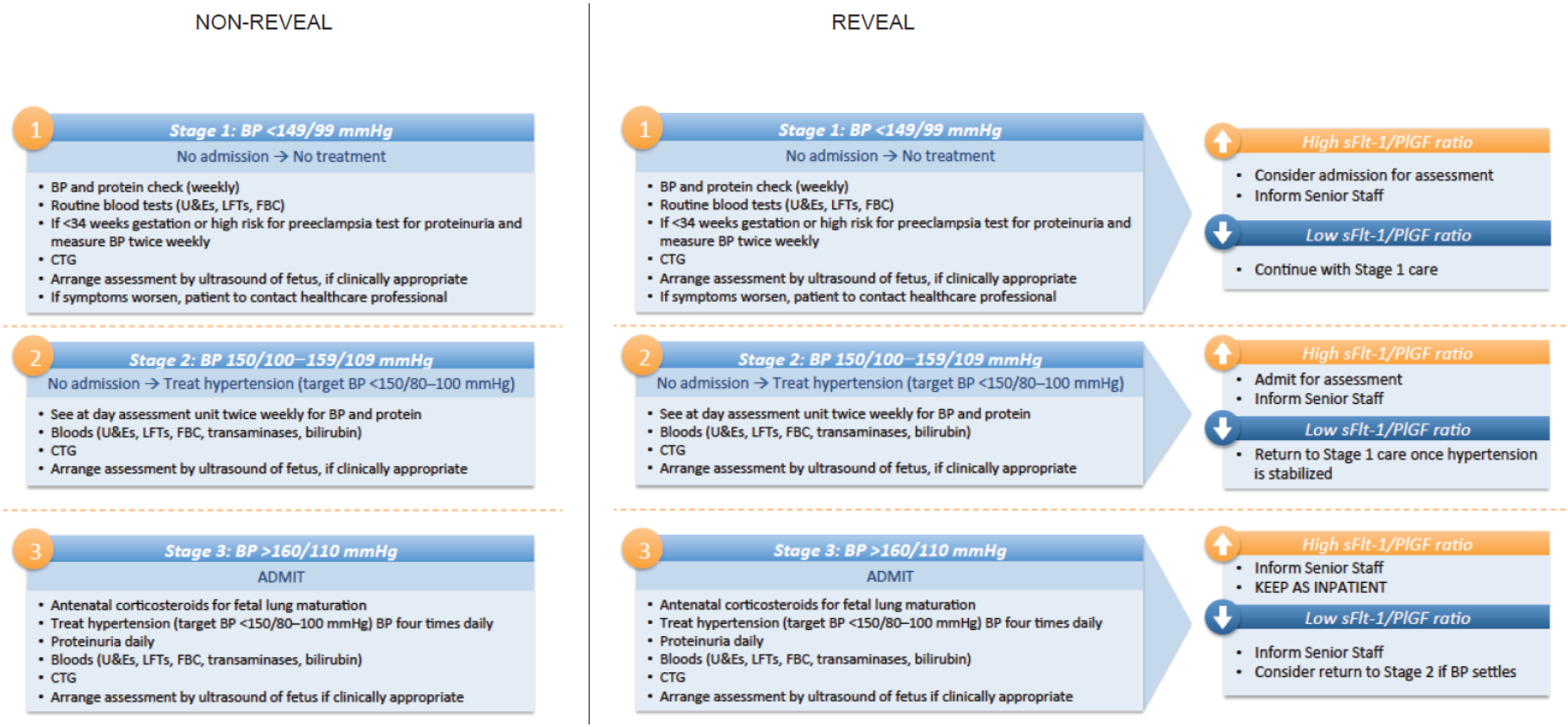
For an initial cohort of 6,000 women, 777 receiving PlGF test plus usual care vs. 489 receiving usual care alone were correctly identified with pre-eclampsia. The cost per additional correctly identified case of pre-eclampsia was 43,319 NOK (£3,710). The cost of the test was varied in sensitivity analyses.

Appendix 8. Clinical management algorithms used in the clinical trials



Source: Duhig 2019[15]

Figure 10 Clinical management algorithm incorporating PlGF testing (PARROT)



Source: Cerdeira 2019[32]

Figure 11 Clinical decision pathways for Non-reveal (standard clinical care) and Reveal (standard clinical care and sFlt-1/PlGF ratio test, Roche) arms in the INSPIRE trial

UNIVERSITY OF LIVERPOOL

Liverpool Pre-eclampsia PLGF Protocol for Maternity Assessment Unit

Liverpool Women's

Normotensive or mild hypertension BP up to 149/99 mmHg **(Community Care unless ↓ PLGF)**	**Moderate hypertension** BP 150/100–159/109 mmHg **(MAU Care)**	**Severe hypertension** BP ≥ 160/110 mmHg **(In-patient Care)**
• **Do not admit** to hospital • **Do not treat** hypertension • **Measure BP** no more than x1/wk • **Test for proteinuria** at each visit	• **Do not admit** to hospital • Oral labetalol to keep BP <150/ 80–100 mmHg • **Measure BP and PCR** at least x2/wk (If PCR> 30, do not repeat) • **Test Bloods (FBC, LFTs & renal function)**	• **Admit to hospital** until BP ≤159/109 mmHg and treat hypertension to keep BP < 150/80–100 mmHg • **Measure BP** at least x4/day • **Test for proteinuria,** if PCR<30 check daily and once >30, do not repeat • **Test Bloods (FBC, LFTs & renal function)**

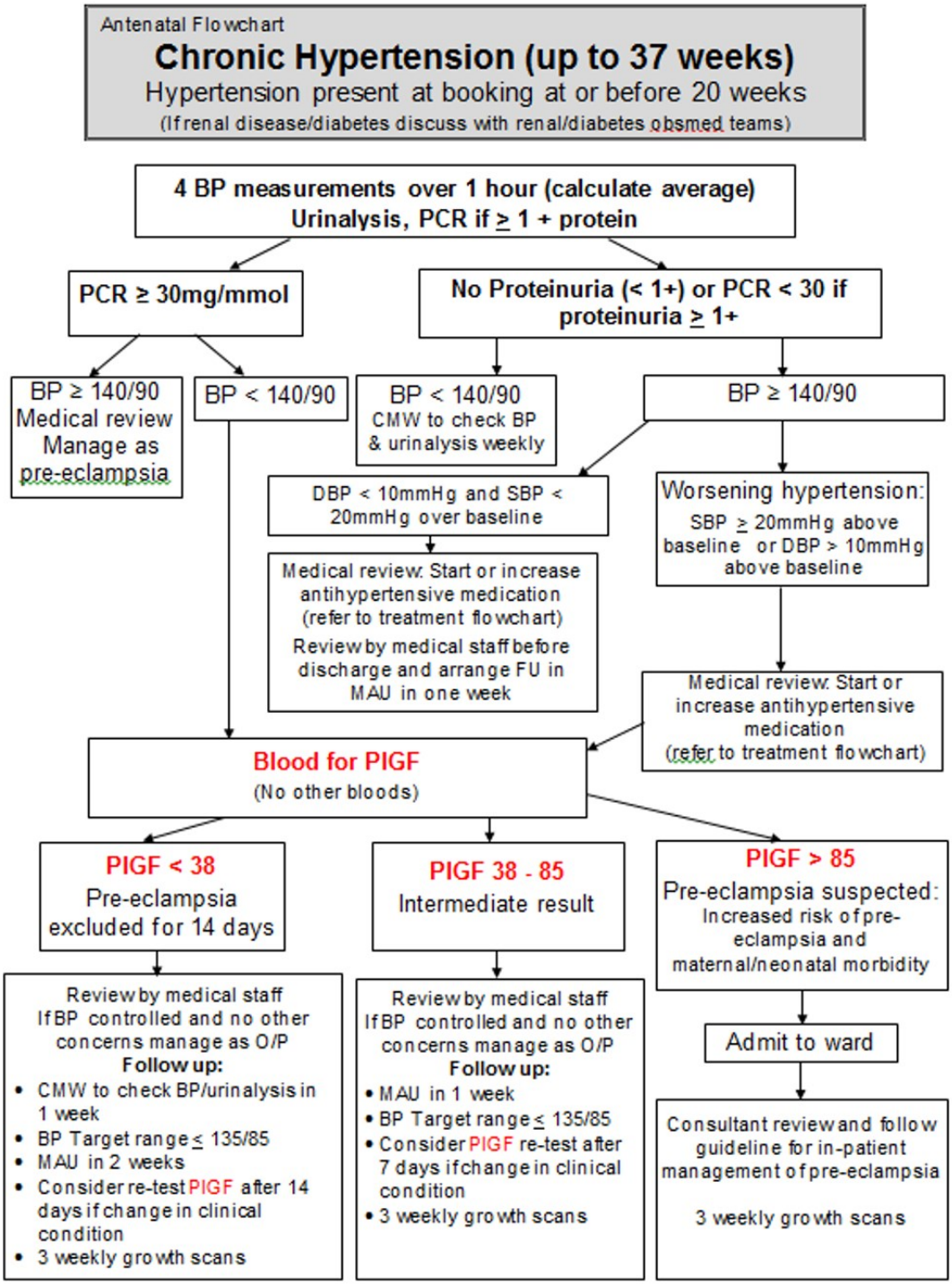
If <35^{+0} weeks test PLGF and follow algorithm below

PLGF < 12 pg/ml Highly abnormal Check PET bloods	**Urgent fetal assessment** (within 24 hours) • FMU growth scan & Doppler • Computerized CTG from 26^{+0} • If normal repeat via MAU twice weekly, if abnormal act accordingly	**PLGF < 12 pg/ml** Highly abnormal Check PET bloods	**Admit** • Urgent FMU growth scan & Doppler • Computerized CTG from 26^{+0} • If normal repeat Doppler weekly and CTG daily • If stable consider ODU monitoring twice weekly	**PLGF < 12 g/ml** Highly abnormal Check PET bloods	**Admit** • Urgent FMU growth scan & Doppler • Computerized CTG from 26+0 • If normal repeat Doppler weekly and CTG daily • If stable and PCR<30 consider daily ODU monitoring
PLGF ≥ 12 <100 Abnormal Check PET bloods	**Home if no immediate clinical concern** • Fetal growth and Doppler within 72 hours • weekly MAU review • PLGF weekly if <35^{+0}	**PLGF ≥ 12 <100** Abnormal Check PET bloods	**Home if no immediate clinical concern** • Growth scan & Doppler within 72 hours • Weekly MAU review • If PCR>30 – MAU twice weekly • PLGF weekly if <35^{+0}	**PLGF ≥ 12 <100** Abnormal Check PET bloods	**Consider MAU once BP controlled** • Growth scan & Doppler within 72 hours •MAU twice weekly • If PCR>30 – MAU daily • PLGF weekly if <35^{+0}
PLGF ≥100 Normal No need for PET bloods	**Refer back to Community care** • CMW monitor weekly • PLGF every 2 weeks if <35^{+0}	**PLGF ≥100** Normal	**Can go home if no immediate clinical concerns.** • MAU weekly • PLGF weekly if <35^{+0}	**PLGF ≥100** Normal	**ODU monitoring once BP controlled and no immediate clinical concerns.** • MAU twice weekly • PLGF weekly if <35^{+0}

Source: Sharp 2018[16]

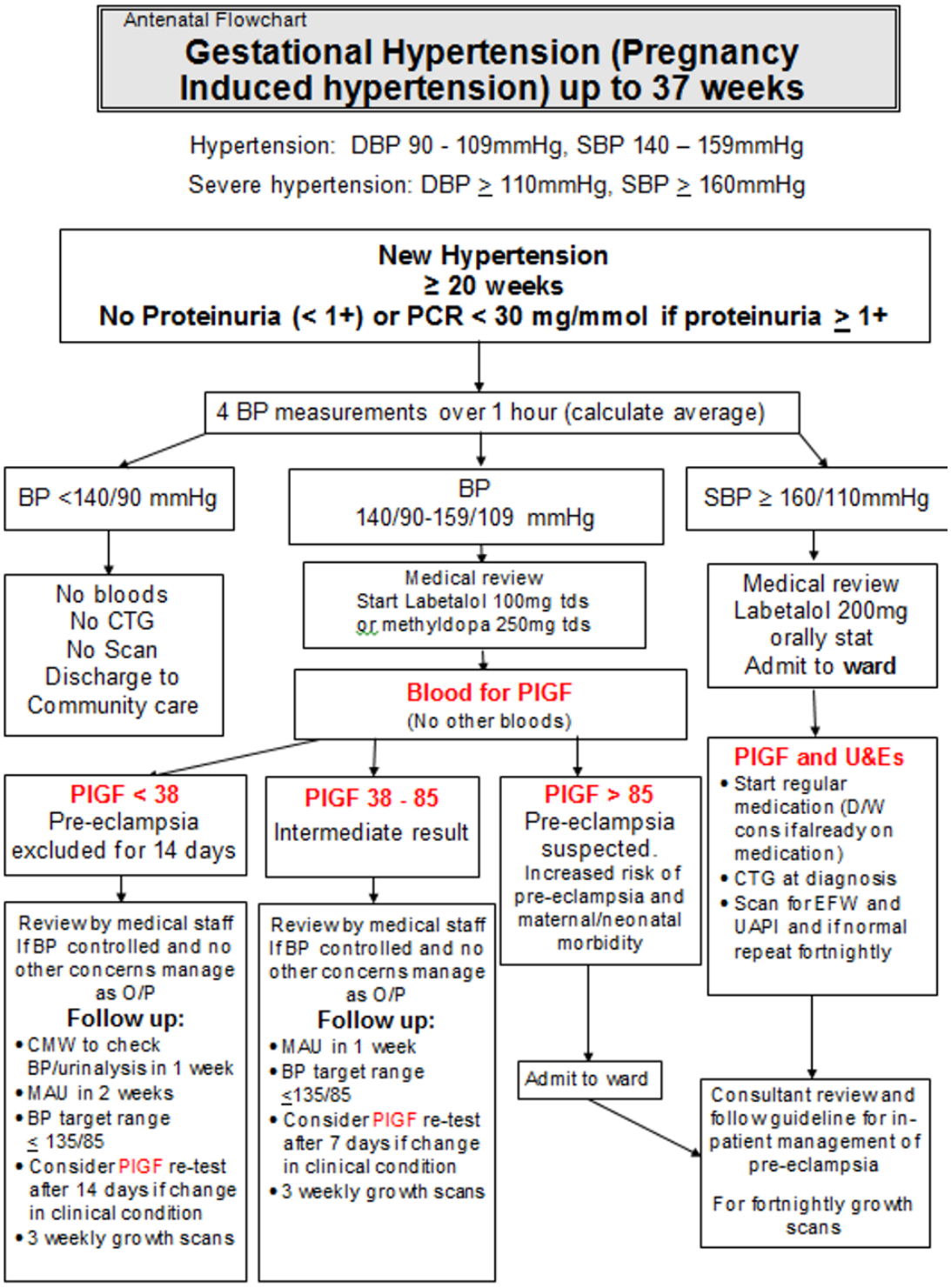
Figure 12 Clinical management algorithm for PlGF (Alere) used in the MAPPLE trial

Appendix 9. Clinical management algorithms used in clinical practice



Source: personal communication with Dr Steve Robson (March 2021)

Figure 13 Managing chronic hypertension: the Newcastle upon Tyne Hospitals NHS Foundation Trust



Source: personal communication with Dr Steve Robson (March 2021)

Appendix 10. Resource use for managing women with suspected pre-eclampsia (base case)

The tables below present the resource use considered in the model for base case to manage women with high-risk (Table 99), intermediate-risk and low-risk of pre-eclampsia (Table 100). The resource use is based on the management of pre-eclampsia and gestational hypertension recommended in CG107. [59]

Table 99 Resource use for the management of women with high risk of pre-eclampsia

1 - Expectant management					
1.1 - Mild hypertension (<149/99 mmHg)			**1.2 - Moderate (<159/109 mmHg) and Severe hypertension (>160/110 mmHg)**		
Resource		**Frequency**	**Resource**		**Frequency**
Hospitalisation	**<35 weeks**	12/17 days [a]	Hospitalisation	**<35 weeks**	12/17 days [a]
	>35 weeks	4/8 days [a]		**>35 weeks**	4/8 days [a]
Standard blood tests		2x/week	Standard blood tests		3x/week
Kidney function + electrolytes + full blood count + transaminases + bilirubin		2x/week	Kidney function + electrolytes + full blood count + transaminases + bilirubin		3x/week
Fetal assessment [b]		1x	Fetal assessment [b]		1x
Oral labetalol		-	Oral labetalol		Until delivery [c]
Corticosteroids		1x [d]	Corticosteroids		1x [d]
2 - Immediate delivery (if women >35w of gestation and severe hypertension)					
Resource		**Frequency**	**Resource**		**Frequency**
Hospitalisation		2 days [e]	Hospitalisation		2 days [e]
Other resources are the same as for expectant management			Other resources are the same as for expectant management		

Source: based on the management of pre-eclampsia recommended in CG107 [59] and clinical expert opinion

[a] Up to 35 weeks of gestation: 12 days in intervention arm and 17 days in comparator arm until delivery; between 35 and 37 weeks of gestation: 4 days in intervention arm and 8 days in comparator arm until delivery (based on PARROT trial [9])

[b] Includes ultrasound fetal growth; amniotic fluid volume assessment, umbilical artery Doppler velocimetry and fetal cardiotocography.

[c] At a dose of 200 mg twice daily.

[d] Two doses of 12mg intramuscularly.

[e] 48 hours until delivery, based on CG107 [59].

Table 100 Resource use for the management of women with intermediate and low risk of pre-eclampsia

1 – Expectant management					
1.1 – Mild hypertension (<149/99 mmHg)		**1.2 – Moderate hypertension (<159/109 mmHg)**		**1.3 – Severe hypertension (>160/110 mmHg)**	
Resource	**Frequency**	**Resource**	**Frequency**	**Resource**	**Frequency**
Hospitalisation	-	Hospitalisation	-	Hospitalisation [a]	3 days
Blood pressure	1x/week	Blood pressure	2x/week	Blood pressure	- [b]
Proteinuria	1x/week	Proteinuria	2x/week	Proteinuria	- [b]
Standard blood tests	1x/week	Standard blood tests	1x/week	Standard blood tests	1x/week
Kidney function + electrolytes + full blood count + transaminases + bilirubin	-	Kidney function + electrolytes + full blood count + transaminases + bilirubin	1x/week	Kidney function + electrolytes + full blood count + transaminases + bilirubin	1x/week
Fetal assessment [c]	1x [d]	Fetal assessment [c]	1x [d]	Fetal assessment [c]	1x
Oral labetalol	-	Oral labetalol	Until delivery [e]	Oral labetalol	Until delivery [e]
Corticosteroids	-	Corticosteroids	-	Corticosteroids	-

Source: based on the management of gestational hypertension recommended in CG107 [59] and clinical expert opinion

[a] Until blood pressure falls <159/109 mmHg, then manage as moderate hypertension.

[b] Performed as part of hospitalisation.

[c] Includes ultrasound fetal growth; amniotic fluid volume assessment, umbilical artery Doppler velocimetry and fetal cardiotocography.

[d] According to CG107, fetal assessment is only performed up to 34 weeks of gestation. Due to data availability, here we assumed that fetal assessment was performed up to 35 weeks of gestation.

[e] At a dose of 200 mg twice daily.

Appendix 11. Model assumptions for the EAG base-case and scenario analyses

Table 101 Model assumptions in the EAG base-case and scenario analyses

Assumption	Analysis	Justification
Population: test, source, GA, cut-offs, pregnancy type	Base case:	
	Triage PlGF: PARROT RCT, GA of 20+0 to 36+6, rule-in cut-offs: <12 and <100 for PE required delivery within 14 days for <35 weeks GA, and before 37 weeks for 35-36+6 GA (Duhig 2021[9]), singleton	The PARROT and INSPIRE RCTs were conducted in the UK.
	Elecsys sFlt-1/PlGF: INSPIRE RCT, GA of 24+0 - 37+0, with the cut-off of 38 for ruling out PE within 1 week and ruling in PE within 4 weeks (Cerdeira 2019[32]), singleton	
	BRAHMS Kryptor sFlt-1/PlGF: Salahuddin 2016[47]	It is assumed that the accuracy of BRAHMS for prediction of adverse events within 2 weeks is the same as for Elecsys (based on Salahuddin 2016[47]).

Assumption	Analysis	Justification
	Scenarios: - Triage PlGF: MAPPLE/PELICAN, Sharp 2018[16] (with PlGF stratified into < 12 pg/ml, 12–100 pg/ml and > 100 pg/ml), <35 weeks, singleton - Elecsys sFlt-1/PlGF: PreOS (parameterised from the number of hospitalised patients with test results of <33, from 33 to <35 and >35 before and after PlGF test results were revealed	
Number of tests	Base case: one per woman	Consistency with the RCTs
	Scenario: none	Repeat testing was not considered in the pivotal RCTs.
GH and PE pathways	Base case: NICE guidelines CG107	Consistency with clinical evidence in the trials used in the base case that were initiated before 2019.
	Scenario: NICE guidelines NG133[3] excluding the use of PlGF testing to rule out PE within 1 week) and online risk assessment tools	Better aligned with the current clinical practice for managing GH and PE.
PE prevalence	Base case: as in the pivotal RCTs	The PARROT and INSPIRE RCTs were conducted in the UK. Therefore, we would anticipate that the prevalence of disease seen in the trial populations would be similar in women presenting with suspected PE in the UK. However, in the pivotal trials the prevalence of PE varied considerably.

Assumption	Analysis	Justification
	Scenario: None	The economic model did not utilise test accuracy estimates directly and was parameterised from the outcomes reported for PlGF subgroups. Therefore, conducting scenarios for PE prevalence was not possible.
Level of hypertension	Base case: the proportion of women with each level of hypertension (mild, moderate, severe) was the same for all levels of risk of PE (high, intermediate and low risk)	Reported data was not stratified by the level of risk of PE as well as PE status (PE or no PE).
	Scenarios: - 70% of patients at high risk of PE have severe hypertension - 30% of patients at low risk of PE have severe hypertension	Assumption
Gestational age	Base case: the proportion of women with a gestational age <35 weeks was: - 85% if median GA at enrolment <33 weeks - 75% if median GA at enrolment <34 weeks - 65% if median GA at enrolment <35 weeks - 50% if median GA at enrolment <35 weeks	In the absence of data, this was based on the median gestational age at enrolment from PARROT and PLUSIRE
	Scenarios: proportion of women with gestational age <35 weeks was - 100% - 0%	Test the impact of extreme values in the model results.
Time to delivery	Base case: time to delivery estimates from PARROT	In line with the pivotal RCT
	Scenarios: time to delivery estimates based on MAPPLE/PELICAN for Triage PlGF test and on PROGNOSIS for Elecsys sFlt-1/PlGF ratio test	Test the impact of different published estimates in the model results

Assumption	Analysis	Justification
Maternal outcomes	Base case: maternal morbidity was informed by PARROT for Triage PlGF test and INSPIRE for Elecsys sFlt-1/PlGF ratio test.	In line with pivotal RCTs
	Scenarios: maternal morbidity informed by MAPPLE/PELICAN for Triage PlGF test	Test the impact of different published estimates in the model results
Incidence of respiratory distress syndrome and intraventricular hemorrhage	Base case: incidence of neonatal respiratory distress syndrome and intraventricular hemorrhage was based on PARROT for Triage. For Elecsys, incidence of respiratory distress syndrome and intraventricular hemorrhage was assumed the same as test and no test arms.	In line with pivotal RCTs
	Scenario: incidence of neonatal respiratory distress syndrome and intraventricular hemorrhage was based on MAPPLE/PELICAN (only for Triage PlGF test)	Test the impact of different published estimates in the model results
Fetal/neonatal outcomes	Base case: For Elecsys sFlt-1/PlGF ratio test, proportion of neonates admitted to critical care units according to data reported by INSPIRE.	In line with pivotal RCTs
	Scenario: Uses neonatal admission data from PARROT for both Triage PlGF test and Elecsys sFlt-1/PlGF ratio test	Test the impact of different published estimates in the model results
Neonatal death	Base case: including stillbirth	To test the impact of inclusion of stillbirth in the total number of deaths on the cost-effectiveness results
	Scenario: excluding stillbirth	
Long-term neonatal costs	Base case: the costs of pre-term babies were only applied to babies with respiratory distress syndrome	We considered that respiratory distress syndrome was a proxy for pre-term birth.
	Scenarios: the costs of pre-term babies were applied to all babies that were admitted to critical care units.	Test the impact of different assumptions for pre-term birth.

Assumption	Analysis	Justification
Cost of testing	Base case: includes the price of test kits, machine costs, maintenance, laboratory material, training, staff time and phone calls.	Most plausible estimate of cost of test.
	Scenarios: 1. Includes the price of test kits only - Triage PlGF test: £40 - Elecsys sFlt-1/PlGF ratio test: £66 - BRAHMS Kryptor sFlt-1/PlGF ratio test: £22 2. Cost of testing based on external sources - Triage PlGF test: £120 - Elecsys sFlt-1/PlGF ratio test: £110 - BRAHMS Kryptor sFlt-1/PlGF ratio test: £63	1. The price of test kits is the only price consistent between biomarker tests. 2. Triage PlGF test cost was based on the paper of Duhig and colleagues;[99] Elecsys sFlt-1/PlGF ratio test cost was informed by an expert advising the EAG; BRAHMS Kryptor sFlt-1/PlGF ratio test cost was assumed as a similar increment as the other two tests (+20%)
Long-term maternal QALYs	Base case: decrement for mothers whose child died applied for lifetime and decrement for mothers whose child had complications applied for two years	As assumed by Varley-Campbell and colleagues[157]
	Scenario: decrement for mothers whose child died and had complications applied for ten years.	Alternative scenario suggested by Varley-Campbell and colleagues[157]
BP, blood pressure; GA, gestational age; GH, hypertension; PE, pre-eclampsia; QALY, quality-adjusted life-year; RCT, randomized controlled trial		

Appendix 12. Critical appraisal checklist of economic studies included in the systematic review of economic evaluations

Table 102 Critical appraisal checklist of economic studies included in the systematic review

	Item	Duckworth et al.	Duhig et al.	Figueira et al.	Frampton et al.	Frusca et al.	Giardini et al.	Hodel et al.	Myrhaug et al.	Ohkuchi et al	Schlembach et al.	Vatish et al.
1	Is there a clear statement of the decision problem?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	Is the comparator usual care without PlGF testing?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	Is the patient group in the study similar to those of interest in UK NHS?	Yes	Yes	Yes	Yes	Yes	Unclear[h]	Unclear[h]	Yes	Unclear[h]	Yes	Yes
4	Is the health care system comparable to UK?	Yes	Yes	Unclear[d]	Yes	Unclear[d]	Unclear[d]	Unclear[d]	Unclear[d]	Unclear[d]	Unclear[d]	Yes
5	Is the setting comparable to the UK?	Yes	Yes	Yes	Yes	Unclear[f]	Yes	Unclear[f]	Unclear[f]	Unclear[f]	Unclear[f]	Yes
6	Is the perspective of the model clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes

	Item	Duckworth et al.	Duhig et al.	Figueira et al.	Frampton et al.	Frusca et al.	Giardini et al.	Hodel et al.	Myrhaug et al.	Ohkuchi et al	Schlembach et al.	Vatish et al.
7	Is the study type appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8	Is the modelling methodology appropriate?	Yes	Yes	Yes	Yes	Yes	No[i]	Yes	Yes	Yes	Yes	Yes
9	Is the model structure described and does it reflect the disease process?	Yes	Unclear[b]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
10	Are assumptions about model structure listed and justified?	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
11	Are the data inputs for the model described and justified?	Yes	Yes	Unclear[e]	Yes	Yes	No	Yes	Yes	Yes	Unclear[e]	Unclear[e]
12	Is the effectiveness of the intervention established based on a systematic review?	No	No	No	Yes	No	No	No	Yes	No	No	No
13	Are health benefits measured in QALYs?	No	No	No	Yes	No	No	No	No	No	No	No

	Item	Duckworth et al.	Duhig et al.	Figueira et al.	Frampton et al.	Frusca et al.	Giardini et al.	Hodel et al.	Myrhaug et al.	Ohkuchi et al	Schlembach et al.	Vatish et al.
14	Are health benefits measured using a standardised and validated generic instrument?	No	No	No	Yes	No	No	No	No	No	No	No
15	Are the resource costs described and justified?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
16	Have the costs and outcomes been discounted?	No	No	No	No	Yes[g]	No	Yes[g]	No	No	No	No
17	Has uncertainty been assessed?	Yes	Unclear[c]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes
18	Has the model been validated?[a]	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Source: [7 32 98-105]

[a] Model validation was only reported by one study; [b] Model structure diagram not shown; [c] Limited sensitivity analyses; [d] Different healthcare systems (Brazilian, Italian, Swiss, Norwegian and German); [e] Some data inputs not reported; [f] The setting is not clearly reported; [g] Only costs has been discounted; in the study by Hodel and colleagues, discounting was applied only for the purposes of budget impact analysis; [h] The study by Giardini and colleagues included women after 36+6 weeks of gestation and the study by Hodel and colleagues did not report until when (weeks of gestation) the test could be used; [i] This study did not use a model.

NHS, National Health Service; QALYs, quality-adjusted life years; UK, United Kingdom

Appendix 13. List of economic base case model inputs

Below are listed all the model inputs used in the base case – clinical parameters (Table 103), cost parameters (Table 104) and HRQoL parameters (Table 105).

Table 103 Clinical inputs: base case

CLINICAL PARAMETERS			Input		Source	Notes
			Intervention	Comparator		
Triage (base case, PARROT)						
Cohort size (n)	PlGF categories	>100 pg/ml	229	156	Duhig 2021[9]	
		12-100 pg/ml	212	173		
		<12 pg/ml	130	106		
PE prevalence (%)	PlGF categories	>100 pg/ml	10.00%	12.00%		
		12-100 pg/ml	39.60%	37.00%		
		<12 pg/ml	73.80%	88.00%		
Admitted after the first assessment (%)	PlGF categories	>100 pg/ml	0%	0%	Duhig 2021[9]	Assumption based on the clinical management algorithm used in PARROT[15] (Figure 10)
		12-100 pg/ml	0%	0%		
		<12 pg/ml	100%	100%	Duhig 2019[15] and Duhig 2021[9]	The assumption on %hospitalised in

						the test arm was based on the clinical management algorithm used in PARROT[15] (Figure 10).The %hospitalised in the comparator arm was estimated from RR=1.31 for the number of patients in test and comparator arms in PARROT diagnosed within 24 hours (reported in Duhig 2019[15]).
Elecsys (base case, INSPIRE)						
Cohort size (n)	Management strategy	Stage 1: DO NOT ADMIT	88	97		Assumed to be the same as the proportion of participants at low risk of PE in PreOS[34]
		Stage 2: DO NOT ADMIT	26	29		Assumed to be the same as the proportion of patients

						at the intermediate risk of PE in PreOS[34]
		ADMIT	72	58	Cerdeira 2019[32]	
PE prevalence (%)	Management strategy	Stage 1: DO NOT ADMIT	0.00%	1.63%	Klein 2016[34] and Cerdeira 2019[32]	Based on Cerdeira 2019[32] and PreOS[34]
		Stage 2: DO NOT ADMIT	0.00%	4.93%		Based on Cerdeira 2019[32] and PreOS
		ADMIT	33.33%	25.86%	Cerdeira 2019[32]	
Level of hypertension						
Triage	Mild	PE	15%	1%	Duckworth and colleagues[98]	Based on Figure 2
		No PE	25%	25%		
	Moderate	PE	43%	43%		
		No PE	33%	33%		
	Severe	PE	42%	42%	PARROT[15]	
		No PE	42%	42%		
Elecsys	Mild	PE	[redacted]	[redacted]	INSPIRE [32]	
		No PE	[redacted]	[redacted]		
	Moderate	PE	[redacted]	[redacted]		
		No PE	[redacted]	[redacted]		
	Severe	PE	[redacted]	[redacted]		
		No PE	[redacted]	[redacted]		
Gestational age (<35 weeks)						

Triage	High-risk PE	85%	75%	Assumption	Assumption based on PARROT median gestational age at enrolment. We assumed that: - 85% of women <35 weeks if median GA <33 weeks. - 75% if GA <34 weeks - 65% if GA <35 weeks - 50% if GA >35 weeks
	Intermediate-risk PE	65%	50%		
	Low-risk PE	85%	85%		
Elecsys		[redacted]	[redacted]	INSPIRE	Information provided by the authors after EAG request
Time to delivery					
High-risk PE	<35 weeks	[illegible]	[illegible]	PARROT[9]	
	35-37 weeks	4	8		
Inter-risk PE	<35 weeks	26	27		
	35-37 weeks	13	11		
Low-risk PE	<35 weeks	50	50		
	35-37 weeks	20	21		
Immediate delivery		2 days	2 days	CG107[59]	For women >35 weeks of gestation

						with severe hypertension
Onset of delivery						
Spontaneous				14%	18%	PARROT[15]
Induced				46%	47%	
Planned C section				40%	35%	
Mode of delivery						
Unassisted		High-risk PE		35%	36%	Adjusted to a sum of 100%
		Intermediate-risk PE		50%	61%	
		Low-risk PE		63%	67%	
Assisted		High-risk PE		6%	6%	Adjusted to a sum of 100%
		Intermediate-risk PE		11%	29%	
		Low-risk PE		1%	17%	
Emergency C section		High-risk PE		59%	58%	Adjusted to a sum of 100%
		Intermediate-risk PE		38%	27%	
		Low-risk PE		26%	16%	
Magnesium sulphate						
High-risk PE				36.2%	36.9%	Only applied to women with pre-eclampsia
Intermediate-risk PE				9%	11.2%	PARROT[9]
Low-risk PE				2.9%	3.1%	
Maternal outcomes						
Major complications	Triage	High-risk PE	PE	9.3%	8.6%	Adjusted to differentiate PE/no PE women
			No PE	3.4%	3.1%	PARROT[9]
		Intermediate-risk PE	PE	5.7%	10.4%	
			No PE	2.1%	3.8%	

		Low-risk PE	PE	3.9%	5.7%		
			No PE	1.4%	2.1%		
	Elecsys		PE	2.4%	4.9%	INSPIRE[2]	We assumed that pulmonary edema, abruption and eclampsia were the major maternal complications and that they were independent (i.e., each woman only experience one complication). Adjusted to differentiate PE/no PE women
			No PE	1.2%	2.4%		
Length of stay in ICU, days						Previous NOAR[7]	
Fetal/neonatal outcomes							
Child death	Triage	High-risk PE	PE	5.9%	8.6%	PARROT[9]	Includes stillbirth and neonatal death. Adjusted to differentiate PE/no PE women
			No PE	2.1%	3.1%		
		Intermediate-risk PE	PE	2.9%	1.8%		
			No PE	1.0%	0.7%		
		Low-risk PE	PE	0%	2.9%		
			No PE	0%	1.0%		
	Elecsys	High-risk PE	PE	7.2%	7.2%	Assumption	

			No PE	2.6%	2.6%		INSPIRE did not report child death. Assume same % for both arms, based on PARROT's average between arms. Adjusted to differentiate PE/no PE women
		Intermediate-risk PE	PE	2.3%	2.3%		
			No PE	0.9%	0.9%		
		Low-risk PE	PE	1.4%	1.4%		
			No PE	0.5%	0.5%		
Neonatal unit admission	Triage	High-risk PE	PE	94.2%	87.8%	PARROT[32]	Adjusted to differentiate PE/no PE women
			No PE	39.3%	32.2%		
		Intermediate-risk PE	PE	51.6%	46.8%		
			No PE	18.9%	17.2%		
		Low-risk PE	PE	19.1%	26.0%		
			No PE	7.0%	9.5%		
	Elecsys	High-risk PE	PE	56.8%	35.5%	INSPIRE[32]	Adjusted based on the proportion of SCBU reported in INSPIRE. Adjusted to differentiate PE/no PE women
			No PE	28.4%	17.8%		
		Intermediate-risk PE	PE	44.4%	40.2%	Assumption	As INSPIRE do not report results for intermediate risk, we applied the ratio
			No PE	22.2%	20.1%		

							intermediate:low as for Triage test to the low-risk values reported by INSPIRE
		Low-risk PE	PE	16.4%	22.3%	INSPIRE[32]	Adjusted based on the proportion of SCBU reported in INSPIRE. Adjusted to differentiate PE/no PE women
			No PE	8.2%	11.2%		
Admission to ICU				11%	11%	PHOENIX[154]	Based on the ratio reported in PHOENIX study
Admission to HDU				19%	19%		
Admission to SCBU				71%	71%		
Length of stay in ICU/HDU, days				15.2	24.2	PARROT[15]	
Length of stay in SCBU, days				14.7	13.09		
Incidence of RDS	Triage	High-risk PE	PE	52.4%	34.4%	PARROT[9]	Adjusted to differentiate PE/no PE women
			No PE	19.2%	12.6%		
		Intermediate-risk PE	PE	17.7%	13.5%		
			No PE	6.5%	6.8%		
		Low-risk PE	PE	6.6%	5.7%		
			No PE	2.4%	2.1%		
	Elecsys	High-risk PE	PE	43.4%	43.4%		Assume same % for both arms, based on PARROT's average between arms.
			No PE	21.7%	21.7%		
		Intermediate-risk PE	PE	18.1%	18.1%		
			No PE	9%	9%		

		Low-risk PE	PE	6.2%	6.2%		Adjusted to differentiate PE/no PE women
			No PE	3.1%	3.1%		
Incidence of IVH	Triage	High-risk PE	PE	6.0%	10.1%	PARROT	Adjusted to differentiate PE/no PE women
			No PE	2.2%	3.7%		
		Intermediate-risk PE	PE	0.8%	1.8%		
			No PE	0.3%	0.7%		
		Low-risk PE	PE	0.6%	0.9%		
			No PE	0.2%	0.3%		
	Elecsys	High-risk PE	PE	8%	8%		Assume same % for both arms, based on PARROT's average between arms. Adjusted to differentiate PE/no PE women
			No PE	4%	4%		
		Intermediate-risk PE	PE	1.3%	1.3%		
			No PE	0.6%	0.6%		
		Low-risk PE	PE	0.8%	0.8%		
			No PE	0.4%	0.4%		

DAR, diagnostic assessment report; EAG, external assessment group; GA, gestational age; HDU, high-dependency unit; ICU, intensive care unit; IVH, intraventricular hemorrhage; PE, pre-eclampsia; RDS, respiratory distress syndrome; SCBU, special care baby unit

Table 104 Cost inputs: base case

COST PARAMETERS	Input		Source	Notes
	Intervention	Comparator		
Cost per test				

Triage PlGF test	£50	£0	Quidel/expert opinion	See Appendix 14
Elecsys sFlt-1/PlGF ratio test	£79	£0	Roche/expert opinion	
BRAHMS Kryptor sFlt-1/PlGF ratio test	£52	£0	ThermoFisher/expert opinion	
Management costs				
Blood pressure	£49		NHS Payment by Results Tariff 2020/21[151]	N01A (maternity prices)
Proteinuria test (dipstick)				
Standard blood tests	£1.79		NHS Reference Costs 2018/19[150]	Standard blood tests
Kidney function + electrolytes + full blood count + transaminases + bilirubin	£5.49		NHS Reference Costs 2018/19[150]	DAPS04
Fetal assessment	£134		NHS Reference Costs 2018/19[150]	NZ22Z (OPROC, service code 501)
Oral labetalol	£5.25		eMIT 2020[152]	56x200mg tablets
Corticosteroids	£46.26		BNF 2021[153]	6x4mg/1ml ampoules
Ante-natal hospitalisation cost (3 days)	£661.67		NHS Payment by Results Tariffs 2020/21[151]	NZ18B-NZ20B, NZ26B
Ante-natal hospitalisation cost (<35 weeks of gestation) - 12 days - 17 days	£3,505		NHS Payment by Results Tariffs 2020/21[151]	NZ18A (Maternity prices): £1,873 (8 days ante-natal) £408 (each extra ante-natal day)

				£5,545		
Ante-natal hospitalisation cost (>35 weeks of gestation) - 2 days - 4 days - 8 days				£703 £703 £1,373	NHS Payment by Results Tariffs 2020/21[151]	NZ18B, NZ19A, NZ20A (5 days ante-natal) (Maternity prices) NZ18A (8 days ante-natal) (Maternity prices)
Management pathway costs						
High-risk PE	PE	Mild HT	<35 weeks	£3,714.65	£5,765.49	See table in report section "Resource use and costs associated with the management of patients with suspected pre-eclampsia"
			35-37 weeks	£892.72	£2,072.19	
		Moderate HT	<35 weeks	£3,733.10	£5,790.85	
			35-37 weeks	£902.71	£2,086.9	
		Severe HT	<35 weeks	£3,733.10	£5,790.85	
			35-37 weeks	£895.61	£2,095.61	
	No PE	Mild HT	<35 weeks	£2,109.28	£3,134.70	
			35-37 weeks	£587.34	£1,180.78	
		Moderate HT	<35 weeks	£2,318.38	£3,347.25	
			35-37 weeks	£672.81	£1,272.50	
		Severe HT	<35 weeks	£2,649.21	£3,678.08	
			35-37 weeks	£1,067.09	£1,074.69	
Inter-risk PE	PE	Mild HT	<35 weeks	£2,020.5	£3,049.62	
			35-37 weeks	£561.45	£1,143.78	
		Moderate HT	<35 weeks	£2,133.56	£3,170.02	

			35-37 weeks	£619.67	£1,196.58	
		Severe HT	<35 weeks	£2,464.39	£3,500.85	
			35-37 weeks	£1,013.95	£998.77	
	No PE	Mild HT	<35 weeks	£326.35	£333.75	
			35-37 weeks	£230.18	£215.38	
		Moderate HT	<35 weeks	£534.01	£549.19	
			35-37 weeks	£336.63	£306.26	
		Severe HT	<35 weeks	£1,195.68	£1,210.86	
			35-37 weeks	£1,[illegible]82.30	£[illegible]1.93	
Low-risk PE	PE	Mild HT	<35 weeks	£2,[illegible]09.28	£[illegible]4.70	
			35-37 weeks	£587.34	£1,180.78	
		Moderate HT	<35 weeks	£2,318.38	£3,347.25	
			35-37 weeks	£672.81	£1,272.5	
		Severe HT	<35 weeks	£2,649.21	£3,678.08	
			35-37 weeks	£1,067.09	£1,074.69	
	No PE	Mild HT	<35 weeks	£903.91	£903.91	
			35-37 weeks	£[illegible]1.96	£289.36	
		Moderate HT	<35 weeks	£903.65	£903.65	
			35-37 weeks	£442.91	£458.10	
		Severe HT	<35 weeks	£1,565.32	£1,565.32	
			35-37 weeks	£1,238.58	£1,253.76	
Delivery costs						
Spontaneous delivery		Unassisted		£2,009	NHS Reference Costs 2018/19 [150]	NZ30A-NZ30C

	Assisted	£2,591	NHS Reference Costs 2018/19 [150]	NZ40A-NZ40C
Induced delivery	Unassisted	£2,946	NHS Reference Costs 2018/19 [150]	NZ31A-NZ32C
	Assisted	£4,053	NHS Reference Costs 2018/19 [150]	NZ41A-NZ44C
Caesarean section	Planned	£3,948	NHS Reference Costs 2018/19 [150]	NZ50A-NZ50C
	Emergency	£5,293	NHS Reference Costs 2018/19 [150]	NZ51A-NZ51C
Magnesium sulphate		£8.31	BNF 2021[153]	1 dose of 4g injection and then 1g/hour infusion for at least 24 hours - costed as 1 vial of 100 ml of magnesium sulphate 50% solution for infusion - 500mg per ml (10 vials = £83.10)
Maternal costs				
Maternal care, standard postnatal phase		£252	NHS Payment by Results Tariffs 2020/21 [151]	Non-delivery phases 2b (Maternity prices)
Maternal critical care, intensive care unit		£1,697	NHS Reference Costs 2018/19 [150]	XC04Z
Neonatal costs				
Neonatal critical care, intensive care unit and high dependency unit		£1,241	NHS Reference Costs 2018/19 [150]	XA01Z-XA02Z

Neonatal critical care, special care unit	£614	NHS Reference Costs 2018/19 [150]	XA03-XA04Z
Long-term costs			
Babies with IVH	£93,251	Kurse and colleagues [158]	Assumed as the cost of babies with cerebal palsy, as done by Varley-Campbell et al. [157]
Babies with RDS	£1,137	Khan and colleagues [155]	Assumed as the cost of babies born between 32-37 weeks of gestation
Other babies	£0	Khan and colleagues [155]	For those babies born >37 weeks, all costs were incurred during the initial hospitalisation
BNF, British National Formulary; HT, hypertension; IVH, intraventricular hemorrhage; NHS, National Health Service, PE, pre-eclampsia; RDS, respiratory distress syndrome			

Table 105 HRQoL inputs: base case

HRQoL PARAMETERS		Input			Source	Notes
		Utilities	Duration	QALYs		
Decrement for women with false positive result	**Immediate delivery**	0.028	8 days	0.0002	Prosser and colleagues [159]	Decrement is applied until delivery
	Intervention		12.5 days	0.0006		
	Comparator		2 days	0.001		
Birth to 3 weeks post-partum (vaginal delivery)		0.6766	3 weeks	0.039	Jansen and colleagues [277]	
Birth to 3 weeks post-partum (C section)		0.5895	3 weeks	0.005	Jansen and colleagues [277]	

Birth to 3 weeks post-partum (emergency C section)		0.5167	3 weeks	0.009	Jansen and colleagues [277]	
3 weeks to 12 weeks post-partum		0.8676	9 weeks	0.150	Bijlenga and colleagues [144]	
12 weeks to 6 months post-partum		0.8683	14.09 weeks	0.234	Bijlenga and colleagues [144]	
Decrement for women admitted to an intensive care unit		0.039	3 weeks	0.002	Seppänen and colleagues [107]	Decrement declines in a linear manner over 6 weeks
Decrement for babies and parents of babies admitted to critical care unit		0.039	3 weeks	0.002	Seppänen and colleagues [107]	Decrement declines in a linear manner over 6 weeks
Decrement for mothers whose child died		-	Lifetime	3.97	Varley-Campbell and colleagues [157]	
Decrement for mothers whose child had complications (RDS and IVH)		-	2 years	0.37	Varley-Campbell and colleagues [157]	
Decrement for babies with complications	Respiratory distress syndrome	-	Lifetime	0.41	Varley-Campbell and colleagues [157]	
	Intraventricular hemorrhage	-	Lifetime	1.91	Varley-Campbell and colleagues [157]	
Decrement for child's death		-	Lifetime	24.70	Ara and Brazier[161]	Assuming a life expectancy of 80 years

Appendix 14. List of model inputs for scenario analyses

Below are listed the model inputs used for scenario analyses – clinical parameters (Table 106), cost parameters (Table 107) and HRQoL parameters (Table 108). Please note that the parameters not described in the tables below were not changed.

Table 106 Clinical inputs: scenario analyses

CLINICAL PARAMETERS		Input		Source	Notes
		Intervention	Comparator		
Triage (scenario based on MAPPLE/PELICAN)					
Cohort size (n)	>100 pg/ml	143	121	MAPPLE/PELICAN[16]	
	12-100 pg/ml	137	97		
	<12 pg/ml	116	69		
PE prevalence (%)	>100 pg/ml	56.20%	30.60%		
	12-100 pg/ml	53.10%	74.20%		
	<12 pg/ml	48.60%	97.10%		
Admitted after the first assessment (%)	>100 pg/ml	0%	0%	MAPPLE/PELICAN[16]	The assumption on %hospitalised in the test arm was based on the clinical management algorithm used in MAPPLE[16`] (Figure 12).The %hospitalised
	12-100 pg/ml	0%	0%		

	<12 pg/ml		100%	71.56%		in the comparator arm was assumed to be the same as in the base case for Triage.
Time to delivery	High-risk PE		3	9	MAPPLE/PELICAN[16]	Applied to women with GA <35 weeks only
	Intermediate-risk PE		19	23	PARROT[9]	As for base case
	Low-risk PE		48	61	MAPPLE/PELICAN[16]	Applied to women with GA <35 weeks only
Maternal complications	High-risk PE	PE	24%	1[illegible]%	MAPPLE/PELICAN[16]	Adjusted by level of risk and to differentiate PE/no PE women
		No PE	10.1%	6.[illegible]%		
	Intermediate-risk PE	PE	14.7%	18.1%		
		No PE	6.2%	7.7%		
	Low-risk PE	PE	10.1%	10.0%		
		No PE	4.3%	4.2%		
Incidence of RDS	High-risk PE	PE	98.8%	38.2%	MAPPLE/PELICAN[16]	Adjusted by level of risk and to differentiate PE/no PE women
		No PE	41.8%	16.2%		
	Intermediate-risk PE	PE	33.4%	20.5%		
		No PE	14.1%	8.7%		
	Low-risk PE	PE	12.5%	6.3%		
		No PE	5.3%	2.7%		
Incidence of IVH	High-risk PE	PE	0.5%	0%	MAPPLE/PELICAN[16]	Adjusted by level of risk and to differentiate PE/no PE women
		No PE	0.4%	0%		
	Intermediate-risk PE	PE	0.6%	0%		
		No PE	0.2%	0%		

	Low-risk PE	PE	0.5%	0%		
		No PE	0.2%	0%		
Elecsys (scenario based on PreOS)						
Cohort size (n)	<33		75	75	PreOS[34]	
	33 to <85		22	22		
	≥85		21	21		
PE prevalence in hospitalised women (%)	<33		20.9%	9.3%		Prevalence in hospitalised and non-hospitalised women in the comparator arm are assumed to be the same as the prevalence for the respective PlGF category reported in PreOS,[34] whereas prevalence in the test arm was based on changes in decision regarding hospitalisation with knowledge of test results (Klein 2016[34] p. 11).
PE prevalence in non-hospitalised women (%)	<33		0.4%	9.5%	PreOS[34]	
	33 to <85		23.1%	28.1%		
	≥85		30.6%	40.5%		
Level of hypertension						

Triage	High-risk PE	Mild	PE	8%	8%	Assumption	We assumed that: - High-risk of PE: 70% with severe HT - Intermediate-risk of PE: same as for base case - Low-risk of PE: 30% with severe HT
			No PE	13%	13%		
		Moderate	PE	22%	22%		
			No PE	17%	17%		
		Severe	PE	70%	70%		
			No PE	70%	70%		
	Intermediate-risk PE	Mild	PE	15%	15%	As for base case	
			No PE	25%	25%		
		Moderate	PE	43%	43%		
			No PE	42%	42%		
		Severe	PE	42%	42%		
			No PE	42%	42%		
	Low-risk PE	Mild	PE	19%	19%	Assumption	
			No PE	30%	30%		
		Moderate	PE	51%	51%		
			No PE	40%	40%		
		Severe	PE	30%	30%		
			No PE	30%	30%		
Elecsys	High-risk PE	Mild	PE	17%	17%	Assumption	
			No PE	17%	17%		
		Moderate	PE	13%	13%		
			No PE	13%	13%		
		Severe	PE	70%	70%		
			No PE	70%	70%		
		Mild	PE	74%	74%	As for base case	

	Intermediate-risk PE		No PE	74%	74%		
		Moderate	PE	13%	13%		
			No PE	13%	13%		
		Severe	PE	13%	13%		
			No PE	13%	13%		
	Low-risk PE	Mild	PE	57%	57%		
			No PE	57%	57%		
		Moderate	PE	13%	13%	Assumption	
			No PE	13%	13%		
		Severe	PE	30%	30%		
			No PE	30%	30%		
Gestational age (<35 weeks)							
Low value				0%	0%		Extreme values
High value				100%	100%	Assumption	
Time to delivery, days							
Elecsys	High-risk PE			17	17	PROGNOSIS[36]	Assumed same for both arms
	Intermediate-risk PE			26	27	PARROT[9]	As for base case

	Low-risk PE		51	51	PROGNOSIS[36]	Assumed same for both arms
Immediate delivery, days			1	1	Assumption	
Fetal/neonatal outcomes (Elecsys only)						
Neonatal unit admission	High-risk PE	PE	100%	87.8%	PARROT[9]	Same as for Triage PIGF test
		No PE	53.6%	43.9%		
	Intermediate-risk PE	PE	51.6%	46.8%		
		No PE	25.8%	23.4%		
	Low-risk PE	PE	19.1%	26.6%		
		No PE	9.7%	13%		
Death in neonates: excluding stillbirth						
Triage	High-risk PE	PE	1.2%	2.9%	PARROT[9]	
		No PE	0.4%	1.0%		
	Intermediate-risk PE	PE	2.1%	0.0%		
		No PE	0.8%	0.0%		
	Low-risk PE	PE	0.0%	0.0%		
		No PE	0.0%	0.0%		
Elecsys	High-risk PE	PE	2.0%	2.0%	Assumption	Assumed the same % for both arms, based on the average rate across the arms in PARROT,[9] adjusted to differentiate for PE/no PE status.
		No PE	0.7%	0.7%		
	Intermediate-risk PE	PE	1.1%	1.1%		
		No PE	0.4%	0.4%		
	Low-risk PE	PE	0.5%	0.5%		
		No PE	0.2%	0.2%		
GA, gestational age; HT, hypertension; IVH, intraventricular hemorrhage; PE, pre-eclampsia; RDS, respiratory distress syndrome.						

Table 107 Cost inputs: scenario analyses

COST PARAMETERS					Input		Source	Notes
					Intervention	Comparator		
Cost per test								
Low value			Triage PlGF test		£40	£0	Quidel	Cost of test kit only
			Elecsys sFlt-1/PlGF ratio test		£66	£0	Roche	
			BRAHMS Kryptor sFlt-1/PlGF ratio test		£22	£0	ThermoFisher	
High value			Triage PlGF test		£70	£0	Duhig and colleagues[99]	
			Elecsys sFlt-1/PlGF ratio test		£110	£0	EAG expert	
			BRAHMS Kryptor sFlt-1/PlGF ratio test		£70	£0	Assumption	Based on the approximate increment applied to the other two tests (20%)
Management pathway costs based on NG133								
Triage	High-risk PE	PE	Hypertension	<35 weeks	£3,718.90	£5,770.74	See section "Resource use and costs associated with the management of patients with suspected pre-eclampsia" for the differences between CG107 and NG133 in terms of resource use.	
				35-37 weeks	£895.32	£1,530.34		
			Severe HT	<35 weeks	£3,733.10	£5,790.85		
				35-37 weeks	£898.72	£1,536.53		
		No PE	Hypertension	<35 weeks	£2,311.28	£3,337.20		
				35-37 weeks	£669.11	£994.22		

			Severe HT	<35 weeks	£2,649.21	£3,678.08
				35-37 weeks	£1,068.65	£1,395.14
	Intermediate-risk PE	PE	Hypertension	<35 weeks	£2,126.46	£3,159.96
				35-37 weeks	£615.97	£918.30
			Severe HT	<35 weeks	£2,464.39	£3,500.85
				35-37 weeks	£1,015.51	£1,319.23
		No PE	Hypertension	<35 weeks	£534.01	£549.19
				35-37 weeks	£336.63	£306.26
			Severe HT	<35 weeks	£1,165.68	£1,210.86
				35-37 weeks	£1,132.30	£1,101.93
	Low-risk PE	PE	Hypertension	<35 weeks	£2,311.28	£3,337.20
				35-37 weeks	£669.11	£994.22
			Severe HT	<35 weeks	£2,649.21	£3,678.08
				35-37 weeks	£1,068.65	£1,395.14
		No PE	Hypertension	<35 weeks	£903.65	£903.65
				35-37 weeks	£442.11	£459.10
			Severe HT	<35 weeks	£1,565.32	£1,565.32
				35-37 weeks	£1,238.58	£1,253.76
Elecsys	High-risk PE	PE	Hypertension	<35 weeks	£3,718.90	£5,770.74
				35-37 weeks	£894.98	£1,221.27
			Severe HT	<35 weeks	£3,733.10	£5,790.85
				35-37 weeks	£898.21	£1,225.60
		No PE	Hypertension	<35 weeks	£2,311.28	£3,337.20
				35-37 weeks	£668.95	£839.68
			Severe HT	<35 weeks	£2,649.21	£3,678.08

				35-37 weeks	£1,068.40	£1,239.68	
	Intermediate-risk PE	PE	Hypertension	<35 weeks	£2,126.46	£3,159.96	
				35-37 weeks	£615.80	£763.76	
			Severe HT	<35 weeks	£2,464.39	£3,500.85	
				35-37 weeks	£1,015.26	£1,163.76	
		No PE	Hypertension	<35 weeks	£534.01	£549.19	
				35-37 weeks	£336.63	£306.26	
			Severe HT	<35 weeks	£1,[illegible]5.6[illegible]	£1,21[illegible].86	
				35-37 weeks	£1,132.[illegible]0	£1,101.9[illegible]	
	Low-risk PE	PE	Hypertension	<35 weeks	£2,311.28	£3,337.20	
				35-37 weeks	£668.95	£839.68	
			Severe HT	<35 weeks	£2,649.21	£3,678.08	
				35-37 weeks	£1,068.40	£1,239.68	
		No PE	Hypertension	<35 weeks	£903.65	£903.65	
				35-37 weeks	£442.91	£4[illegible]8.1[illegible]	
			Severe HT	<35 weeks	£1,56[illegible].32	£1[illegible]65.32	
				35-37 weeks	£1,238.58	£1,253.76	
Long-term costs							
All babies admitted to critical care units					£1,037	Khan and colleagues [155]	Not applied to babies with IVH
HT, hypertension; IVH, intraventricular hemorrhage; PE, pre-eclampsia.							

Table 108 HRQoL inputs: base case

HRQoL PARAMETERS	Input	Source	Notes

	Utilities	QALYs		
Decrement for mothers whose child died	-	1.48	Varley-Campbell et al.[157]	Decrement is applied for 10 years
Decrement for mothers whose child had complications (RDS and IVH)	-	1.20	Varley-Campbell et al.[157]	Decrement is applied for 10 years
HRQoL, health-related quality-of-life; IVH, intraventricular hemorrhage; QALY, quality-adjusted life-year; RDS, respiratory distress syndrome.				

Appendix 15. Cost breakdown of PlGF tests

The estimation of costs related to PlGF testing was based on the information provided by the manufacturers of the tests. Inputs from clinical experts and laboratory staff were also provided for the Triage PlGF test and Elecsys sFlt-1/PlGF ratio test as these two tests are currently used in clinical practice. However, companies, clinical experts and laboratory staff were not able to provide all of the required cost items and the EAG made certain assumptions in order to fill in data gaps.

A distinction was made between tests when apportioning capital and overheads costs dependent upon our information on how these were paid for. The manufacturers of the Triage PlGF test and BRAHMS Kryptor sFlt-1/PlGF ratio test provided capital costs which have been annuitised by the EAG and also maintenance and equipment costs as described below. However, the manufacturer of Elecsys sFlt-1/PlGF ratio test declined to provide the above mentioned costs. The manufacturer further clarified that contracts included machine costs, cost of laboratory materials and consumables, maintenance, and training costs. This argument was supported by our experts (one of whom was a laboratory manager) who noted that machines and maintenance costs are not borne directly by providers but are typically paid for via a managed service agreement with manufacturers. Hence, we assumed that the cost of the Elecsys sFlt-1/PlGF ratio test includes capital, maintenance, and equipment costs. This same approach was reported by the manufacturer of the DELFIA tests (not used in the economic analysis) which provided a range of charges based on volume, with increasing discount offered for higher volume. The other manufacturers did not refer to any such contractual arrangements in their submissions. The EAG approach therefore used the most reliable data available and thus minimised our assumptions.

The component costs included in the base case are summarised in Table 109 and explained in further detail below. Full calculations are provided below.

Table 109: Components of testing costs (base case)

Cost component	Triage PlGF test	Elecsys sFlt-1/PlGF ratio	BRAHMS Kryptor sFlt-1/PlGF ratio
Cost of test kit	Yes	-	Yes

Charge per reportable test (includes capital, maintenance and equipment costs)	-	Yes	-
Machine costs	Yes	-	Yes
Service charges and maintenance costs	Yes	-	Yes
Equipment (laboratory materials and consumables)	Yes	-	Yes
Staff time for training	Yes	Yes	Yes
Staff time to perform and analyse test and staff time for quality control	Yes	Yes	Yes
Phone calls to communicate test results	Yes	Yes	Yes

Cost per test kit

- Triage PlGF test: cost of £1,000 (provided by the manufacturer), with each kit containing 25 tests – resulting in a cost per test of £40.
- BRAHMS Kryptor sFlt-1 / PlGF ratio test: cost of £825 for sFlt-1 reagent kit and £825 for PlGF reagent kit (provided by the manufacturer), with each kit containing 75 tests – resulting in a cost per test of £22.

Charge per reportable test

- Elecsys sFlt-1/PlGF ratio test: charge of £70 per reportable test, as advised by one of our experts working at a teaching hospital that pays approximately this charge for the Elecsys sFlt-1/PlGF ratio test. A reportable test consists of those that gives a reliable result for patients (excluding those used for machine calibration, quality control, and retests). An estimated 60-70% of tests conducted are reportable, according to our expert.
- This charge is based on the e411 machine which could also be used for Down's syndrome but wasn't currently. One of our experts suggested that around 73% of NHS laboratories use multi-purpose e602 or e811 machines compared to 27% using the e411 based on UKNEQAS data, however it is not known whether hospitals using these larger multi-purpose machines may face similar or different charges.
- Typically, bigger hospitals generating a large volume of tests may be able to negotiate more favourable contracts.

To calculate the following costs (machine, maintenance, laboratory material, training, staff time and phone calls), we assumed that 365 PlGF tests were run per machine per year (based on expert advice). However, some laboratories would run these tests only weekly whilst others run the tests more than once per day, resulting in a relatively crude estimate of number of tests per machine per year. This figure was based on a general hospital. Where capital costs have been annuitized, these have been applied as per NICE Diagnostic Guideline 31[278] and NICE Diagnostic Guideline 39,[279] assuming a lifetime of 10 years discounted at 3.5%.

Machine costs:

- Triage PlGF test: cost of £1,400 (provided by the manufacturer). This cost was annuitized with an assumed lifetime of 10 years, using a discount rate of 3.5%, resulting in an annuity factor of 8.32 and a cost per year of £168 – resulting in a cost per test of £0.46.
- BRAHMS Kryptor sFlt-1/PlGF ratio test: cost of £35,000 for Kryptor Compact Plus machine and £49,000 for Kryptor Gold machine (provided by the manufacturer). These costs were annuitized with an assumed lifetime of 10 years, using a discount rate of 3.5%, resulting in an annuity factor of 8.32 and a cost per year of £4,208 for Kryptor Compact Plus and £5,892 for Kryptor Gold. Based on data from the manufacturer ([redacted] of laboratories use Kryptor Compact Plus), we assumed that the BRAHMS Kryptor sFlt-1/PlGF ratio test is performed in the Kryptor Compact Plus machine for base case. We know from the manufacturers that Kryptor machines run many tests, not only the sFlt-1/PlGF ratio test. Due to lack of better evidence, we here assume the apportion of the ratio test to be 1 in 4000 tests (0.025%) as informed by one of our experts for the apportion of the ratio test in Roche e801 machines – resulting in a cost per test of £0.003.

Annual service charge/maintenance:

- Triage PlGF test: cost of £259 after the second year of contract (provided by the manufacturer) – resulting in a cost per test of £0.64.
- BRAHMS Kryptor sFlt-1/PlGF ratio test: cost of £5,000 after the second year of contract (provided by the manufacturer) – resulting in a cost per test of £0.003.

Cost of laboratory material (include quality control costs):

- Triage PlGF test: includes cost of reagents for quality control. Two reagents are needed and each costs £50 (provided by the manufacturer). According to our

experts, some laboratories perform monthly quality control (use 3 units of each reagent) while others perform it weekly (use 11 units of each reagent). The two options were assumed to be adopted in equal proportions (50% each) – resulting in a cost per test of £1.92.

- BRAHMS Kryptor sFlt-1/PlGF ratio test: includes cost of reagents for calibration and quality control and consumables. The unit cost of each material as well as the number of units required per year were provided by the manufacturer resulting in a cost per test of £21.04.

Costs of training:

- All manufacturers provide free training. However, we have incorporated the cost of NHS personnel time spent on training. The personnel cost was assumed to be that of a healthcare scientist derived from Unit Costs of Health and Social Care 2020 with an annual salary of £31,240. This was deemed a valid proxy for biomedical scientists who run the analysers and clinical scientists who interpret the results (comments from committee member). We note that nurses/midwives could also be involved in the process of PlGF testing but the differences between the annual salaries of a nurse and a healthcare scientist are small according to Unit Costs of Health and Social Care 2020 and therefore it is not likely to affect model outcomes. An average of 253 working days per year with seven work hours per day was assumed.
- According to expert opinion, approximately three biochemists per site would be trained for half a day (3 hours) per year. Therefore, an estimate of 9 hours for training per site per year was used for the three tests resulting in a cost per test of £0.43.

Staff costs for performing test and quality control:

- As above, the personnel cost was assumed to be that of a healthcare scientist.
- An estimate of 0.08 hours (5 minutes) to prepare and perform one test was used. This refers to the average time spent preparing and performing one Elecsys sFlt-1/PlGF ratio test as informed by one of the EAG experts. Similarly, ThermoFisher provided the same estimate for the BRAHMS Kryptor sFlt-1/PlGF ratio test. Since these are both ratio tests, we assumed that half the time is needed to perform a PlGF test only (0.04 hours).
- An estimate of 41 hours per year to quality control testing was used. This estimate was provided by Quidel. Therefore, we assumed twice the time is needed for the Elecsys and BRAHMS Kryptor sFlt-1/PlGF ratio tests.

- Triage PlGF test: 0.04 hours to prepare and perform one test and 41 hours per year to quality control testing resulting in a cost per test of £2.67.
- Elecsys sFlt-1/PlGF ratio test or the BRAHMS Kryptor sFlt-1/PlGF ratio test: 0.08 hours to prepare and perform one test and 82 hours per year for quality control testing– resulting in a cost per test of £5.33.

Other costs:

- We assumed that the results of tests performed in laboratories were communicated to patients via phone calls. We assumed a cost per phone call of £3.47. This has been previously used in NICE Diagnostic DG36.[280]
- Triage PlGF test: the manufacturer informed that around 50% of tests were performed in laboratories and the other 50% were performed at the point of care. For the base case, we considered that all tests were run in laboratories, therefore one phone call per test is required, resulting in a cost per test of £3.47.
- Elecsys sFlt-1/PlGF ratio test and BRAHMS sFlt-1 KRYPTOR/ BRAHMS PlGF plus KRYPTOR PE ratio test: both these tests are performed in laboratories, therefore one phone call per ratio test is required – resulting in a cost per test of £3.47.
- For the purposes of modelling the costs of biomarker tests, assuming that some tests are performed at the point of care impacts the cost of informing the patient about test results and also the cost of quality control per test. One of our experts informed that more time for quality control per test would be necessary when tests are performed at the point of care. For the purposes of modelling the management of women with pre-eclampsia, we assumed this has a negligible impact as it is assumed that other tests are concurrently awaited from the labs.
- We assumed no costs were incurred for antenatal appointments, as no extra appointments are needed to collect blood samples for PlGF testing. Based on clinical expert advice, blood samples are usually routinely collected and tested for several biomarkers (including the PlGF ones). Hence, no staff costs for collecting blood were included.
- Based on expert opinion, we also considered that usually samples are transported to laboratories in existing transports. Therefore, no transportation costs were added to the cost of the tests.
- Our costs do not contain an overhead charge for the use of hospital lab space given we were unable to obtain an estimate of this cost.

Triage PlGF test costs amounted to £50, Elecsys sFlt-1/PlGF ratio test to £79 and BRAHMS Kryptor sFlt-1/PlGF ratio test to £52. The main difference in costs between the tests came from the cost per kit and from the cost of laboratory materials (including quality control).

Our estimated cost of the Elecsys sFlt-1/PlGF ratio test is generally consistent with external sources. Vatish and colleagues[106] reported a cost of £65, although it is unclear what this figure includes. Another expert advising the EAG estimated a cost between £90 and £110 noting it was the "most expensive diagnostic test" at his hospital. We considered this higher value (£110) in our scenario analysis.

The studies by Duhig and colleagues[99] and Duckworth and colleagues[98] reported the cost of the Triage PlGF test as £70 and £50, respectively, although they clarified that it only includes the cost of the test itself, which was provided by the manufacturer. This figure is somewhat higher than our estimate therefore is considered in a scenario analysis.

Table 110 Cost breakdown of Quidel Triage PlGF test

Cost component	Price	Cost per test	Rationale/Formula
Test kit	£1,000	£40	price/number of tests in kit (n=25)
Machine			
Quidel Triage Meter Pro	£1,400	£0.46	lifetime=10y; discount rate= 3.5% cost per year (£168)/number of tests per year (n=365)
Laboratory material			
Quidel Triage PlGF Control L1	£50	£1.92	number of units per year: 6 (monthly QC) or 22 (weekly QC) proportion of labs with monthly QC: 50% price*number of units per year/number of tests per year (n=365)
Quidel Triage PlGF Control L2	£50		
Annual Service Charge			
Year 1	£0	£0.64	lifetime=10y [(price Year 1*1/10) + (price Year 2*9/10)]/number of tests per year (n=365)
Year 2+	£259		
Training			
Standard training	£0	£0	Quidel provides training for free
Staff time	£17.43	£0.43	Salary of a healthcare scientist per hour = £17.43 Time spent in training per year: 3h*3 persons=9h Cost of training per year (£17.43*9h)/number of tests per year (n=365)
Staff			

Staff who process samples in lab	£17.43	£1.39	Salary of healthcare scientist per hour/time spent per test (0.08h)
Staff who perform device QC	£17.43	£1.97	Time spent per device QC per year: 41h Cost of device QC per year (£17.43*41h)/number of tests per year (n=365)
Other costs			
Phone calls	£3.47	£3.47	Proportion of tests processed in labs: 100% (100%*365=365 tests) Cost per year (£3.47*365)/number of tests per year (n=365)
TOTAL		**£49.58**	
QC, quality control			

Table 111 Cost breakdown of Roche Elecsys sFlt-1/PlGF ratio test

Cost component	Price	Cost per test	Rationale/Formula
Cost per reportable test	NA	£70	Assumption as informed by one of our experts
Training			
Standard training	£0	£0	Roche provides training for free
Staff time	£17.43	£0.43	Salary of a healthcare scientist per hour = £17.43 Time spent in training per year: 3h*3 persons = 9h Cost of training per year (£17.43*9h)/number of tests per year (n=365)
Staff			
Staff who process samples in lab	£17.43	£1.39	Salary of healthcare scientist per hour/time spent per test (0.08h)
Staff who perform device QC	£17.43	£3.94	Time spent per device QC per year: 82h Cost of device QC per year (£17.43*82h)/number of tests per year (n=365)
Other costs			
Phone calls	£3.47	£3.47	Proportion of tests processed in labs: 100% (100%*365=365 tests) Cost per year (£3.47*365)/number of tests per year (n=365)
TOTAL		**£79.23**	
NA, not applicable; QC, quality control			

Table 112 Cost breakdown of ThermoFisher BRAHMS sFlt-1 KRYPTOR/ BRAHMS PlGF plus KRYPTOR PE ratio test

Cost component	Price	Cost per test	Rationale/Formula
Test kits			

BRAHMS sFlt-1 KRYPTOR	£825	£11	price/number of tests in kit (n=75)
BRAHMS PlGF plus KRYPTOR	£825	£11	price/number of tests in kit (n=75)
Machine			
Kryptor Compact Plus	£35,000	£0.003	lifetime=10y; discount rate= 3.5% cost per year (£4,208)/number of tests per year (n=365) Apportion of pre-eclampsia share = 0.025%
Annual Service Charge			
Year 1	£0	£0.003	lifetime=10y [(price Year 1*1/10)+(price Year 2*apportion of pre-eclampsia share*9/10)]/number of tests per year (n=365)
Year 2+	£5,000		
Laboratory material			
BRAHMS sFlt-1 plus KRYPTOR CAL	£97.16	£2.40	Price*number of units per year (n=9)/number of tests per year (n=365)
BRAHMS PlGF plus KRYPTOR CAL	£97.16	£1.33	Price*number of units per year (n=5)/number of tests per year (n=365)
BRAHMS sFlt-1 plus KRYPTOR QC	£124.77	£7.86	Price*number of units per year (n=23)/number of tests per year (n=365)
BRAHMS PlGF plus KRYPTOR QC	£124.77	£7.86	Price*number of units per year (n=23)/number of tests per year (n=365)
Kryptor Buffer	£48.28	£0.40	Price*number of units per year (n=3)/number of tests per year (n=365)
Kryptor Compact Solution 1	£33.26	£0.09	Price*number of units per year (n=1)/number of tests per year (n=365)
Kryptor Compact Solution 2	£33.26	£0.00	Price*number of units per year (n=0)/number of tests per year (n=365)
Kryptor Compact Solution 3	£33.26	£0.27	Price*number of units per year (n=3)/number of tests per year (n=365)
Kryptor Compact Solution 4	£33.26	£0.27	Price*number of units per year (n=3)/number of tests per year (n=365)
Kryptor Compact DILCUP	£64.58	£0.18	Price*number of units per year (n=1)/number of tests per year (n=365)
Kryptor Compact REACT	£137.78	£0.38	Price*number of units per year (n=1)/number of tests per year (n=365)
Training			
Standard training	£0	£0	ThermoFisher provides training for free
Staff time	£17.43	£0.43	Salary of a healthcare scientist per hour = £17.43 Time spent in training per year: 3h*3 persons = 9h Cost of training per year

			(£17.43*9h)/number of tests per year (n=365)
Staff			
Staff who process samples in lab	£17.43	£1.39	Salary of healthcare scientist per hour/time spent per test (0.08h)
Staff who perform device QC	£17.43	£3.94	Time spent per device QC per year: 82h Cost of device QC per year (£17.43*82h)/number of tests per year (n=365)
Other costs			
Phone calls	£3.47	£3.47	Proportion of tests processed in labs: 100% (100%*365=365 tests) Cost per year (£3.47*365)/number of tests per year (n=365)
TOTAL		**£52.28**	
QC, quality control			

National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Evidence overview

PLGF-based testing to help diagnose suspected pre-eclampsia (update of DG23)

This overview summarises the key issues for the diagnostics advisory committee's consideration. This document is intended to be read with the final scope issued by NICE for the assessment and the diagnostics assessment report. There is a glossary of terms in appendix B.

1 Background

1.1 Introduction

This is an assessment of the clinical and cost effectiveness of the following PlGF (placental growth factor)-based tests:

- the Triage PLGF test
- Elecsys immunoassay sFlt-1/PLGF ratio
- DELFIA Xpress PLGF 1-2-3 test (with or without DELFIA Xpress sFlt-1 test)
- BRAHMS sFlt-1 Kryptor/PLGF plus Kryptor PE ratio.

The assessment is of their use in addition to clinical assessment to help diagnose pre-eclampsia in the second and third trimesters of pregnancy.

Using PLGF-based tests in addition to current clinical practice could help make decisions about the care of women with suspected pre-eclampsia (that is, who have some symptoms of pre-eclampsia but not enough to confirm a diagnosis). For example, they could allow women who have pre-eclampsia ruled out with the PLGF-based test to receive outpatient care instead of being

admitted to hospital. They could also ensure that women who have pre-eclampsia diagnosed (ruled in) are monitored more frequently or admitted to hospital earlier to receive the most appropriate care.

This assessment is an update of NICE diagnostics guidance 23 (DG23). DG23 recommended the Triage PLGF test and the Elecsys immunoassay sFlt-1/PLGF ratio test, with standard clinical assessment and subsequent clinical follow up, to help rule out pre-eclampsia in women presenting with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of pregnancy. When pre-eclampsia was not ruled out using a PLGF-based test result, DG23 recommended that the result should not be used to diagnose (rule in) pre-eclampsia. DG23 did not recommend the DELFIA Xpress PLGF 1-2-3 test and BRAHMS sFlt-1 Kryptor/BRAHMS PLGF plus Kryptor PE ratio for routine adoption in the NHS. Further research was recommended on:

- Using repeat PLGF-based testing in women presenting with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of pregnancy, who had had a negative PLGF-based test result.
- Using the Triage PLGF test and Elecsys immunoassay sFlt-1/PLGF ratio, with standard clinical assessment, to rule-in pre-eclampsia. Specifically, how this would affect management decisions on time to delivery and the outcomes associated with this.

The diagnostics advisory committee will make provisional recommendations about these technologies on 15 June 2021.

1.2 Scope of the assessment

Decision question

What is the clinical and cost effectiveness of the Triage PLGF test, Elecsys immunoassay sFlt-1/PLGF ratio, DELFIA Xpress PLGF 1-2-3 test (with or without DELFIA Xpress sFlt-1 test) and BRAHMS sFlt-1 Kryptor/PLGF plus

Kryptor PE ratio when used in addition to clinical assessment to diagnose pre-eclampsia in the second and third trimesters of pregnancy?

Populations

Women between 20 weeks and 36 weeks plus 6 days of pregnancy who have suspected pre-eclampsia.

If data permits, subgroup analyses could be done for women:

- between 20 weeks and 34 weeks plus 6 days of pregnancy
- between 35 weeks and 36 weeks plus 6 days of pregnancy
- with chronic hypertension
- with severe hypertension (BP of 160/110 mmHg or more)
- with pre-existing or gestational diabetes
- with renal disease
- with an autoimmune disease
- with a multiple pregnancy (for example, twin or triplet pregnancy).

Test results may be affected by ethnicity and maternal weight. If data are available these variables should be taken into account.

Interventions

Use of the following tests to help diagnose pre-eclampsia and make subsequent decisions about care (in addition to any clinical assessments):

- Triage PLGF test
- Elecsys immunoassay sFlt-1/PLGF ratio
- DELFIA Xpress PLGF 1-2-3 test with or without DELFIA Xpress sFlt-1 test
- BRAHMS sFlt-1 Kryptor/PLGF plus Kryptor PE ratio.

Use of the interventions should be assessed when used once per episode of suspected pre-eclampsia, and when the interventions are also used for repeat testing of women who have had an initial PLGF-based test for suspected pre-

eclampsia that was negative, and who have no additional signs or symptoms of possible pre-eclampsia.

Comparator

No further assessment (that is, beyond clinical assessments already done, such as blood pressure measurement, urinalysis and fetal monitoring) to help make a decision about a diagnosis of pre-eclampsia and subsequent decisions about care.

Healthcare setting

Secondary care

Outcomes

Intermediate measures for consideration may include:

- diagnostic accuracy (including positive and negative predictive values)
- concordance between tests
- prognostic accuracy
- time to test result
- impact of test result on clinical decision making
- test failure rate
- time to diagnosis
- proportion of women diagnosed with pre-eclampsia
- time to onset of pre-eclampsia and/or eclampsia
- proportion of women returned to less intensive follow up
- number of women admitted to hospital/length of inpatient hospital stay
- time to delivery
- gestation at diagnosis of pre-eclampsia
- use of antihypertensive drugs.

Clinical outcomes for consideration may include:

- maternal morbidity and mortality

- fetal morbidity and mortality
- neonatal morbidity and mortality.

Patient-reported outcomes for consideration may include health-related quality of life.

Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include:

- costs of equipment, reagents and consumables
- cost of staff and associated training
- medical costs arising from testing and care such as hospital stay
- medical costs arising from adverse events including those associated with false test results and inappropriate treatment.

The cost effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.

Time horizon

The time horizon for estimating clinical and cost effectiveness should be long enough to reflect any differences in costs or outcomes between the technologies being compared.

Further details, including descriptions of the interventions, comparator, care pathway and outcomes, are in the final scope for DAP53.

2 The evidence

This section summarises data from the external assessment group's (EAG) diagnostics assessment report.

2.1 Clinical effectiveness

The EAG did a systematic review to identify evidence on the clinical effectiveness and diagnostic accuracy of PLGF-based testing to diagnose pre-

eclampsia in the second and third trimesters of pregnancy. Test evaluations included in the review were categorised as either:

- Add-on tests, which used the results of the PLGF-based test alongside standard clinical assessment to inform clinical management. Some of these add-on studies included a separate trial arm, in which the results were concealed (that is, they were not used in clinical decision making).
- Standalone tests, which used the results of the PLGF-based test to directly predict pre-eclampsia or other related outcomes without taking into account standard clinical assessment.

The EAG prioritised the add-on studies because they directly addressed the decision problem, and classed the standalone studies as supporting evidence. Full details of the systematic review and the selection criteria are available from page 36 in the diagnostics assessment report.

Overview of included studies

Seventeen studies (reported in 38 publications) met the selection criteria for the systematic review. Seven were categorised as add-on test assessments and 10 were standalone assessments. There is an overview of the studies in table 1 of the diagnostics assessment report (page 43).

Of the included studies, 6 evaluated the Triage PLGF test (3 add-on and 3 standalone), 11 evaluated the Elecsys immunoassay sFlt-1/PLGF ratio test (3 add-on and 8 standalone), and 2 evaluated the BRAHMS sFlt-1 Kryptor/BRAHMS PLGF plus Kryptor PE ratio test (1 add-on and 1 standalone). One study evaluated the DELFIA Xpress sFlt-1 test as a standalone test; none evaluated it alongside standard clinical assessment.

Of the 7 add-on test studies, 5 were prospective and 2 were retrospective. Two of the prospective studies were randomised controlled trials (RCTs: PARROT and INSPIRE). Three of the add-on test studies, PARROT, MAPPLE (Triage PLGF) and INSPIRE (Elecsys sFlt-1/PLGF ratio) included a comparison between a test result-revealed arm and a test result-concealed

arm. This was either as separate randomised trial arms (PARROT and INSPIRE) or as an indirect unadjusted comparison (MAPPLE). The PreOS study compared intended clinical decisions, recorded both before and after the Elecsys sFlt-1/PLGF ratio result was known. The intended procedures could then be amended after the sFlt-1/PLGF ratio result had been revealed. The 2 retrospective cohort studies were both single cohort analyses, 1 of multiple pregnancies only (Binder 2020) and 1 was a conference abstract done outside the UK (Andersen 2019). Most of the add-on test studies were in Europe (Germany, Austria, Denmark and the UK), although the MAPPLE study had 1 Australian site. The PARROT and INSPIRE studies were done in the UK.

Details of the studies' designs are in table 2 (add-on studies) and table 3 (standalone studies) of the diagnostics assessment report.

The EAG said that the studies included in the systematic review were heterogeneous in terms of gestational age, criteria used to define pre-eclampsia, how outcomes were defined, and whether test results were revealed or concealed. Therefore, the EAG did not do any meta-analyses.

Add-on test use

The add-on studies varied slightly in their approach to testing, in terms of:

- timing of the test
- cut-off values used
- how the revealed test results were used to inform in patient care
- definitions of pre-eclampsia.

Details are in table 4 of the diagnostics assessment report (page 52).

All studies used the cut-offs recommended by the respective manufacturers. The Binder (2020) study also investigated ratio cut-offs of over 80 and over 67 and intermediate values of 38 to 80 and 38 to 67 because it was investigating different sFlt-1/PLGF ratio measures in twin pregnancies.

Overview of suspected pre-eclampsia in the add-on test study populations

In 6 of the add-on test studies all patients had suspected pre-eclampsia: PARROT, MAPPLE, Ormesher (2018), INSPIRE, PreOS, Binder (2020). The MAPPLE and Ormesher (2018) studies included suspected fetal growth restriction as a presenting condition. Fetal growth restriction was considered to be a sign of suspected pre-eclampsia because the current NICE guidance includes 'suspected fetal compromise'. The Anderson (2019) study included high-risk pregnancies referred for observation of pre-eclampsia but did not report what constituted high risk. Full details of suspected pre-eclampsia in the study populations are in tables 6 and 7 of the diagnostics assessment report.

Standalone test use

An overview of the diagnostic test assessments done in the standalone studies is in table 5 of the diagnostics assessment report (page 54).

Quality assessment of studies

Test accuracy in the add-on studies

The risk of bias and applicability of test accuracy data in the add-on studies was assessed using the QUADAS 2 tool. An overview of the QUADAS 2 assessment is in table 9 of the diagnostics assessment report (page 69).

RCTs clinical effectiveness outcomes

The risk of bias with respect to the clinical effectiveness outcomes of the PARROT and INSPIRE studies was assessed using the Cochrane risk of bias tool for randomised trials (version 1). The EAG said that overall, both trials could be considered to be a low risk of bias, but there were 2 criteria in each trial with a high risk of bias. Both trials were considered to be at high risk of performance bias because of the revealed nature of the PLGF testing, because it was not possible to blind the clinicians or study participants to the

intervention and comparator status. The PARROT trial was also considered at high risk of bias for concealment of the random allocation, although the EAG noted that it was unlikely that the results were affected by selection bias. The EAG said that the INSPIRE trial was considered at high risk of selective reporting because results were not presented for all the intended outcome measures in the trial protocol. These included fetal growth and total blood count. The EAG also said that the trial reported the appearance, pulse, grimace, activity, and respiration (APGAR) score at delivery, maternal abruption, maternal pulmonary oedema, eclampsia, maternal estimated blood loss at delivery and small for gestational age, which were not listed in the protocol.

Clinical outcomes

The EAG considered that the PARROT and INSPIRE RCTs provided the most rigorous and comprehensive evidence on the impact of PLGF-based testing (alongside standard clinical assessment) on clinical effectiveness outcomes. Both trials were in the UK. The EAG therefore prioritised PARROT and INSPIRE to inform the assumptions and input parameters used in the base case economic modelling.

The PARROT trial

The PARROT trial was a stepped wedge cluster RCT of the Triage PLGF test done in 11 UK maternity units with 1,023 women with suspected pre-eclampsia who were between 20 weeks and 36 weeks plus 6 days of pregnancy. Initially usual care was used to assess and manage pre-eclampsia, with the PLGF result concealed from clinicians. The units were then randomised over time to reveal the PLGF test results to clinicians, who used the results alongside usual care to make clinical decisions. Usual care followed local hospital practice, NICE's guideline on diagnosing and managing hypertension in pregnancy and national guidance on managing fetuses suspected to be small for gestational age. When revealed testing took place, clinicians used a clinical management algorithm that integrated the PLGF test

result with NICE's hypertension in pregnancy guideline, with guidance on clinical decisions to take depending on the PLGF result. The algorithm used in the PARROT trial is in appendix 8 of the diagnostics assessment report (figure 10). The algorithm defined a PLGF result of less than 12 picograms per ml as very low and instructed clinicians to assess as pre-eclampsia (rule in). A PLGF result of 12 to 100 picograms per ml was considered low and increased surveillance was considered. PLGF values of more than 100 picograms per ml were considered normal and clinicians continued with usual management.

The number of women with pre-eclampsia in the revealed and concealed arms was 205 (36%) and 155 (35%), respectively.

Results for the trial's primary outcome, median days to diagnosis, were:

- 1.9 days (interquartile range [IQR] 0.5 to 9.2) for the revealed PLGF test result (n=573)
- 4.1 days (IQR 0.8 to 14.7) for the concealed PLGF test result (n=446).

The time ratio was 0.36 (95% CI 0.15 to 0.87; p=0.027).

A summary of the rest of the key findings from the PARROT trial is in tables 1 to 3.

Table 1 Time to delivery and preterm delivery in the PARROT trial

Outcome	**Revealed PLGF test result n=573**	**Concealed PLGF test result n=446**	**Difference**
Time to delivery (all diagnoses), days, geometric mean (SD) (Used in the EAG's economic model base case)	19.0 (3.1)	17.8 (3.1)	Ratio of means 1.10 (CI 0.99 to 1.24)
Preterm deliveries under 37 weeks, n/N (%)	234/573 (41)	167/446 (37)	Paper states no differences observed

Abbreviations: CI, confidence interval; EAG, external assessment group; PLGF, placental growth factor; SD, standard deviation.

Table 2 Maternal outcomes in the PARROT trial

Outcome	Revealed PLGF test result n=573	Concealed PLGF test result n=446	Difference
Number of nights in inpatient care, mean (SE)	7.43 (0.36)	7.26 (0.38)	-0.06 (type of statistic not reported) (95% CI -0.22 to 0.09)
Number of women with adverse outcomes, defined by the fullPIERS consensus, n/N (%) (Used in the EAG's economic model base case)	22/573 (4)	24/446 (5)	Adjusted OR 0.32, 95% CI 0.11 to 0.96; p=0.043

Abbreviations: CI, confidence interval; EAG, external assessment group; OR, odds ratio; PLGF, placental growth factor; SE, standard error.

Table 3 Perinatal and neonatal outcomes in the PARROT trial

Outcome	Revealed PLGF test result n=573	Concealed PLGF test result n=446	Difference
Neonatal unit admission, % (n/N)	34.0 (195/573)	32.7 (146/446)	Paper states no differences observed
Number of nights in neonatal unit mean (SE)	22.1 (25.9); N=573	24.6 (35.2); N=446	Not reported
Number of nights in SCBU, mean (SE)	14.7 (14.4); N=573	13.09 (12.6); N=446	Paper states no difference between groups
Number of inpatient nights in ICU or HDU, mean (SD)	15.2 (1.7)	24.2 (3.8)	Mean difference -10.6 (95% CI -20.81 to -0.47)
Perinatal adverse outcomes, n/N (%) (post-hoc)	86/573 (15)	63/446 (14)	Adjusted OR 1.45, 95% CI 0.73 to 2.90

Outcome	Revealed PLGF test result n=573	Concealed PLGF test result n=446	Difference
Perinatal deaths, n/N (%) (Used in the EAG's economic model base case and categorised as stillbirth, neonatal death and in-hospital death)	6/573 (1)	4/446 (1)	Adjusted OR 1.00, 95% CI 0.61 to 1.63
Late neonatal deaths (8 to 27 complete days of life), n/N (%) (Used in the EAG's economic model base case and categorised as stillbirth, neonatal death and in-hospital death)	3/573 (1)	1/446 (under 1)	Not reported
Any grade of intraventricular haemorrhage [perinatal], n/N (%) (Used in the EAG's economic model base case)	7/573 (1)	11/446 (3)	Not reported
Respiratory distress syndrome [perinatal], n/N (%) (Used in the EAG's economic model base case)	78/573 (14)	54/446 (12)	Not reported
Delivery gestation, mean weeks (SD)	36.6 (3.0)	36.8 (3.0)	Mean difference -0.52 (CI -0.63 to 0.73)

Abbreviations: CI, confidence interval; EAG, external assessment group; HDU, high dependency unit; ICU, intensive care unit; OR, odds ratio; PLGF, placental growth factor; SCBU, special care baby unit; SD, standard deviation. SE, standard error.

Use of the Triage PLGF Test to rule in pre-eclampsia

A Triage PLGF test result of less than 12 picograms per ml, when used alone and not in addition to standard clinical assessment (that is, the test accuracy analysis was in the concealed arm only) had a positive predictive value of 44.6% (95% CI 32.3 to 57.5) for predicting pre-eclampsia requiring delivery within 14 days in a subgroup of women who presented between 20 weeks and 35 weeks of pregnancy.

Assessment of delivery and related perinatal outcomes

PARROT trial data on the onset of labour and mode of delivery showed that more women had a pre-labour caesarean section in the revealed arm (40%) than the concealed arm (35%). More women also had an emergency caesarean section in the revealed arm (26%) than the concealed arm (21%). This was consistent across all PLGF level subgroups, with the highest rates reported in women with PLGF levels under 12 picograms per ml.

The INSPIRE trial

The INSPIRE trial was an RCT of the Elecsys sFlt-1/PLGF ratio test done in a tertiary referral hospital in the UK. The study included 370 participants with suspected pre-eclampsia who were between 24 weeks and 37 weeks pregnant. The design was similar to the PARROT trial but women, rather than maternity units, were randomly allocated to standard clinical management with the test result concealed or standard clinical management with the sFlt-1/PLGF ratio result revealed.

Clinicians followed a clinical management algorithm, and in the revealed testing group, the sFlt-1/PLGF ratio result was integrated into this. Details of the INSPIRE trial clinical management algorithm are in appendix 8 of the diagnostics assessment report (figure 11). The study used cut-offs of 38 or less to suggest a low risk of developing pre-eclampsia within 7 days and of more than 38 to suggest elevated risk of developing pre-eclampsia within 7 days. These cut-offs are the same as those recommended by the company for ruling out or ruling in the development of pre-eclampsia within 1 and 4 weeks, respectively. The clinical algorithm for the reveal group was considered alongside clinical features, with women grouped based on blood pressure into stage 1 (less than 149/99 mmHg), 2 (150/100 to 159/109 mmHg) or 3 (more than 160/110 mmHg). The algorithm advised the discharge of women with a ratio of 38 or less unless there were any concerning clinical features. For women with a ratio of more than 38, those in stage 1 were considered for

admission for assessment. Women in stage 2 were admitted for assessment and women in stage 3 were kept as inpatients.

In the trial, 25.2% of women in the revealed testing group and 20.6% in the concealed testing group were diagnosed with pre-eclampsia.

Results for the trial's primary outcome, admission for suspected pre-eclampsia within 24 hours of the test, were:

- 60 out of 186 patients (32.3%) for the revealed PLGF test result
- 48 out of 184 patients (26.1%) for the concealed PLGF test result.

The risk ratio was 1.24 (95% CI 0.89 to 1.70) and the risk difference was 0.06 (95% CI -0.03 to 0.15).

A summary of the rest of the key findings from the INSPIRE trial is in tables 4 and 5.

Table 4 Maternal outcomes in the INSPIRE trial

Outcome	Revealed PLGF test result n=186	Concealed PLGF test result n=184	Difference
Pulmonary oedema, n/N (%) used in the EAG's economic model base case	1/186 (0.54)	1/184 (0.54)	p=0.994
Abruption, n/N (%) used in the EAG's economic model base case	2/186 (1.1)	5/184 (2.7)	p=0.246
Eclampsia used in the EAG's economic model base case	0	0	-
Severe PE (ACOG criteria), % as a proportion of those diagnosed with PE (n/N) used in the EAG's economic model base case	72.3 (34/47)	63.3 (24/38)	9.0 (absolute percentage difference as calculated by reviewer); p=0.366

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; EAG, external assessment group; IQR, interquartile range; PE, pre-eclampsia; PLGF, placental growth factor.

Table 5 Perinatal and neonatal outcomes in the INSPIRE trial

Outcome	Revealed PLGF test result n=186	Concealed PLGF test result n=184	Difference
Gestational age (weeks) at delivery, median (IQR)	38.4 (37.3 to 39.6)	38.1 (37.1 to 39.3)	p=0.479
SCBU admission, % (n/N)	18.3	15.2	p=0.430

Abbreviations: IQR, interquartile range; SCBU, special care baby unit.

The INSPIRE trial did not report any data on neonatal or perinatal mortality.

Use of the Elecsys sFlt-1/PLGF ratio test to rule in pre-eclampsia

In a post-hoc analysis of the revealed arm the trial reported that an Elecsys sFlt-1/PLGF ratio test cut-off of more than 38 had a positive predictive value of 0.411 (95% CI 0.281 to 0.550) for ruling in the development of pre-eclampsia

within 1 week of testing, when it was used alone (that is, not in addition to standard clinical management).

Maternal adverse outcomes

The INSPIRE study reported the frequency of a select number of outcomes. These are summarised in table 25 of the diagnostics assessment report (page 94). No statistically significant differences were observed between trial arms for these outcomes. However the EAG said that these results should be interpreted with caution because the study was not powered to detect differences for these outcomes.

Assessment of delivery and related perinatal outcomes

No data on delivery mode and preterm delivery were reported in the INSPIRE trial.

MAPPLE and PreOS add-on studies

Of the remaining add-on test studies, the 3 single arm observational cohort studies (Binder 2020, Ormesher 2018 and Andersen 2019) did not assess the effect of using the PLGF or sFlt-1/PLGF ratio tests on clinical outcomes because they did not have a control arm. Therefore, in addition to the PARROT and INSPIRE trials, the EAG focused on a selection of clinical outcomes reported in the 2 other add-on studies, which compared the tests alongside standard clinical assessment with standard clinical assessment only: the MAPPLE study (Triage PLGF test) and PreOS study (Elecsys sFlt-1/PLGF ratio test). No clinical outcome data were available for the BRAHMS Kryptor sFlt-1/PLGF ratio test or DELFIA Xpress PLGF tests. Outcome data from these trials are in the diagnostics assessment report on pages 90 to 107.

Assessment of test accuracy

Details of the assessment of test accuracy from the add-on studies are on pages 78 to 85 in the diagnostics assessment report.

In its economic model, the EAG modelled the BRAHMS Kryptor sFlt-1/PLGF ratio test. It used the same model parameters (except test cost) as the Elecsys test based on an assumption of equal predictive accuracy, in line with Salahuddin et al. (2016). Salahuddin et al. reported accuracy for prediction of adverse events within 2 weeks for the BRAHMS and Elecsys tests by reanalysing frozen samples from the ROPE cohort study. The EAG said that this study estimated an identical area under the curve for the 2 tests, using a model that also accounted for systolic blood pressure and proteinuria.

Assessment of the predictive concordance between tests

The EAG identified 11 studies that compared 2 or more of the Triage PLGF, Elecsys, BRAHMS Kryptor and DELFIA Xpress PLGF 1-2-3 tests. No studies compared all 4 tests. Details are in table 72, appendix 4 of the diagnostics assessment report.

In a study of healthy pregnant Chinese women, Cheng et al. (2019) identified inter-test differences in determining measured PLGF and sFlt-1 concentrations and concluded that the rule in/rule out decision levels are test-specific and not interchangeable. The rule out and rule in cut-offs of the Elecsys sFlt-1/PLGF ratio of 38 and 110 respectively were estimated to have equivalent values of 55 and 188 for the BRAHMS Kryptor sFlt-1/PLGF ratio test. The manufacturer of the BRAHMS Kryptor sFlt-1/PLGF ratio test recommends a cut-off of 85.

The COMPARE study (McCarthy et al. 2019) was a secondary analysis of PLGF samples from women in the PEACHES study and in parts 1 and 2 of the PELICAN study who presented with suspected pre-eclampsia or a suspected small for gestational age fetus before 37 weeks of pregnancy. This study compared the commercially recommended cut-offs for the Triage PLGF test (less than 100 picograms per ml), Elecsys sFlt-1/PLGF ratio (over 38) and an optimally derived cut-off for the DELFIA Xpress PLGF 1-2-3 test (less than 150 picograms per ml). The DELFIA cut-off was determined by the study authors based on producing the same number of positive results (without

knowing if they were true or false positive) as the Triage PLGF test. McCarthy et al. concluded that the tests' ability to predict delivery within 2 weeks did not differ significantly when using the specified cut-offs, with areas under the ROC curve similar among the tests. The EAG noted that the population analysed in the COMPARE study did not fully match the NICE scope because it comprised women suspected of having pre-eclampsia and women suspected of having a small for gestational age baby.

Another secondary analysis study by Giblin et al. (2020) analysed PLGF samples from the same population as the COMPARE study. Giblin et al. reported the test performance statistics (sensitivity, specificity, PPV, NPV and likelihood ratios) for PLGF or the sFlt-1/PLGF ratio for predicting delivery within 14 days using the Triage PLGF, Elecsys sFlt-1/PLGF ratio and DELFIA Xpress tests. They concluded that the Triage and Elecsys tests have slightly different sensitivities and specifies, but AUCs were similar and the tests had similar clinical applicability for prediction of delivery.

Health-related quality of life outcomes

No health-related quality of life outcomes were reported in the published studies. The ongoing PARROT Ireland trial is assessing health-related quality of life.

Ongoing studies

The EAG identified 7 ongoing studies that are likely to meet the eligibility criteria for the systematic review, at least 5 of which are RCTs:

- 4 studies of the Elecsys test
- 1 study (PARROT Ireland) has completed and is of the Triage PLGF test
- 1 company study is of the DELFIA Xpress test
- 1 study (Fernández Oliva) does not give details of the index test used.

The PARROT 2 trial will provide data on using repeat PLGF testing. Further details of the ongoing studies are in appendix 6 of the diagnostics assessment report.

2.2 Costs and cost effectiveness

Systematic review of cost-effectiveness evidence

The EAG did a systematic review to identify any published economic evaluations of PLGF-based testing in addition to clinical assessment to diagnose pre-eclampsia in the second and third trimesters of pregnancy. Full details of the systematic review results are in the diagnostics assessment report from page 109. Eleven economic evaluation studies met the inclusion criteria. Six were evaluations of the Elecsys sFlt-1/PLGF ratio test, 2 were evaluations of the Triage PLGF test and 2 assessed more than 1 PLGF test (Elecsys sFlt-1/PLGF ratio, Triage PLGF and BRAHMS sFlt-1 Kryptor/BRAHMS PLGF plus Kryptor). One study did not report which PLGF test or tests were evaluated. Only 1 model measured the effects in QALYs (quality-adjusted life years), 2 considered maternal and neonatal outcomes, and the other 9 concentrated on potential savings from using PLGF-based testing. Details of the included economic studies are in tables 42 and 43 on pages 112 to 118 in the diagnostics assessment report.

The studies suggested that including PLGF-based tests alongside usual care has the potential to reduce maternal adverse events and reduce the number of women who receive inappropriate treatment (mainly hospitalisation) because of false positive diagnoses. Six studies reported a cost saving within a range of £94 to £2,896 per woman tested from having a first PLGF test in addition to usual care, compared with usual care alone. Five studies reported a cost saving between £26 and £607 for women who received a retest. One study (Myrhaug et al. 2020) reported that introducing PLGF-based testing (Elecsys sFlt-1/PLGF ratio test, Triage PLGF test, BRAHMS Kryptor sFlt-1/PLGF ratio test along with usual care) was not cost saving, with a cost of £3,710 per additional correctly identified case of pre-eclampsia. Transition

probabilities for admission and pre-eclampsia rates were derived from the INSPIRE study. Details of each study are in appendix 7 of the diagnostics assessment report (starting on page 240).

Economic analysis

The EAG developed a de novo economic model to assess the cost effectiveness of PLGF-based testing in addition to clinical assessment to diagnose pre-eclampsia in the second and third trimesters of pregnancy.

Model structure

The model consisted of a short-term decision tree, incorporating testing and management of people with suspected pre-eclampsia, timing and mode of delivery, and maternal and neonatal outcomes. A lifetime time horizon was used in the base case with the discount rate of 3.5% applied to both costs and QALYs. A shorter time horizon of up to 6 months post-partum was used in a scenario analysis.

The EAG said that the model was similar in design to the model that informed NICE's 2016 guidance on PLGF-based testing in suspected pre-eclampsia (DG23). It differs by adopting a lifetime time horizon and an assessment of the long-term impact on maternal and neonatal outcomes from PLGF-based testing and associated care. The previous model also used data on sensitivity and specificity to link to longer-term outcomes, whereas for this assessment the EAG used data on clinical outcomes from RCTs.

The model has 4 main structural components:

- Stratification of women depending on the risk of pre-eclampsia (low, intermediate, or high) based on the results of standard clinical assessment with or without PLGF testing.
- Pregnancy management.
- Maternal outcomes (admission to intensive care, extended hospital stay, and morbidity associated with pre-eclampsia).

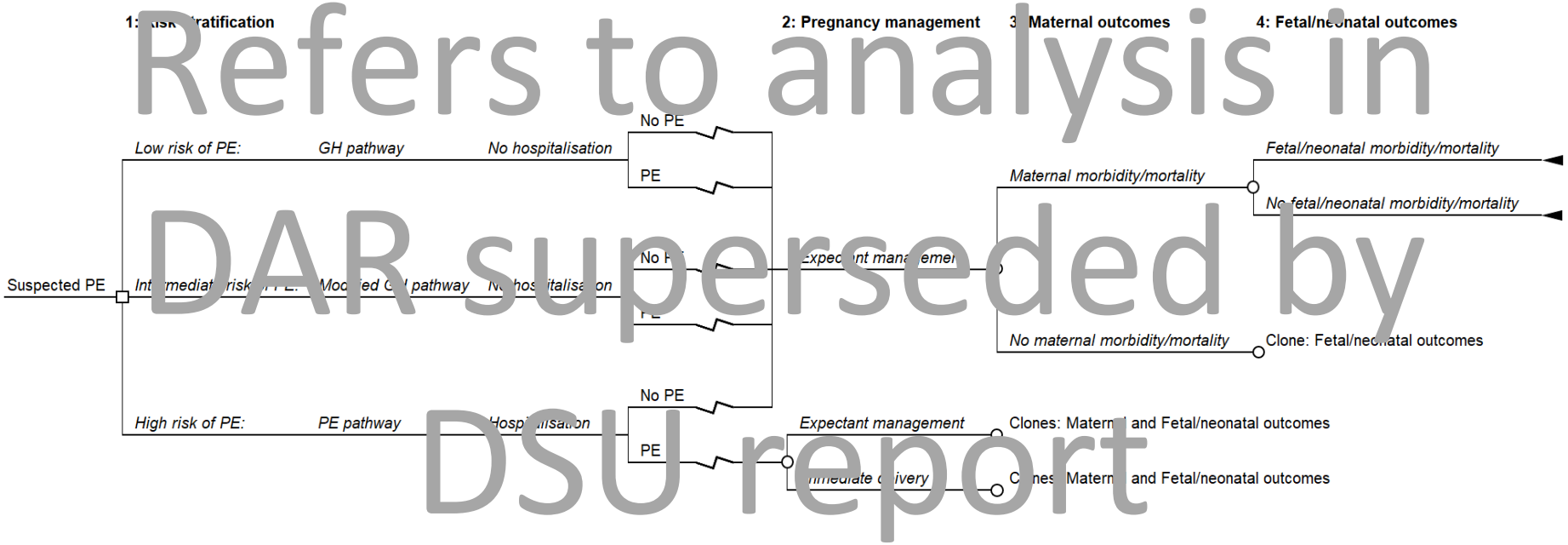
- Fetal and neonatal outcomes (admission to intensive care, extended hospital stay, and morbidity associated with fetal conditions that may be caused by maternal pre-eclampsia, with or without early delivery).

The model structure (figure 1) does not include repeat testing of women who have had an initial negative PLGF-based test for suspected pre-eclampsia.

Because of a lack of data for the BRAHMS sFlt-1 Kryptor/BRAHMS PLGF plus Kryptor PE ratio test, the EAG modelled this test using the same data as the Elecsys sFlt-1/PLGF ratio test, only varying the cost per test. The EAG said it assumed the Elecsys and BRAHMS test had similar effectiveness, based on Salahuddin et al. (2016). The EAG did not model the DELFIA Xpress PLGF 1-2-3 test.

In the base case, current care was modelled according to the 2010 NICE guideline on managing hypertension and pre-eclampsia (CG107) which stratifies hypertension into mild, moderate and severe. Although CG107 was replaced in 2019 by the NICE guideline on diagnosing and managing hypertension in pregnancy (NG133), the PARROT and INSPIRE trials, which inform many of the parameters and assumptions in the economic evaluation, were started before NG133. The clinical management algorithms of the PARROT and INSPIRE trials, incorporating PLGF testing, are therefore based on CG107. The EAG did a scenario analysis that assumed that gestational hypertension and pre-eclampsia would be managed according to NG133, which distinguishes between hypertension and severe hypertension.

Figure 1 Model structure



Abbreviations: GH, gestational hypertension; PE, pre-eclampsia

Risk stratification and pregnancy management

The model assumed that a decision about the care of women with suspected pre-eclampsia was made at an initial appointment. This was with or without a PLGF-based test to help identify who will develop the full symptoms of pre-eclampsia, and decide whether to admit to hospital. The distribution of test results across the women tested, prevalence of pre-eclampsia and level of hospitalisation were taken from data and assumptions based on clinical management algorithms from INSPIRE for assessment of the Elecsys sFlt-1/PLGF ratio test and PARROT for the Triage PLGF test. In a scenario analysis for the Elecsys sFlt-1/PLGF ratio test, the EAG used data from the PreOS study instead of INSPIRE for the distribution of women by test result, and the proportions with pre-eclampsia.

The costs of testing were applied if a PLGF-based test was used.

All women in the model were assumed to have mild, moderate or severe hypertension. The proportions of each were taken from the INSPIRE trial for the Elecsys sFlt-1/PLGF ratio test and from the PARROT trial (for incidence of severe hypertension) and from Duckworth et al. (for incidence of mild and moderate hypertension) for the Triage PLGF test. The distribution of women in the model by hypertension category is in table 55 in the diagnostics assessment report.

A cost was applied for women admitted to hospital, to include cost of hospital stay and any assessment and treatment done, which differed by the level of hypertension and by whether a woman had pre-eclampsia. Time to delivery also affected the cost of hospitalisation and was modelled using estimates from the PARROT study. Times varied (for women at high risk of pre-eclampsia) by whether a PLGF-based test was used or not, gestational age (up to 35 weeks or between 35 and 37 weeks) and level of hypertension. See table 56 in the diagnostics assessment report for further detail.

For women who were misdiagnosed (false positive or negative), for management costs the EAG assumed that their care would be according to the correct classification for half the time, and incorrect classification for the remaining time. To take account of any anxiety a false positive test may cause, the EAG applied a QALY decrement for women with false positive results.

For women not admitted to hospital costs were based on the management of gestational hypertension. Women at low or intermediate risk of pre-eclampsia were assumed to use the same healthcare resources but those at low risk had longer time until delivery (based on PARROT study data as above; see table 56 in diagnostics assessment report for further detail).

Maternal outcomes

Figure 2 Delivery management and maternal outcomes

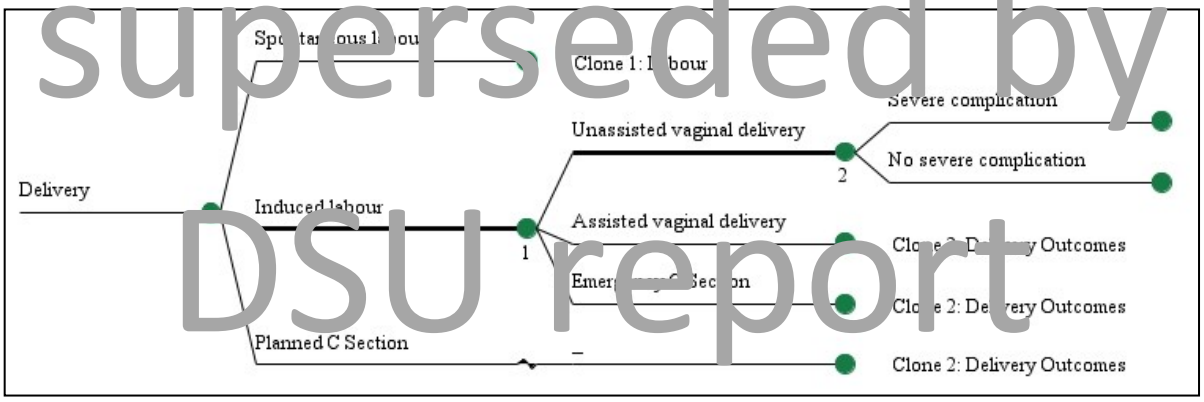


Figure 2 shows a sub-tree for the delivery and maternal outcome component of the model. Delivery could be by spontaneous labour, induced labour, or planned caesarean section. The probability of each depended on whether a PLGF-based test was used or not (from the PARROT trial for both the Triage PLGF and Elecsys sFlt-1/PLGF ratio tests). For women in spontaneous or induced labour, mode of delivery could be by vaginal delivery (assisted or unassisted) or emergency caesarean section. The probability of each differed by whether labour was spontaneous or induced, whether a PLGF-based test

was used (PARROT data was used for both tests) and the risk classification of the women as assessed by the tests.

Different costs and health-related quality of life utilities were incurred by mode of delivery. Women who had a caesarean section had a lower utility (from birth to 3 weeks post-partum) than women who had a vaginal delivery. This was even lower for emergency caesarean section deliveries.

Major maternal complications could occur during delivery. Differences in the occurrence of these complications between use of the Triage PLGF test and current care were taken from the PARROT trial (defined by the fullPIERS consensus), and for the Elecsys sFlt-1/PLGF ratio test, complication rates were from the INSPIRE trial (the EAG assumed that pulmonary oedema, abruption and eclampsia were the major maternal complications). Occurrence of a major complication was assumed to lead to a 2-day stay in an intensive care unit (which has higher costs than standard postnatal care). A health-related quality of life utility decrement was also applied for 3 weeks for women admitted to intensive care.

A proportion of women with pre-eclampsia were assumed to be treated with magnesium sulfate. The proportion was based on data from the PARROT trial and differs by risk classification and by whether a PLGF-based test is used or not.

Fetal/neonatal outcomes

Figure 3 Fetal and neonatal outcomes

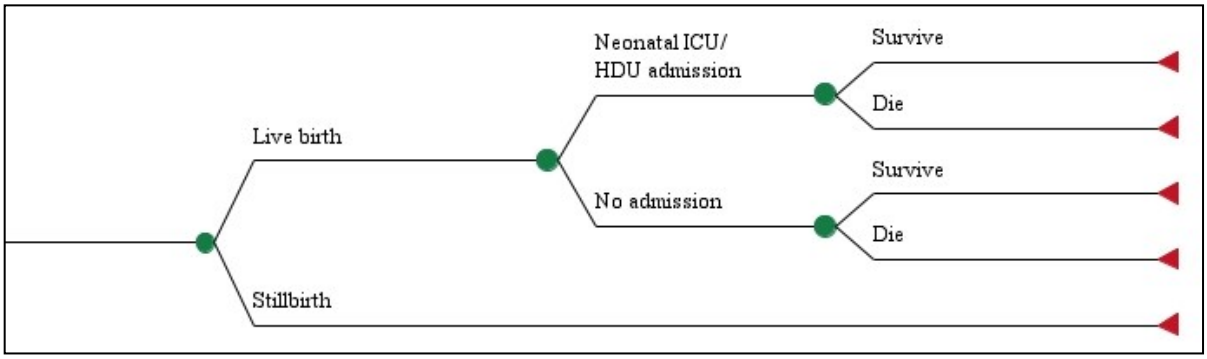


Figure 3 shows a sub-tree for the fetal and neonatal outcome component of the model. Differences between the incidence of fetal or neonatal mortality with or without the Triage PLGF test were taken from PARROT. Because of a lack of data for the Elecsys sFlt-1/PLGF ratio test, the EAG assumed no difference in mortality between using this test and current care. A QALY decrement was applied for mothers whose child dies. If a child dies, the QALYs they would have accrued if they had lived (based on a life expectancy of 80 years) are forgone.

Neonates could also be admitted to a neonatal unit for care. Differences between admission to care for the Triage PLGF test and current care were taken from PARROT. Differences between admission to care for the Elecsys sFlt-1/PLGF ratio test and current care were taken from INSPIRE.

Admission could be to an intensive care unit, high dependency unit or special care baby unit, with the proportions admitted based on the PHOENIX study (same for both test and current care). Length of stay in the units was taken from the PARROT trial. Additional costs were incurred if an admission to these units was needed.

A QALY decrement was also applied for babies admitted to critical care, and their parents for 3 weeks.

Neonates could also have complications in the model; either respiratory distress syndrome (RDS) or intraventricular haemorrhage (IVH). Differences between the incidence of these complications for the Triage and current care were taken from PARROT. Because of a lack of data for the Elecsys sFlt-1/PLGF ratio test, the EAG assumed no difference in these complications between the test and current care. Long-term costs were associated with neonatal complications (IVH or RDS).

A QALY decrement was applied for babies with complications (RDS or IVH). A decrement was also applied for mothers whose child had complications.

Model population

The populations considered in the in the EAG base case and scenario analyses are summarised in table 52 of the diagnostics assessment report (page 135). In the base case the relative effectiveness of the Triage PLGF and Elecsys sFlt-1/PLGF ratio tests used in addition to usual care compared with usual care alone was estimated from the PARROT and INSPIRE studies, respectively.

The EAG used unadjusted trial data from the INSPIRE trial for the number of women who developed pre-eclampsia when the model was run with use of the Elecsys sFlt-1/PLGF ratio test (25%) and without (21%). Unadjusted data from the PARROT trial was also used for the number of women who developed pre-eclampsia when the model was run with use of the Triage PLGF test (36%) and without (35%).

Comparator

The comparator was no further assessment (that is, beyond clinical assessments already done, such as blood pressure measurement, urinalysis and fetal monitoring) to help make a decision about a diagnosis of pre-eclampsia and subsequent decisions about care. That is, no use of PLGF-based testing.

Model inputs

A full list of model parameters is in table 103 in appendix 13 of the diagnostics assessment report.

Onset and mode of delivery

The EAG used data from PARROT for both tests because no information on delivery was reported in INSPIRE for the Elecsys sFlt-1/PLGF ratio test. Inputs used in the base case for onset of delivery and mode of delivery are in tables 6 and 7, respectively.

Table 6 Onset of delivery model inputs - base case

Onset of delivery	Intervention	Comparator	Source
Spontaneous	14%	18%	PARROT
Induced	46%	47%	PARROT
Planned C section	40%	35%	PARROT

Table 7 Mode of delivery model inputs - base case

Mode of delivery	Group	Intervention	Comparator	Source
Unassisted	High-risk PE	35%	36%	PARROT
Unassisted	Intermediate-risk PE	50%	61%	PARROT
Unassisted	Low-risk PE	63%	67%	PARROT
Assisted	High-risk PE	6%	6%	PARROT
Assisted	Intermediate-risk PE	12%	12%	PARROT
Assisted	Low-risk PE	11%	17%	PARROT
Emergency C section	High-risk PE	59%	58%	PARROT
Emergency C section	Intermediate-risk PE	38%	27%	PARROT
Emergency C section	Low-risk PE	26%	16%	PARROT

Abbreviations: PE, pre-eclampsia.

Maternal outcomes – major complications

Table 8 Maternal outcomes (major complications) model inputs - base case

Test	Group	Pre-eclampsia	Intervention	Comparator	Source
Triage	High-risk PE	PE	9.3%	8.6%	PARROT
Triage	High-risk PE	No PE	3.4%	3.1%	PARROT
Triage	Intermediate-risk PE	PE	5.7%	10.4%	PARROT
Triage	Intermediate-risk PE	No PE	2.1%	3.8%	PARROT
Triage	Low-risk PE	PE	3.9%	5.7%	PARROT
Triage	Low-risk PE	No PE	1.4%	2.1%	PARROT

Test	Group	Pre-eclampsia	Intervention	Comparator	Source
Elecsys	-	PE	2.4%	4.9%	INSPIRE
Elecsys	-	No PE	1.2%	2.4%	INSPIRE

Abbreviations: PE, pre-eclampsia.

Fetal and neonatal outcomes

Fetal and neonatal outcome included neonatal unit admission rates, incidence of RDS and IVH. Mortality incidences are in table 9 and 10. The EAG said that, because of a lack of data for the Elecsys test, it assumed no difference in incidence of IVH and RDS or mortality between use of the Elecsys test and no use of the test.

Table 9 Fetal and neonatal mortality outcomes model inputs for the Triage test - base case (source: PARROT)

Group	Pre-eclampsia	Intervention (%)	Comparator (%)
High-risk PE	PE	5.9	8.6
High-risk PE	No PE	2.1	3.1
Intermediate-risk PE	PE	2.9	1.8
Intermediate-risk PE	No PE	1.0	0.7
Low-risk PE	PE	0	2.9
Low-risk PE	No PE	0	1.0

Abbreviations: PE, pre-eclampsia.

Table 10 Fetal and neonatal mortality outcomes model inputs for the Elecsys test - base case (source: assumption)

Group	Pre-eclampsia	Intervention (%)	Comparator (%)
High-risk PE	PE	7.2	7.2
High-risk PE	No PE	2.6	2.6
Intermediate-risk PE	PE	2.3	2.3
Intermediate-risk PE	No PE	0.9	0.9
Low-risk PE	PE	1.4	1.4
Low-risk PE	No PE	0.5	0.5

Abbreviations: PE, pre-eclampsia

Costs

A full list of costs used in the model is in table 104 in appendix 13 of the diagnostics assessment report.

Costs of PLGF-based tests

Test costs were estimated from information provided by the manufacturers, and from clinical experts and laboratory staff who use the Triage PLGF test and Elecsys sFlt-1/PLGF ratio test in clinical practice. If there was no information, the EAG made assumptions to inform cost estimates. The cost components and the total cost per PLGF tests are in table 11.

Table 11 Cost components and total cost per PLGF test used in the base case analysis

Cost component	Triage PLGF	Elecsys	BRAHMS
Cost of test kit	£40	-	£22
Cost per reportable test (including capital, maintenance, and equipment costs)	-	£70	-
Machines costs	£0.46	-	£0.003
Service charges and maintenance costs	£0.64	-	£0.003
Equipment (laboratory materials and consumables)	£1.92	-	£21.04
Staff time for training	£0.43	£0.43	£0.43
Staff time to perform and analyse test and staff time for quality control	£2.67	£5.33	£5.33
Phone calls to communicate test results	£3.47	£3.47	£3.47
Total	£50	£79	£52

Cost of managing suspected pre-eclampsia

The total costs incurred in managing a high, intermediate and low risk of pre-eclampsia, split by hypertension status and gestational age, is in the diagnostics assessment report in table 57 on page 154 of the diagnostics assessment report.

Long-term costs

The long-term costs model inputs in the base case were:

- £93,251 for babies with IVH (from Kurse et al.; assumed as the cost of babies with cerebral palsy, as done by Varley-Campbell et al)
- £1,037 for babies with RDS (from Khan et al.; assumed as the cost of babies born between 32 to 37 weeks of pregnancy).

Health-related quality of life and QALY decrements

The EAG did identified data on health-related quality of life in gestational hypertension, pre-eclampsia and general pregnancy to inform utility values for the economic model. These are described in the diagnostics assessment report from page 119. Some of the health-related quality of life values used in the EAG's base case model are in table 12.

Table 12 Base case health-related quality of life inputs

Decrement for	Utility	Duration of decrement	QALYs	Source
False positive result Immediate delivery	0.028	8 days	0.0002	Prosser et al. (2008)
False positive result Intervention	0.028	12.5 days	0.0006	Prosser et al. (2008)
False positive result Comparator	0.028	2 days	0.001	Prosser et al. (2008)
Mother admitted to an intensive care unit	0.039	3 weeks	0.002	Seppänen et al.
Babies and parents of babies admitted to critical care units	0.039	3 weeks	0.002	Seppänen et al.
Mothers whose child died	-	Lifetime	3.97	Varley-Campbell et al.
Mothers whose child had complications (RDS and IVH)	-	2 years	0.37	Varley-Campbell et al.
Baby with RDS	-	Lifetime	0.41	Varley-Campbell et al.
Baby with IVH	-	Lifetime	0.91	Varley-Campbell et al.
Decrement for child's death	-	Lifetime	24.70	Ara and Brazier

Abbreviations: IVH, intraventricular haemorrhage; QALY, quality-adjusted life year; RDS, respiratory distress syndrome.

Base case results

For the purposes of decision making, the ICERs (incremental cost-effectiveness ratios) per QALY gained or lost will be considered.

Cost-effectiveness results for the Triage PLGF test

The base case results indicated that using the Triage PLGF test to assess pre-eclampsia was more effective and less expensive compared with standard clinical assessment (see table 13). A breakdown of costs and QALYs is in tables 14 and 15.

Table 13 Base case: results for Triage PLGF test

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Standard assessment	13,051	16.99	-	-	-
Triage PLGF test	11,305	17.20	-1,746	0.204	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; PLGF, placental growth factor; QALY, quality-adjusted life year.

Table 14 Base case: breakdown results for Triage PLGF test costs

Components	Triage PLGF test	Standard assessment	Incremental
First testing	£50	£0	£50
Management	£1,561	£1,791	-£230
Delivery	£3,880	£3,740	£140
Maternal care	£370	£410	-£40
Neonatal care	£3,969	£4,661	-£692
Neonatal care - long term	£1,476	£2,450	-£974
Total	£11,305	£13,051	-£1,746

Abbreviations: PLGF, placental growth factor.

Table 15 Base case: breakdown results for Triage PLGF test QALYs

Components	Triage PLGF test	Standard assessment	Incremental
Management	0.0000	-0.0001	0.0000
Delivery	0.0348	0.0353	-0.0005
Maternal - short term	0.3841	0.3840	0.0000
Neonatal - short term	-0.0007	-0.0007	0.0000
Maternal - long term	17.2887	17.2668	0.0219
Neonatal - long term	-0.5107	-0.6936	0.1829
Total	17.1961	16.9918	0.2043

Abbreviations: PLGF, placental growth factor; QALY, quality-adjusted life year.

Cost-effectiveness results for the Elecsys sFlt-1/PLGF ratio test

The base case results indicated that using the Elecsys sFlt-1/PLGF ratio test to assess pre-eclampsia is more expensive and produces less QALYs than standard clinical assessment (see table 16). A breakdown of costs and QALYs is in tables 17 and 18.

Table 16 Base case: results for the Elecsys sFlt-1/PLGF ratio test

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Standard assessment	£10,321	17.17	-	-	-
Elecsys sFlt-1/PLGF ratio test	£10,942	17.03	£621	-0.140	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; PLGF, placental growth factor; QALY, quality-adjusted life year.

Table 17 Base case: breakdown results for Elecsys sFlt-1/PLGF ratio test costs

Components	Elecsys sFlt-1/PLGF ratio test	Standard assessment	Incremental
First testing	£79	£0	£79
Retesting	£0	£0	£0
Management	£1,185	£1,492	-£308
Delivery	£3,912	£3,751	£161
Maternal care	£299	£344	-£45
Neonatal care	£2,935	£2,679	£256
Neonatal care - long term	£2,532	£2,055	£477
Total	£10,942	£10,321	£621

Abbreviations: PLGF, placental growth factor.

Table 18 Base case: breakdown results for Elecsys sFlt-1/PLGF ratio test QALYs

Components	Elecsys sFlt-1/PLGF ratio test	Standard assessment	Incremental
Management	-0.0001	-0.0002	0.0001
Delivery	0.0347	0.0353	-0.0006
Maternal - short term	0.3841	0.3841	0.0000
Neonatal - short term	-0.0006	-0.0004	-0.0001
Maternal - long term	17.2630	17.2896	-0.0267
Neonatal - long term	-0.6485	-0.5356	-0.1129
Total:	17.0325	17.1728	-0.1402

Abbreviations: PLGF, placental growth factor; QALY, quality-adjusted life year.

The difference in the base case results for the Triage PLGF and Elecsys sFlt-1/PLGF ratio test is likely to be caused by differences in neonatal outcomes (see tables 14, 15, 17 and 18). Incremental costs were lower for neonatal short-term and long-term care for the Triage PLGF test (-£692 and -£974) than standard assessment, but higher when the Elecsys test was used (+£256

and +£477). More QALYs were generated for maternal long-term care and neonatal long-term care when the Triage PLGF was used (0.0219 and 0.1829 respectively), whereas fewer QALYs were generated by use of the Elecsys test (-0.0267 and -0.1129, respectively). Long-term decrements to maternal health-related quality of life were caused by neonatal mortality of neonatal complications.

Cost-effectiveness results for BRAHMS Kryptor sFlt-1/PLGF ratio test

Total QALYs are the same as the Elecsys sFlt-1/PLGF ratio test. Using the BRAHMS Kryptor sFlt-1/PLGF ratio test was estimated to be more expensive and produce less QALYs than standard clinical assessment. See table 19.

Table 19 Base case: results for BRAHMS Kryptor sFlt-1/PLGF ratio test

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Standard assessment	£10,321	17.17	-	-	-
BRAHMS ratio test (ThermoFisher)	£10,915	17.03	£594	-0.140	Dominated

Abbreviations: QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio

Analysis of alternative scenarios

A list of the scenario analyses done by the EAG is in the diagnostic assessment report on page 164. Details of the model inputs used are in appendix 14 of the diagnostics assessment report. Selected results are described below.

Scenario analyses for the Triage PLGF test

The Triage PLGF test dominated standard assessment (that is, no use of the test) in all but 2 of the scenarios (see table 20). Full details of the Triage PLGF test scenario analyses results are in tables 64 and 65 of the diagnostics assessment report (page 166).

Table 20 Scenario analyses: results for Triage PLGF test

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY) compared with standard assessment
Base case	-£1,746	0.204	Dominant
Time horizon: 6 months post-partum	-£772	-0.0005	£1,698,809
Death in neonates: excluding stillbirth	-£1,652	-0.018	£91,557

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Scenario analyses for the Elecsys sFlt-1/PLGF ratio test

Using the inputs from PreOS study instead of INSPIRE for some parameters had a significant impact on the results. Full details are on page 285 of the diagnostics assessment report. In contrast to the base case results, the Elecsys sFlt-1/PLGF ratio test produced lower costs (-£595) than standard clinical assessment. This is mainly driven by savings in the short and long-term neonatal costs compared with the base case. The EAG said that the difference in QALYs was negligible (-0.0006) as there were no differences between arms related with long-term outcomes. Notably the proportion of women with pre-eclampsia in the standard assessment and Elecsys arms of the model when the PreOS data were used were the same, whereas in the base case (which used unadjusted data from the INSPIRE trial) more women had pre-eclampsia in the Elecsys arm.

For all other scenarios done in the base case model the Elecsys sFlt-1/PLGF ratio test was more expensive and produced fewer QALYs than standard clinical assessment (that is, it was dominated). Full details of the Elecsys sFlt-1/PLGF ratio test scenario analyses results are in tables 66 and 67 of the diagnostics assessment report (pages 167 to 168).

Sensitivity analyses

The EAG also did a one-way deterministic sensitivity analysis. Parameters with the greatest sensitivity to variation in estimates were presented as tornado plots of the net monetary benefit of PLGF-based testing compared with standard clinical assessment. These are on page 170 of the diagnostics assessment report.

The EAG considered that a probabilistic sensitivity analysis would be of limited value given the available data. This was because of uncertainty about whether test sensitivity and specificity could be introduced into such an analysis because the model does not use accuracy estimates directly. Instead, the EAG used data from RCTs assessing the impact of following the clinical management algorithms used on outcomes such as neonatal and maternal outcomes. Also, uncertainty around most estimates for maternal and neonatal outcomes used in the model were not reported. Finally, non-linearity in the model would not be accounted for because of a lack of evidence on correlation between the model parameters. Further discussion of this is on page 176 of the diagnostics assessment report.

3 Summary

Clinical effectiveness

Two RCTs provided the main source of data discussed by the EAG; INSPIRE for the Elecsys sFlt-1/PLGF ratio test and PARROT for the Triage PLGF test. The EAG said that these trials provided rigorous evidence linking using the tests in the real world to clinically relevant maternal, fetal, perinatal and neonatal clinical outcomes. Both assessed the PLGF-based tests using 1 trial arm in which the test result was revealed and used in clinical decision making and 1 arm in which the test result was concealed and not used. Both assessed the PLGF-based tests in clinical algorithms that used the tests to help rule in and rule out pre-eclampsia.

Data on hospitalisation were not reported in PARROT. In INSPIRE, higher levels of hospitalisation were reported when the Elecsys test was used (32.3% when the test result was revealed compared with 26.1% when the test result was concealed; risk ratio 1.24, 95% CI 0.89 to 1.70). This was not statistically significant.

PARROT reported a non-statistically significant increase in time to delivery using the Triage PLGF test. Preterm delivery (before 37 weeks) occurred for 41% of women in the reveal arm of this trial and 37% of women in the conceal arm.

There was a statistically significant reduction in adverse maternal outcomes (defined using fullPIERS consensus criteria) in PARROT when the Triage PLGF test was used. The INSPIRE study reported the frequency of a number of selected outcomes only. No statistically significant differences were observed between trial arms for these outcomes. However the EAG said that these results should be interpreted with caution because the study was not powered to detect differences for these outcomes.

Gestational age at delivery was similar if the test was used or not used for both Triage PLGF in PARROT (36.6 compared with 36.8 weeks) and for Elecsys in INSPIRE (38.4 compared with 38.1 weeks).

Perinatal adverse outcomes (adjusted odds ratio 1.45; 95% CI 0.73 to 2.90) and perinatal deaths (adjusted odds ratio 1.00; 95% CI 0.61 to 1.63) were similar for the reveal and conceal arms in PARROT. The INSPIRE trial did not report any data on neonatal and perinatal mortality. In INSPIRE, the trial found no statistically significant difference in 4 outcomes: birthweight, APGAR score, special care baby unit admissions and the proportion of small for gestational age babies.

No data on clinical outcomes using the DELFIA Xpress PLGF 1-2-3 test and BRAHMS sFlt-1 Kryptor/BRAHMS PLGF plus Kryptor PE ratio test were identified by the EAG.

Several studies compared whether the tests gave similar results in terms of their predictive accuracy. There were some data showing similar performance of the BRAHMS and DELFIA tests to the Triage PLGF and Elecsys tests.

The EAG said it was able to find only 1 study on repeat PLGF-based testing for suspected pre-eclampsia.

Cost effectiveness

The Triage PLGF test dominated standard assessment (no use of the test) in the base case and almost all scenario analyses run by the EAG.

The Elecsys sFlt-1/PLGF ratio test was dominated by standard assessment in the base case and all scenarios run by the EAG. It was the same for the BRAHMS Kryptor sFlt-1/PLGF ratio test. The EAG modelled this test assuming equal predictive accuracy to the Elecsys sFlt-1/PLGF ratio test (except for the cost per test).

The EAG said that results of the cost-effectiveness analysis are less certain because of a lack of relevant data for certain outcomes. For example, the INSPIRE trial did not report clinical outcomes such as neonatal death, and incidence of neonatal complications, which appear to be key drivers of modelled cost effectiveness. The EAG therefore used estimates for these outcomes from the PARROT trial.

When data from the PreOS trial were used for some model parameters (instead of INSPIRE), the Elecsys sFlt-1/PLGF ratio test had lower costs than standard assessment (was cost saving), and had almost no difference in incremental QALYs (-0.0006).

Neonatal outcomes were a major driver of the costs and QALYs.

4 Issues for consideration

In NICE diagnostics guidance 23, the committee concluded that the Triage PLGF test and the Elecsys immunoassay sFlt 1/PLGF ratio, used with

standard clinical assessment and subsequent clinical follow up, showed promise in helping to diagnose (rule in) pre-eclampsia in women presenting with suspected pre-eclampsia. However, the committee felt there was not enough evidence at the time to recommend their routine adoption for diagnosing pre-eclampsia in the NHS. Clinical experts said that the decision on when to deliver is based on clinical symptoms that indicate risk to the mother or baby, rather than the presence of pre-eclampsia alone. The committee was concerned that, in women with suspected pre-eclampsia and a positive PLGF-based test result, a decision may be made to deliver the baby sooner on the basis of the PLGF-based test result alone, rather than on clinical symptoms indicating risk to the mother or baby. This could lead to more unnecessary medical intervention and a greater number of premature babies (see sections 5.9 and 5.10 of DG23). It recommended further research on the tests' performance in helping rule in pre-eclampsia. Specifically to find out how if a positive PLGF-based test result (Triage PLGF test result of 12 picograms/ml or less; Elecsys immunoassay sFlt 1/PLGF ratio of greater than 38) is used to rule in pre-eclampsia, this affects management decisions about time to delivery and the associated outcomes (see section 6.2 of DG23).

Further data are now available on how PLGF-based tests affect neonatal outcomes, including gestational age at delivery and outcomes related to neonates and perinates. The RCTs that underpin the base case model (INSPIRE and PARROT) assess using PLGF-based tests as part of clinical management algorithms (described in appendix 8 of the diagnostics assessment report for each trial) that included using them to decide whether to admit the woman based on the likelihood that she has pre-eclampsia (rule in).

The EAG's model includes the impact of neonatal outcomes (mortality and complications) on long-term costs and QALYs. This is a large driver of incremental QALYs in the model results. For Triage PLGF, data on neonatal outcomes were taken from the PARROT trial. Because of a lack of data, for

the Elecsys test the EAG assumed no difference in the probability of neonatal mortality or complications between use of this test and no use of the test.

There are more people with pre-eclampsia in the arms of the model in which the Triage PLGF and Elecsys tests are used than in the corresponding comparator arms, based on unadjusted data from the PARROT and INSPIRE trials used by the EAG. Because women with pre-eclampsia had a higher risk of adverse outcomes, such as neonatal mortality or complications, there is a greater impact of these events in the PLGF-based test arms of the model than the corresponding comparator model arms, incurring higher costs and lower QALYs. This is particularly the case for the Elecsys, which is assumed to give no benefit in terms of neonatal outcomes. This is likely to have negatively impacted on the cost effectiveness of the Elecsys test (which was dominated by standard assessment) based on chance allocation of more women with pre-eclampsia to the reveal arm of the trial, rather than because of the test's performance. In a scenario analysis data from the PreOS study inputs were used for the Elecsys test. The proportion of women with pre-eclampsia was the same (18%) in the test and comparator arms when these data were used. This scenario produced lower costs (-£595) than standard clinical assessment for the Elecsys test, and almost the same QALYs.

Because of a lack of data, the EAG used data from the PARROT study in the model to estimate cost effectiveness for the Elecsys and BRAHMS tests. This included data on the impact of PLGF-based testing on time to delivery, mode of delivery and whether labour was spontaneous or induced.

The EAG modelled the BRAHMS Kryptor sFlt-1/PLGF ratio test based on an assumption of equal predictive accuracy with the Elecsys test (only varying test costs), citing Salahuddin et al. in support of this.

Data from the PARROT trial were used to model the comparator (no PLGF-based testing) in the base case model for the Triage PLGF test assessment. Data from the INSPIRE trial were used to model the comparator in the base case model for the Elecsys and BRAHMS tests assessment. Total costs and

QALYs for the standard assessment arms of the 2 models were therefore different (£13,051 and 16.99 QALYs for the Triage PLGF model standard assessment arm, and £10,321 and 17.17 QALYs for the Elecsys standard assessment arm).

The INSPIRE and PARROT studies assess a care algorithm that uses PLGF-based tests to help rule in and rule out pre-eclampsia.

The EAG's model for this assessment does not use test accuracy estimates directly. Instead it models the impact on outcomes such as neonatal and maternal outcomes of following the clinical management algorithms used in the RCTs with and without PLGF-based tests. The EAG said that it is not possible to use these data to assess PLGF-based tests when they are used only to rule out pre-eclampsia. For NICE diagnostics guidance 23, only data on test accuracy were available for tests and were directly used in the economic model. For DG23 the EAG provided analysis in an addendum to the main report, based on using the Elecsys and Triage PLGF tests to rule out pre-eclampsia only (addendum 3). The accuracy estimates used in the addendum model for DG23 and those from the INSPIRE and PARROT trial are similar (see table 21).

Table 21 Sensitivity and specificity values used in economic model in diagnostics guidance 23 and from the INSPIRE and PARROT trials

Test	Sensitivity (95% CI)	Specificity (95% CI)	Source
Triage PLGF in DG23 Threshold used: <100pg/ml To identify women likely to develop pre-eclampsia needing delivery within 14 days of testing	0.960 (0.89 to 0.99)	0.557 (0.49 to 0.63)	DG23 addendum 3. Data from the PELICAN study, see table 5 in DG23
Triage PLGF in PARROT study Threshold used: <100 picograms/ml	0.949 (0.827-0.994)	0.527 (0.459-0.593)	Table 17 in DAR

Test	Sensitivity (95% CI)	Specificity (95% CI)	Source
To predict pre-eclampsia requiring delivery by 2 weeks			
Elecsys sFlt-1/PLGF in DG23 Threshold used: >38 To rule out of pre-eclampsia within 1 week	0.857 (0.73 to 0.94)	0.791 (0.77 to 0.82)	DG23 addendum 3. Data from the PROGNOSIS study, see table 8 in DG23
Elecsys sFlt-1/PLGF in INSPIRE study Threshold used: >38 To rule out pre-eclampsia within 1 week	0.958 (0.789-0.999)	0.796 (0.726-0.855)	Table 15 in DAR

Abbreviations: PLGF, placental growth factor.

The DELFIA Xpress PLGF 1 2 3 test and BRAHMS sFlt 1 Kryptor/BRAHMS PLGF plus Kryptor PE ratio were not recommended for routine adoption in the NHS in DG23. The committee said that further research by the companies was needed to show the clinical effectiveness of these tests, including diagnostic accuracy and analytical validity. It concluded that the diagnostic accuracy of the DELFIA Xpress PLGF 1-2-3 test and the BRAHMS sFlt-1 Kryptor/BRAHMS PLGF plus Kryptor PE ratio could not be assumed to be equivalent to the diagnostic accuracy of the Triage PLGF test and the Elecsys immunoassay sFlt-1/PLGF ratio (see section 5.6 of DG23).

Further data are now available comparing the accuracy of these tests with the Triage PLGF and Elecsys tests.

INSPIRE and PARROT only included singleton pregnancies, and there were limited data on multiple pregnancies. The EAG said that some studies suggested that the sFlt-1/PLGF ratio is higher in twins across all gestational ages compared with singleton pregnancies, and that different ratio cut-offs may need to be applied.

DG23 recommended further research on repeat PLGF-based testing, with standard clinical assessment, in women presenting with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation, who have had a negative PLGF-based test result that was used to rule out pre-eclampsia (section 6.1 of DG23). The EAG did not model repeat testing because of a lack of data. Ongoing studies were identified that will provide data on using the tests in this way in the future.

Several studies were identified that will provide further data how these PLGF-based tests affect outcomes, including 5 RCTs. Further data on outcomes included in this report, and used in the economic model, may therefore be available in the future. The EAG said that data from these studies are likely to have significant implications for clinical practice in the NHS. Full details of the ongoing studies are in appendix 6 of the diagnostics assessment report.

5 Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Pregnancy and maternity are protected characteristics in the Equality Act (2010). Pregnant women who have pre-existing conditions such as autoimmune disease, chronic kidney disease or diabetes may be at a higher risk of developing pre-eclampsia. People of African-Caribbean origin may be at increased risk of severe adverse pregnancy outcomes.

Levels of PLGF may differ according to ethnicity and maternal weight.

6 Implementation

Use of PLGF-based tests in a near patient setting may require changes to the existing infrastructure in antenatal clinics and maternity units. The feasibility of centrifuging blood in a near patient setting will also need to be considered.

If PLGF-based tests are used in a laboratory, changes to laboratory infrastructure may be needed to ensure that tests results can be returned on the same day for women presenting with suspected pre-eclampsia. If PLGF-based tests are used in a near patient or laboratory setting, internal and external quality assurance processes will also be needed.

Antenatal services will need to develop local protocols for incorporating PLGF-based testing into the care pathway for women presenting with suspected pre-eclampsia.

7 Authors

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June 2021

Appendix A: Sources of evidence considered in the preparation of the overview

A. The diagnostics assessment report for this assessment was prepared by Southampton Health Technology Assessments Centre (SHTAC)

Frampton, G; Pickett, K; Tikhonova I; Souto Ribeiro, I; Woods, L; Cooper, K; Hazell, L; Scott, D; and Shepherd, J. Placental growth factor (PlGF)-based testing to help diagnose suspected pre-eclampsia (update of DG23). Southampton Health Technology Assessments Centre (SHTAC), 2021.

B. The following organisations accepted the invitation to participate in this assessment as stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report.

Manufacturer(s) of technologies included in the final scope

- PerkinElmer Health Sciences
- Quidel Ireland
- Roche Diagnostics Ltd
- Thermo Fisher Scientific

Other commercial organisations

- Advanced Global Health Ltd
- Diabetomics Inc.

Professional groups and patient/carer groups

- Action on Pre-eclampsia (APEC)
- Association for Improvements in the Maternity Services
- British Maternal & Fetal Medicine Society (BMFMS)
- Birth Trauma Association
- Royal College of Midwives
- Royal College of Obstetricians and Gynaecologists
- Royal College of Physicians

- The Renal Association

Research groups

- None

Associated guideline groups

- None

Others

- Department of Health
- Healthcare Improvement Scotland
- Medicines and Healthcare products Regulatory Agency
- NHS England
- NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC)
- Welsh Government

Appendix B: Glossary of terms

Chronic hypertension

Hypertension that is present at the booking visit, or before 20 weeks, or if the woman is already taking antihypertensive medication when referred to maternity services. It can be primary or secondary in aetiology

Eclampsia

A convulsive condition associated with pre-eclampsia.

fullPIERS

Risk estimation model developed and validated with the aim of identifying the risk of fatal or life-threatening complications in women with pre-eclampsia within 48 h of hospital admission for the disorder.

Gestational hypertension

New hypertension presenting after 20 weeks of pregnancy without significant proteinuria.

Hypertension

Blood pressure of 140 mmHg systolic or higher, or 90 mmHg diastolic or higher.

Intraventricular haemorrhage

Bleeding inside or around the ventricles in the brain

Pre-eclampsia

New onset of hypertension (over 140 mmHg systolic or over 90 mmHg diastolic) after 20 weeks of pregnancy and the coexistence of 1 or more of the following new-onset conditions:

- proteinuria (urine protein:creatinine ratio of 30 mg/mmol or more or albumin:creatinine ratio of 8 mg/mmol or more, or at least 1 g/litre [2+] on dipstick testing) or
- other maternal organ dysfunction:

  - renal insufficiency (creatinine 90 micromol/litre or more, 1.02 mg/100 ml or more)
  - liver involvement (elevated transaminases [alanine aminotransferase or aspartate aminotransferase over 40 IU/litre] with or without right upper quadrant or epigastric abdominal pain)
  - neurological complications such as eclampsia, altered mental status, blindness, stroke, clonus, severe headaches or persistent visual scotomata
  - haematological complications such as thrombocytopenia (platelet count below 150,000/microlitre), disseminated intravascular coagulation or haemolysis
- uteroplacental dysfunction such as fetal growth restriction, abnormal umbilical artery doppler waveform analysis, or stillbirth. [Definition from NICE's hypertension in pregnancy guideline].

Proteinuria

The presence of a detectable level of protein in the urine. Initially, this is determined by an automated reagent-strip reading device and confirmed, and quantified, by either a spot urinary protein:creatinine ratio or 24 hour urine collection. A significant level of proteinuria is considered to be more than 300 milligrams per day or a protein:creatinine ratio of 30 milligrams/millimole.

Pulmonary oedema

An excess of watery fluid in the lungs

Respiratory distress syndrome

Occurs when a baby's lungs are not fully developed and cannot provide enough oxygen, causing breathing difficulties.

Severe hypertension

Blood pressure over 160 mmHg systolic or over 110 mmHg diastolic.

Severe pre-eclampsia

Pre-eclampsia with severe hypertension that does not respond to treatment or is associated with ongoing or recurring severe headaches, visual scotomata, nausea or vomiting, epigastric pain, oliguria and severe hypertension, as well as progressive deterioration in laboratory blood tests such as rising creatinine or liver transaminases or falling platelet count, or failure of fetal growth or abnormal doppler findings

Small for gestational age

A baby born with a birth weight less than the 10th centile.

NICE National Institute for Health and Care Excellence

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Advanced Global Health	1.	-	-	To whom it may concern, We would like to make the Southampton Health Technology Assessments Centre (SHTAC) and the Diagnostics Advisory Committee members aware of an alternative biomarker, which has not been included in the assessment. The timing of this communication is unfortunate given the progress to date, however, we think it is appropriate for the members and wider NHS committee, to be aware of another technology that in clinical studies to date has demonstrated an improved efficacy and ease of use. We would like to draw your attention to a biomarker named Glycosylated Fibronectin (GlyFn), which has been found to be an accurate indicator of pre-eclampsia and unlike PLGF is produced in a linear progression throughout pregnancy. Three important studies have been published outlining the efficacy of GlyFn: Rasanen et al. (2015) Maternal serum glycosylated fibronectin as a point of care biomarker assessment of preeclampsia. *ACOG*. 212.1. P82.E1-82.E1 Huhn, et al (2020). Maternal serum glycosylated fibronectin as a short-term predictor of preeclampsia: a prospective cohort study. *BMC Pregnancy Childbirth* 20, 128 https://doi.org/10.1186/s12884-020-2809-2 Nagalla, SR. et al. (2020) Glycosylated fibronectin point-of-care test for diagnosis of pre-eclampsia in a low resource setting; a prospective Southeast Asian population study. *BJOG*. 127, 13:1687-1694	Thank you for notifying us of this biomarker and the associated evaluation publications. Any decision to include additional biomarkers in the scope of this appraisal would be made by the NICE Diagnositc Assessment Programme. It would not be possible for the EAG to include additional biomarkers in our report without a change to our protocol, as agreed by NICE and the NIHR.

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				It should be noted that the studies have compared GlyFn with placental growth factor (PLGF), soluble fms-like tyrosine kinase-1 (sFlt-1) and PLGF/sFlt-1 ratio. As indicated, in the studied populations, GlyFn was shown to have a greater AUROC and thus in those populations a better diagnosis marker. May I also direct the committee members to https://diabetomics.com/lumella/ This provides information on the point of care device to detect GlyFn. It should be noted that a 5ul serum sample is required (finger prick), the cartridges are to be stored at room temperature and the cost per test is lower than what has been in outlined in DAP23 documents for the other markers. Given the importance of this clinical guideline, may I suggest that GlyFn is evaluated as part of this consultation to determine the most effective pre-eclampsia markers. Yours sincerely, [redacted] [redacted] Managing Director Advanced Global Health Ltd	
Roche Diagnostics Ltd	2			Overview of comments from Roche Diagnostics We thank NICE and the EAG for preparing the review and economic model and allowing us the opportunity to comment. Overall, we are extremely concerned about the proposed economic model, particularly for the Elecsys test, and do not believe it can be used to inform decision making. We have grouped our responses into a number of key themes:-	Please see our responses below.

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				1. The model is based on a small subset of the available data (two trials) and is unrepresentative of average practice across the UK. 2. The model is unbalanced, with between trial and between trial arm differences in the numbers of high-risk patients. 3. The differences in QALYs appear largely driven by neonatal outcomes that are based on assumptions rather than evidence. 4. We have concerns with other parameters and assumptions used in the model. 5. The model's conclusions are at odds with all the published cost-effectiveness evidence identified by the EAG and known assay performance/clinical utility. 6. Adopting the EAG's analysis as the base case will seriously affect patient access and we would urge NICE to consider redeveloping the model using a linked-evidence approach or waiting for ongoing trials to publish before making any change to existing guidance.	
Roche Diagnostics Ltd	3			<u>The model is based on a small subset of the available data (two trials) and is unrepresentative of average practice across the UK.</u> A. While we accept that the RCT is usually considered by NICE as the highest form of evidence, we would note that all evidence must be assessed in its proper context and that NICE's strategy commits it to not over-rely on RCTs. This is an area where the linked-evidence approach usually taken in the Diagnostic Assessment Programme may actually be more appropriate than relying on an RCT because the link between test results and management	A. As rightly pointed out, RCTs are considered by NICE as the highest form of evidence. This is because, as stated in the Diagnostics Assessment Programme manual, "other comparative designs, such as controlled studies, cohort studies and case-control studies may provide useful evidence, but are at a higher risk of bias."[1] B. The PARROT and INSPIRE RCTs had pragmatic 'real world' trial design. They were

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				are well known and accepted. B. The INSPIRE trial took place in a tertiary referral centre in a large teaching hospital well known in the field of pre-eclampsia research. We would urge the NICE committee to consider whether this setting is representative of other UK hospitals, particularly smaller hospitals with less expertise/experience managing women with suspected pre-eclampsia and/or those in rural, less-accessible, settings. Among the INSPIRE clinical staff were professors of obstetrics and other staff highly skilled in the diagnosis/management of pre-eclampsia and in the trial only 26% of women with suspected pre-eclampsia were admitted within 24 hours in the clinical decision alone arm (without sFlt-1/PlGF testing). In comparison, the sensitivity and specificity for clinical decision alone in NICE DG23 were 94% and 36% respectively, which is likely to be more representative of the cautious way in which suspected pre-eclampsia is managed without PlGF-based testing. C. The management strategies in the two models are different with the Elecsys model being based on a traditional rule-out strategy and the Triage model being based on a newer strategy where a cohort of intermediate risk patients are given more active surveillance. The standard of care arm appears to be different in each model as well. The EAG states that the strategy in PARROT is based on the NICE guideline on managing hypertension in pregnancy but this does not appear to be the case. The only NICE guidance on PlGF-based tests is for ruling out pre-eclampsia. While we accept that clinical practice may be changing at some centres (particularly those that were part of PARROT), we believe that differential management of low and intermediate risk groups is unrepresentative of the majority of centres in the UK.	the only RCTs of Triage and Elecsys identified in the systematic review. Moreover, these RCTs were the only studies conducted in the UK, where Triage and Elecsys tests were used alongside standard clinical assessment, with the exception of MAPPLE which had only a small proportion of UK patients. Therefore, we believe that PARROT and INSPIRE represent the best available clinical evidence relevant to the decision problem. C. In the base-case analysis, the cost of managing suspected pre-eclampsia was based on the NICE guideline CG107 (the rationale for this is provided in the EAG report, section 5.4.4). For all tests considered in the economic analysis the following assumptions were made: • Women at high risk of pre-eclampsia are managed according to the pre-eclampsia pathway. • Women at low risk of pre-eclampsia are managed according to the gestational hypertension pathway. • For women at intermediate risk of pre-eclampsia, we assumed the same management strategy as for the low-risk patients but with a shorter time to delivery. To address the uncertainty in management strategies for women from the latter group, we have conducted a scenario analysis in which we assumed that intermediate-risk patients are managed as high-risk patients. The results of this analysis suggest that this assumption has

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				D. The prevalence and severity of pre-eclampsia in the two trials was highly heterogeneous. Can two separate models based on this small subset of available data both be considered representative of the average clinical situation in the UK, especially given that there were other differences in patient characteristics and the management strategy between the trials?	a low impact on the ICERs (see section 7 in the Addendum) D. The PARROT trial reported the prognostic characteristics of participants (e.g. hypertension, blood pressure), but the INSPIRE trial did not. We are therefore unable to judge the level of heterogeneity between the two trials in this respect. The management strategies likely differ between trials (see Figure 10 and 11 in EAG report) PARROT - clinicians used a clinical management algorithm that integrated the PlGF test result with NICE's hypertension in pregnancy guidelines; INSPIRE - clinicians followed a clinical management algorithm, and in the revealed testing group, the sFlt-1/PlGF ratio result was integrated into this Please also see our response to comments 3B and 4A-B.
Roche Diagnostics Ltd	4			<u>The model is unbalanced, with between trial and between trial arm differences in the numbers of high-risk patients.</u> A. The model includes many imbalances in patient characteristics between the arms. This is less of a problem in the Quidel model, where granular outcomes for specific patient subpopulations are reported, but is a major issue for the Elecsys model where they are not, and data are replaced by assumptions. Several examples of how these imbalances and assumptions illogically affect the	A-B. We agree that the modelled treatment arms should be balanced. However, in the base-case analysis we modelled arm-specific prevalence of pre-eclampsia as reported in the RCTs for the reason which was rightly pointed out in the comment: it was not clear whether the (implicit) assumption in such an analysis that changes in pre-eclampsia management

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				outcome of the model are detailed throughout our consultation response. B. The prevalence of pre-eclampsia was found to differ between the testing and non-testing arms of the two trials. For example, the prevalence of pre-eclampsia in the Elecsys model was 13.8% vs. 9.8% in the shorter term and 25.3% vs. 20.1% in the longer term for the testing vs. non-testing arms. The prevalence of the condition should always be the same between model arms in DAP appraisals because this is the only way to make a fair comparison. The only way the prevalence could conceivably be modelled differentially is if the test and consequent interventions could plausibly affect the emergence of the condition. C. We also note differences in pre-eclampsia severity between the trial arms. Specifically, in the testing arm of the Elecsys model, 38% of patients have an underlying disease classification of "high-risk" in the decision tree whereas only 31% of patients are in this "high-risk" group in the no-testing arm. This imbalance is a major concern given that these patients have an increased risk of worse outcomes than those in lower risk groups, irrespective of management strategy. We would like to highlight that simply setting the distribution of sFlt-1/PlGF categories (low/medium/high risk) equal between the arms in the model makes Elecsys cheaper than no test and eliminates most of the difference in QALYs. D. There are considerable differences in the patient characteristics between the two trials. Prevalence and severity of pre-eclampsia were much higher in PARROT compared to INSPIRE. This, combined with the fact that the standard of care management strategy was different in	driven by PlGF test results have no impact on the course of pre-eclampsia would be clinically valid. In response to this comment, we have consulted our expert. We have been advised that this assumption is clinically justifiable. Therefore, we have conducted scenario analyses assuming the same prevalence of pre-eclampsia in both arms. The results suggest that the assumption of equal prevalence would not change the cost-effectiveness of the tests, with Triage remaining dominant, and Elecsys and BRAHMS dominated (see Table 1 in Addendum). D. The EAG modelled the intervention and comparator arms in the analyses for Triage and Elecsys based on two different RCTs (PARROT and INSPIRE). The standard care costs are therefore dependent on the outcomes reported in each of the RCTs. Please also see our response to comments 3B and 4A-B.

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				the two trials, has resulted in the calculated costs of standard assessment (without PlGF-based testing) being very different for the two assays (£13,051 vs. £10,321).	
Roche Diagnostics Ltd	5			The differences in QALYs for Elecsys appear to be largely driven by neonatal outcomes that are based on assumptions rather than evidence. A. The costs and QALYs in the model appear to be largely driven by rare outcomes such as neonatal death that were not reported in INSPIRE. These outcomes can also be attributed to a combination of modelling assumptions and the underlying severity of the patients in the testing arm of each trial, which are imbalanced between the model arms and cannot be logically ascribed to be the effects of testing. B. The long term clinical outcomes associated with each strategy should either be dictated by the events in the decision tree (e.g. admissions) apportioning patients to outcome nodes differently between the arms or be modelled as a 'treatment effect' (e.g. via differential outcomes for the same outcome nodes between the arms as in the Quidel model) but in the Elecsys model neither happens and the long term outcomes are instead dictated by patients' initial distribution of PlGF scores and the prevalence of pre-eclampsia. An initial distribution that was coincidentally skewed towards milder disease in the no testing arm. C. In the Quidel model there is an intrinsic benefit of having the test, unrelated to appropriate admission for pre-eclampsia, whereas in the Elecsys model there is not. This can be illustrated by looking at a specific patient 'type', for example, a patient who has a high risk test score, was	A. In the absence of neonatal data from the INSPIRE trial, for Elecsys (and BRAHMS) we assumed no difference in these outcomes between the test and comparator arms using the average estimates from PARROT. We acknowledge that other assumptions may be preferable. To address this uncertainty, we have conducted a scenario analysis in which we assumed that neonatal complications (IVH and RDS) and death for Elecsys/BRAHMS occur at the same (arm-specific) rates as for Triage. This assumption affects the model results significantly: using Elecsys and BRAHMS alongside standard clinical assessment now yields more QALYs and less costs (see Table 3 in Addendum). B. Long-term outcomes are assumed to depend on pre-eclampsia status (as described in section 5.4.7.4 of the EAG report). Please also see our response to comment 5A. C-G. Please see our response to comment 5A above.

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				admitted, and developed pre-eclampsia. Each of these patients gains 15.67 QALYs in the testing arm and 14.99 QALYs in the no-testing arm. For the Elecsys model there is no difference. We question the appropriateness of taking a different approach in the two different models? D. Whether the Elecsys test is dominant (cost saving and better outcomes) or dominated (more costly and worse outcomes) can be altered by changing a single assumption made by the EAG. Namely, the assumption that there is no difference in per-patient neonatal outcomes among patients between the testing and no testing arm. For example, in the Quidel model, 6% of high risk pregnancies with pre-eclampsia result in neonatal death in the intervention arm and 9% in the control arm. Both of these values are assumed to be 7% in the Elecsys arm. Given that the Elecsys test was reported to be 100% sensitive for identifying patients who developed pre-eclampsia within 7 days in INSPIRE, we are unclear on the rationale for modelling the Elecsys test with no benefit for neonatal death, when the Quidel test is modelled to have a beneficial effect. E. If the average per patient outcomes and costs from the Quidel model are used within the Elecsys model, the Elecsys test becomes dominant (i.e. the values from sheets cTRIAGE and uTRIAGE). In the model's current format the main driver of the overall incremental outcomes and costs are driven by these differences in the per patient outcomes and costs between the test and no test arm. These differences are clear to see in the sheets uTRIAGE and cTRIAGE (e.g. uTRIAGE column AV). For specific outcomes that weren't reported in INSPIRE these outcomes were assumed to be equal across the test and no test arm in the Elecsys model (e.g. uELECSYS column	

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				AV) even though they differed markedly in PARROT. If the outcomes are set to be equal, the sensitivity of the test plays the sole role in determining risk and therefore overall outcomes. A less sensitive test would then define fewer people as high risk and therefore produce an incremental benefit, even when missing more pre-eclampsia patients. F. Given both PARROT and MAPPLE found differences in neonatal outcomes between the conceal and reveal arms (see pg 98,99), we question why the assumption was made that these outcomes would be equal across both the reveal and conceal arms of the Elecsys model. G. As discussed, the total outcomes for each strategy in the Elecsys model are mostly dependent on the proportion of patients that occupy each risk category. Since more patients are in the intermediate and low risk categories in the no-testing arm and since appropriate management has no treatment effect, it is not surprising that this arm generates higher QALYs and lower costs.This approach has resulted in considerable differences in long-term neonatal care costs between the assays, which appears unjustifiable based on reported maternal and neonatal outcomes. H. The rationale is unclear for the following statement on page 156 of the report: “Therefore, we adjusted the proportion of women and babies with complications using a ratio of 3:1 for women with and without pre-eclampsia for the Triage PlGF test and 2:1 for the Elecsys sFlt-1/PlGF ratio test.” Does this mean that outcomes for women with pre-eclampsia are assumed to be relatively less severe in the Elecsys model and therefore detecting a case of pre-eclampsia and managing it is relatively less valuable?	H. As noted in the DAR (section 5.4.7.4), reported maternal outcomes were not stratified by risk levels for women with and without pre-eclampsia, so we had to make assumptions in order to allocate different risks of maternal outcomes to those with and without pre-eclampsia. We have used calibration to adjust the risk in each group to obtain the same total level of maternal outcomes but with a differential in risk between pre-eclampsia/no pre-eclampsia groups. Our calibration produced different ratios between the Triage and Elecsys test as reported. This does not mean that outcomes for women with pre-eclampsia are assumed to be relatively less severe in the Elecsys model and therefore detecting a case of pre-eclampsia and managing it is relatively less valuable.

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					When a scenario was run using the same ratio for Elecsys as for Triage, the incremental costs for the intervention versus the comparator increased only slightly, from £621 to £696.
Roche Diagnostics Ltd	6			We have concerns with other parameters and assumptions used in the model. A. Currently there is no QALY benefit associated with hospitalisation or increased surveillance. This means that within each risk category, the QALY outcomes are modelled to be exactly the same for patients with pre-eclampsia whether they are admitted or not. Given that determining management is the primary reason for conducting the test, we ask how such a modelling assumption can be justified, particularly for the Elecsys model where outcomes are also assumed to be equal between the arms? B. Many of the outcomes and costs assigned to patients in the Elecsys model lack internal validity. Under the current assumptions a woman not admitted who develops pre-eclampsia (FN) has a greater QALY benefit than a woman admitted who develops pre-eclampsia (TP). In the Elecsys no-test model, a false negative accrues roughly 2 more QALYs per patient than a true positive. The model therefore implies that not admitting a woman who subsequently develops pre-eclampsia is beneficial, which cannot be clinically valid. The reason for this is that the underlying assumption in the model is that the only women who are sent home but later develop pre-eclampsia in the no-test arm are those who would have a lower risk PlGF-based score, had it been measured. Using this model structure, decreasing the sensitivity of pre-eclampsia testing would automatically lead to an increased benefit	A. Our systematic review and manual searches did not find any studies that reported quality of life associated with hospitalisation or increased surveillance for pre-eclampsia. One study (Almeida et al. 2020[2]) that estimated the utility associated with hospitalisation in patients with chronic heart failure concluded that hospitalisation had a small effect on utility, although the result was associated with substantial uncertainty. Therefore, the EAG considers that there is limited evidence to support the direction of QALY change associated with hospitalisation. We also note that utility values associated with hospitalisation, if included, would not have a significant impact on model results due to the relatively short duration of hospitalisation. B. The EAG used data reported in the PARROT study to model neonatal complications (IVH and RDS) and death. PARROT reported higher rates of neonatal complications and death for the high-risk group than for the low- and intermediate-risk groups. Therefore, a greater proportion of babies of women from the high-risk group who had pre-eclampsia (true positives) died or had complications than babies of women with pre-eclampsia from low- and intermediate-risk

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				because all the FNs would immediately change underlying risk status and have better outcomes. C. The admission probabilities used in the Quidel arms of the model are not based on empirical data. Given the importance of this parameter, we question the validity of relying on modelling assumptions. The assumptions are that all patients with high risk PlGF in the testing arm are admitted, which seems fair enough, but the probability of admission in the no testing arm is calculated essentially by applying the relative risk of diagnosing pre-eclampsia within 24 hours between the arms to this 100% figure to get 72%. The 72% is then applied to the patients who have an underlying PlGF <12/ml in the no-testing arm but this doesn't seem to make clinical sense. It assumes that the clinician does not admit a single patient from the intermediate and low risk PlGF groups, despite not knowing their PlGF score and that they are significantly more likely to send someone with an underlying PlGF <12/ml home. D. In the standard care arm of the Elecsys model, 58/184 patients were admitted whereas the figure in the paper is 48/184. In the Elecsys arm of the Elecsys model, 72 patients were admitted whereas the figure in the paper is 60. E. We note that a maternal outcome reported in INSPIRE (table S5b), estimated blood loss (EBL), was not included in the EAGs model. Is there a reason for this? F. Data from the PreOS study was applied to the Elecsys model. We believe this is inappropriate given the patient characteristics in the two trials (the proportion of patients in each category that developed pre-eclampsia in PreOS	groups (false negatives). Long-term consequences of neonatal complications and death appear to be the main drivers of costs and QALYs in the model. Consequently, women with false negative test results are assigned with a greater QALY benefit than true positives. C. As is rightly pointed out, the assumption on hospital admission of patients in the no testing arm was based on the relative risk of diagnosing pre-eclampsia within 24 hours between the trial arms estimated in PARROT. The proportion of patients from the comparator arm who were hospitalised within 24 hrs was tested in the Tornado analysis where the differential admission rate varied by 20%. The results suggested that this had only a very small impact on the outcomes. In response to this comment, we conducted an additional Tornado analysis with the proportion of admitted patients in the no testing arm varied between 60% and 83% (which corresponds to the variation in the differential admission rate of 40%), with the same outcome, i.e. this parameter is not a key driver of cost-effectiveness. D. In the model, admission for any reason (including suspected pre-eclampsia) within 24 hrs of the test was used (Cerdeira 2019[3]) for the sake of consistency with the outcomes reported in the INSPIRE RCT, because the outcomes were not reported separately for

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				was far higher than in the INSPIRE trial), differences in the trial designs (PreOS was non-interventional) and considering that the two trials were conducted in different countries, where their own national guidelines for patient management apply. G. We believe for this model to yield coherent results, the same level of risk should be implemented in each arm, and that admission to hospital (or increased surveillance) provides a treatment effect (when used appropriately), e.g. for women that develop pre-eclampsia within 7 days, you would expect hospitalisation to provide, on average, a positive effect vs not admitting them, irrespective of underlying risk of adverse events. H. Because of the disconnect between test outcomes and clinical outcomes in the model structure it is not possible to do informative sensitivity analysis on a number of parameters. For example, as True Positives have worse outcomes than False Negatives in the Elecsys model, a sensitivity analysis that decreased the sensitivity of the Elecsys test would paradoxically increase its cost-effectiveness. I. Since outcomes are pre-determined by risk score, the underlying assumption in the EAG's Elecsys model seems to be that patients who are ruled out by clinical decision alone are only likely to get a mild/moderate case of pre-eclampsia at worst (the non-admitted patients are distributed only among the low and intermediate PlGF based risk categories in the model). We do not believe this reflects clinical experience. Some patients should therefore be ruled out within the "high risk"/"poor outcomes" group as well.	those women who were admitted for suspected pre-eclampsia. Using the rates of admission for suspected pre-eclampsia within 24 hrs (**60/186** and 48/184 in the reveal and nonreveal arms, respectively, see Table 2 in Cerdeira 2019[3]) does not change the cost-effectiveness of Elecsys (with the incremental cost of £529 and incremental QALYs of -0.1304) because the differential rate of admission changes only by 1%. E. The EAG has not modelled EBL because the proportion of patients with this complication is not reported in INSPIRE. Table S5b from INSPIRE only reports the measurement of EBL at delivery in millilitres. In addition, the cost of blood transfusion is minor and will not affect the model results. F. PreOS and INSPIRE have different trial designs, but they examine the same thing – (intended/actual) clinical decisions made with/without knowledge of the ratio test results. The different countries (PreOS – Germany; INSPIRE – UK) may or may not be an issue affecting applicability to the Elecsys model. The PreOS study publication does not mention whether guidelines or an algorithm was used for care decisions. It states that investigators were free in their clinical deicions (no recommendations beyond cutoff values).

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				J. Within the INSPIRE cohort, 0 women were sent home and subsequently developed pre-eclampsia within 7 days in the intervention arm, whereas 3 women who developed pre-eclampsia were sent home in the clinical decision arm. These women were at risk of adverse maternal and fetal outcomes. The fact that they didn't develop them is down (at least somewhat) to random chance but the health economic model should reflect what the average effect of sending these women home might be across the UK population rather than simply modelling a lack of sensitivity as having no disbenefit. K. Once again, we would urge the NICE committee to consider why a test with both a better PPV and NPV (100%), where 0 patients were inappropriately classified as "rule-out" in the testing arm would lead to worse neonatal outcomes? Since 0 patients are ruled out inappropriately, the model must be suggesting that having a more accurate reassurance that a patient is high risk would somehow lead to worse clinical management and outcomes. This is not logical. L. We believe that Table 54 hasn't captured the true costs of performing the tests, some costs are missing and some have been added unnecessarily. If 'charge per reportable' is used for Elecsys there is no need for additional costs to be added. The cost of £3.47 for 'Phone call to communicate results' should be removed for Elecsys, as the trust ICE system will report with no additional cost. We would like to note that for the Elecsys test the only costs included under the 'staff time' heading should be for the blood draw. All other staff time is included in the charge per reportable. Whereas, for the triage test, the staff time costs should include the blood draw, sample analysis and quality control (performed by a midwife, > 30 min) (ref	G. Please see our response to comment 5A. Also, as previously stated in response to comment 6A, the EAG does not consider relevant and appropriate to include any utility values related to hospitalisation. H. Please see our response to comment 6B. I. As stated in section 5.4.6 of the ERG report, not only women at low or intermediate risk of pre-eclampsia but also women at high risk of pre-eclampsia can be managed as outpatients: if they have been admitted to hospital but do not develop disease they are assumed to be discharged at some point and managed as outpatients up to delivery. J. The assumptions regarding hospitalisation were based on the treatment algorithm used in the INSPIRE RCT and clinical advice on managing women with suspected pre-eclampsia. We appreciate, however, that although the model was parameterised from the best available clinical evidence, it may not represent the "average effect" across England and Wales as the management strategies related to hospitalisation are likely to vary. K. Please see our response to comment 5A. L. The costs of testing were based on data provided by the companies and were informed by expert opinion. When data were not available, assumptions had to be made.

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				NHS: Tariff Information Spreadsheet).	Therefore, it is possible that some of these assumptions do not reflect clinical practice. We conducted a number of scenario analyses where the cost of testing was varied. These scenarios are described in section 5.5.2.1 of the EAG report. Since these model inputs have a relatively minor impact on the incremental costs, additional scenario analyses are unlikely to be of value.
Roche Diagnostics Ltd	7			The model's conclusions are at odds with all the published cost-effectiveness evidence identified by the EAG and known assay performance. A. Ignoring the wealth of identified evidence in the review and relying on a model based on a single trial for each of the tests, where differences in rare outcomes that drive the economic model can be explained by a combination of economic modelling assumptions and differences in the underlying risk and severity of patients between the model arms, is inappropriate. B. We would urge the NICE committee to consider how it is possible that a technology, where the underpinning RCT reported a higher sensitivity and similar specificity compared to clinical decision alone, could possibly lead to worse neonatal outcomes (the main driver of QALYs in the model). C. The findings of the model are contradictory to the findings of the PreOS study, which underpins some parameters in the model. In this study the introduction of the ratio test led to a statistically significant change in the choice to admit or not admit and all of these changes were deemed	Please see our responses to the comments above.

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				appropriate by a panel of adjudicators. These changes to management resulted in an increase in both the sensitivity and specificity of the test compared to clinical decision alone, in turn reducing the total number of admissions. D. The findings of the model are contradictory to a "Shared Learning Example" published on NICE's website in March 2021. This is an example from a hospital in Lancashire where, following the publication of NICE DG23 and the subsequent funding streams, they were able to redevelop their patient pathway to implement the Elecsys test and record observational outcomes e.g. "From audit data, we have shown that the use of the test allowed 100% of mothers, without any other obstetric complications, with a result of <38 to be discharged home safely. Additionally, the test provides reassurance for mothers since a result of <38 rules out pre-eclampsia for one week. We have found the use of the sFlt-1/PlGF ratio test useful in diagnosis of pre-eclampsia and this is particularly useful when risk stratifying which patients to keep as in-patients." We suspect there will be many such examples in the dozens of maternity units that have redeveloped their pathways to include the test. (https://www.nice.org.uk/sharedlearning/implementation-of-placental-growth-factor-plgf-based-testing-to-aid-diagnosis-of-suspected-pre-eclampsia-at-lancashire-teaching-hospitals-nhs-foundation-trust) E. The review identified a great deal of evidence that supports the proposition above, including 6 peer reviewed health economic evaluations of the Elecsys test that all found it to be cost-saving. To completely reverse the conclusion of years of work and analysis of this test on the basis of a model based on two trials characterised by heterogeneous populations is concerning.	

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				F. PIGF-based testing has been recommended by NICE as a rule-out test for 5 years, however we propose it would have been more appropriate to include the following comparator strategies in the EAG model: “clinical assessment alone”, “clinical assessment + rule-out test” and “clinical assessment + rule-in/rule-out test”. This way the incremental cost-effectiveness (and certainty of evidence) of adding a rule-in component to the rule-out strategy, which has become standard care in large parts of the UK, could be assessed. G. The EAG identified a large amount of evidence on the diagnostic test accuracy of both the Elecsys and Triage PIGF-based tests in the clinical review, which has been ignored in the economic analysis. The EAG did not consider it appropriate to meta-analyse the data so we do not have point estimates for rule-in and rule-out thresholds available. However, the DAR systematic review did include data on the predictive concordance of the various PIGF based assays. Two of the studies, the COMPARE study, and Giblins et al, found that while there were some small trade-offs between sensitivity and specificity between the Triage and Elecsys tests, the area under the ROC was similar for both tests. The COMPARE study also concluded that the Triage and Elecsys test’s ability to predict pre-eclampsia with 2 weeks did not differ. We ask the committee to consider how two tests that have similar diagnostic performance could possibly lead to such a difference in the primary conclusions of the report, namely that one test is dominant (less costly and improves outcomes) and the other is dominated (more costly and worse outcomes)?	

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Roche Diagnostics Ltd	8			Adopting the EAG's analysis as the base case will seriously affect patient access and we would urge NICE to consider redeveloping the model using a linked-evidence approach or waiting for ongoing trials to publish before making any change to existing guidance. A. Before the advent of PlGF-based testing, women with suspected pre-eclampsia were highly likely to be admitted to hospital. PlGF-based testing is most often used as a "rule-out" test and benefits from an extremely high NPV and sensitivity. This means that clinicians can confidently rule out a cohort of women, providing them with reassurance and reducing unnecessary admissions to hospital. This is why the test achieves savings to the NHS with no/negligible health disbenefits, why it was recommended in NICE DG23, why it was accepted by the AAC as a Rapid Uptake Product, widely implemented across the NHS over a 3 year period involving extensive on-site training and education resulting in pathway redesign. This is also why it currently has a Medtech Funding Mandate attached. B. Currently, both the Triage and Elecsys tests have a Medtech Funding Mandate attached because the analysis in NICE DG23 considered them to be both cost-saving and QALY increasing. The funding mandate has greatly increased the use of the tests across the NHS. When deciding which products will be added to the list, NHSE will consider the results of the economic evaluation that NICE publishes on its website. If the intent of the committee is for patients to retain access to the test, the base case analysis must be amended to more accurately reflect the cost-savings and QALY benefits that would logically be expected in an average hospital in the UK.	No comment.

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				C. The Elecsys test is embedded in routine clinical practice in approximately 80 maternity units across the country yet the EAG's analysis suggests that it is of no benefit (or indeed harmful for patients). Moreover, the test is used extensively across the world and its use is currently reimbursed in countries including, Germany, Korea, Switzerland, Brazil and Croatia. Moreover, use of the sFlt-1/PlGF ratio to rule out pre-eclampsia is recommended in the ESC Clinical Practice Guidelines and in many national guidelines. We would urge the committee to consider why the test would have such widespread adoption, incentivisation and be recommended in guidelines if it was not considered by the medical community to provide clinical and economic value? D. The PARROT-2 trial, which will provide data comparing the two tests, is currently recruiting and will provide higher quality evidence for the committee to consider. The risk of making an incorrect decision based on the current comparison between the two tests is high and will be substantially reduced when this trial reports. E. We would strongly urge NICE to consider redeveloping the model to be based on a linked-evidence approach or waiting for PARROT-2 to publish before considering changing guidance that has widespread uptake and clinical acceptance in the UK.	
Quidel	9	1	General points	Intended use of the tests: 1. The differences between the tests' intended uses are not clearly communicated within the report. 2. The Triage test has an intended use as follows; The test is used in conjunction with other clinical information as an	The manufacturer's intended use of the Triage test is stated in section 1.2 of the EAG report using the manufacturer's wording. The intended use of the tests and clinical management algorithms used in the clinical

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				aid in the diagnosis of preterm pre-eclampsia (i.e., pre-eclampsia requiring delivery preterm) and as an **aid in the prognosis of delivery** in women presenting with signs & symptoms of pre-eclampsia prior to 35 weeks of gestation. Recognition of this "time-limited" (delivery) endpoint is important - it matters to clinicians because it helps to identify women at low/intermediate/high risk for deterioration and delivery. The test's diagnostic accuracy for these endpoints has been validated in the published clinical studies, and the effect on cost- and clinical-outcomes evaluated and reported. Prediction of these clinically relevant endpoints inform clinical management and were utilised in the PARROT study. We request that the intended uses of the tests are fully described in the report. 3. Prognosis of delivery (i.e., using these time-limited" (14d, preterm delivery) endpoints) in women with suspected pre-eclampsia for the Triage test is part of the intended use. This might not be the case for the other tests (see later note about inferences from the McCarthy dataset). For example, we understand that the Elecsys test's intended use is for **aided diagnosis of pre-eclampsia** over short- (one week) and medium-term (four weeks) time intervals (i.e., the **appearance** of the disease meeting diagnostic criteria, **not its deterioration necessitating delivery**). 4. These are important differences between the available tests - the differences are not adequately or correctly summarised within the report. For the Triage test, performance data is reported in the literature and the product insert for the <12, ≥12<100, and ≥100pg/mL PIGF strata (time-to-delivery [median, IQRs] and diagnostic accuracy [SENS, SPEC, NPV, PPV] for the endpoints of	studies are provided in Table 53 and Appendix 8 of the DAR, respectively. The clinical management algorithm from the PARROT RCT did not specify the intended use of the Triage test. As stated in Duhig 2019,[4] this was “a pragmatic trial, to reflect how angiogenic factor measurement could be adopted clinically and realistically within a health-care service.” In PARROT, the outcomes stratified by the risk of pre-eclampsia (which were used in the economic model) were reported for the whole trial population including women with gestational age of more than 35 weeks. We stated in the DAR that modelling a wider population than that specified in the Quidel submission (<35 weeks) was a limitation of the cost-effectiveness analysis for Triage. The DAR does report prognosis of delivery results from PARROT by timepoint (within 2 weeks).

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				delivery (<14d or preterm) in suspected or confirmed pre-eclampsia)). 5. We believe that failure to report differences between the intended uses and endpoints of the different tests creates confusion in the report on how the tests are intended to be used and how they have been evaluated/applied in practice. 6. For example, for the Triage test, a PlGF level of <12pg/mL is described in the report as a rule-in diagnosis of pre-eclampsia. This is incorrect. It would imply that women with PlGF≥12pg/mL and <100pg/mL are unlikely to have or develop pre-eclampsia which is incorrect. 7. **We request that the report is reviewed and corrected to improve clarity on the intended uses of the tests, the applicable endpoints, and how the tests are intended to be used in practice**.	
Quidel	10	173	7 DISCUSSION 7.1 Statement of principal findings 7.1.1 Test accuracy and clinical effectiveness	The report states "Despite advancements in the evidence base for the tests, as described above, some **notable evidence gaps and uncertainties remain**. For example, having recommended the use of the Triage PlGF test and the Elecsys immunoassay sFlt-1/PlGF ratio alongside standard clinical assessment for **ruling out suspected pre-eclampsia**, NICE DG23 recommended further research be done to establish the accuracy of these tests at **ruling-in pre-eclampsia**, specifically on how this affects management decisions on time to delivery and consequent outcomes. The evidence on test performance for ruling-in pre-eclampsia available for this update DAR is **limited in both volume and relevance**." 1. We request consideration here of "relevance to the DG23 research question, as written, and **relevance to the clinical problem faced by clinicians in the delivery of**	We acknowledge all of these points made. Our original point was that The PARROT trial assessed test performance for the Triage PlGF <12 pg/mL cut off (rule-in), but only for the trial arm in which PlGF test results were concealed from the treating clinician. It was not clear why performance wasn't available for the arm where PlGF test results were revealed to the clinician, which is more relevant to the decision problem.

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				care". We believe that the rule-in use to identify women at **risk of delivery for pre-eclampsia** is important, recognised as relevant by clinicians, and has been validated in the PARROT study for the Triage test. 2. The central question underpinning research recommendation DG23 6.2 was whether a woman with PlGF<12pg/mL (shorter time-to-delivery interval, likely more severe disease) would receive inappropriate clinical management, increased rates of preterm delivery, and worse neonatal outcomes. 3. The clinical management algorithm for PlGF-guided testing used in the PARROT study included information for the clinicians on time-to-delivery, a PPV estimate from the PELICAN study for preterm delivery, and clear guidance to not deliver on a finding of PlGF <12pg/mL alone. We note that the PARROT algorithm (Appendix 8) is incomplete [page missing, which outlines expected time to delivery per PlGF strata and PPV/NPV for the 14-day and preterm time intervals]. 4. The product insert, based on the PELICAN study analysis, provides diagnostic accuracy data for the endpoint of delivery for preterm pre-eclampsia (12pg/mL) and endpoint of **delivery for preterm pre-eclampsia** or for **pre-eclampsia requiring delivery within 14d** (100pg/mL). 5. Women with PlGF<100pg/mL are at increased risk for deterioration and required delivery. Further, we note the conclusions of the investigators of the PARROT study in a publication by Duhig (Duhig, K.E., Myers, J.E., Gale, C., Girling, J.C., Harding, K., Sharp, A., simpson, N.A.B., Tuffnell, D., Seed, P.T., Shennan, A.H., Chappell, L.C., Placental Growth Factor	

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				Measurements in the Assessment of Women with Suspected Preeclampsia: a Stratified Analysis of the PARROT Trial, Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health (2020), doi: https://doi.org/10.1016/j.preghy.2020.10.005) that " We found that the difference seen in the severe maternal adverse outcome composite was most marked in the PlGF 12-100pg/ml group (aOR 0.15 (95% CI 0.03 to 0.92) and we anticipate that this may offer clinicians an opportunity to identify women at risk of developing severe preeclampsia complications, who may otherwise be considered at lower risk". In the PARROT clinical management algorithm, clinical guidance for this 12-100pg/mL included increased surveillance with hospital admission determined by hypertensive status. 6. The risk strata of PlGF <12, ≥12<100, and ≥100pg/mL provide clinicians with probable pregnancy outcomes (i.e., Median time to delivery, PPV/NPV for 14d/preterm delivery) to be considered alongside established clinical assessments. **7. We consider that the data reported in the PARROT study (Duhig publications) addresses the question of whether the Triage test can be used safely and cost-effectively for its intended use (stated above) to rule-in and to rule-out deterioration requiring delivery over clinically relevant time intervals (14d, preterm).**	
Quidel	11	73	The PARROT trial	The report states that "The PlGF cut-offs used (>100, 12-100, and <12 pg/mL) were in line with those recommended by the company. If a participant had a PlGF of < 12 pg/mL, the [PARROT study] algorithm defined this as 'very low' and instructed clinicians to 'assess as pre-eclampsia'."	All available data on test accuracy as reported by PELICAN and other standalone tests are reported in Appendix 5.3 of the DAR.

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				1. We wish to make the following further points about rule-in use of the Triage PlGF test. Very low PlGF (<12pg/mL) identifies likely presence of severe placental dysfunction and a high probability of deterioration and delivery (14d, preterm) with pre-eclampsia. 2. We note that the report includes PPV data for the 14d timepoint (PPV of 44.6% for predicting pre-eclampsia requiring delivery within 14 days) but does not report PPV data for 12pg/mL for the preterm endpoint which is available to clinicians and informs decision-making. PPV this preterm delivery endpoint from the PELICAN study is 94.2%). 3. We note that the report does not include PPV data for the 14d timepoint (PPV of 43.4% for predicting pre-eclampsia requiring delivery within 14 days) or the preterm delivery endpoint (PPV 65.1%) from the PELICAN study analysis (product labelling). Both the low (<12pg/mL) and middle (≥12<100pg/mL) PlGF strata were part of the clinical management algorithm and inform clinicians on a median expected time-to-delivery interval and PPV for deterioration/delivery. 4. We note that the report acknowledges on p138 that "The [PARROT] trial also reports a reduction in severe maternal adverse events seen with the implementation of revealed PlGF testing, with the largest reduction in the PlGF 12–100 pg/ml group. The authors argue that the improvement in clinical outcomes in this group may have been mediated by the use of the clinical management algorithm which recommends increasing antenatal surveillance and monitoring; this may be particularly important in the group of women with PlGF 12–100 pg/ml who presented with	

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				clinical features of gestational hypertension but may also have had sub-clinical multi-organ disease features." 5. Evaluating both the Triage and Elecsys tests for the same "rule-in" **diagnosis** incorrectly assumes an equivalent intended use and diagnostic endpoints. The intended uses and their associated endpoints are different. 6. We believe that the model/scenarios correctly maps the Triage PlGF strata to the different risk groups, but the explanation of how the Triage test informs clinical management (expected time-to-delivery, PPV/NPV for delivery (14d, preterm) with pre-eclampsia) for the different cutoffs lacks consistency within the report. **7. We consider that this "rule-in" use (i.e., for time-limited delivery endpoints), for Triage, is clinically relevant and informative to clinicians. We do not agree that a rule-in has not been adequately researched.** **8. We request that the panel reconsider its recommendation for further research to support a rule-in use of the Triage test. The "rule-in" use of the Triage test is intended to identify disease which might deteriorate and require delivery within 14d or preterm and not to predict a clinical diagnosis of pre-eclampsia.**	
Quidel	12	80	4.1.2.1 Testing to predict pre-eclampsia	The report states " Two standalone studies (PETRA, PELICAN)22 25 reported NPVs ranging from 0.530 to 0.901 in patients <35 weeks gestation when using this test at a cut-off PlGF level of 100 pg/mL to predict PE at any time point (Appendix 5, Table 81)." 1. Pre-eclampsia is categorised as early (<34w), early preterm (≥34<37w), and late (≥37w) onset. It is not clear to	Test accuracy data for predicting pre-eclampsia requiring delivery within 14 days are reported in Table 86 in Appendix 5. We report most of the data for the stand

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				us why NPV data is being reported for "all pre-eclampsia" when it is widely known that PlGF-based tests detect the pathophysiology (placental dysfunction) associated primarily with early and early preterm onset (20w-37w). 2. Reporting NPV data for pre-eclampsia at any timepoint does not inform a clinically relevant problem - we believe that the recognised clinical problem is "will this patient with a possible pre-eclampsia diagnosis deteriorate/require delivery within a short time interval (14d, preterm)". Performance for these endpoints informs clinical management and was the basis of the clinical algorithms supporting use of the Triage test. **We request that data also reported from these studies for the endpoints supported by the intended use of the test (delivery (14d, preterm) is included.**	alone test studies in the appendices for the reasons stated in the DAR.
Quidel	13	10	Results	The report states "Other predictive accuracy evidence combined diagnosis of pre-eclampsia with other outcomes such as time to delivery, or requiring preterm delivery: the Triage test had a PPV of 100% (sensitivity 51%) to predict pre-eclampsia and a test to birth interval of 14 days using a test cut-off of <12pg/ml and a PPV of 87% (sensitivity 95%) using a test cut-off of <100pg/ml. The diagnostic and prognostic/predictive accuracy outcomes varied according to rule-in or rule-out for differing time periods and different gestational age ranges." 1. As stated, we believe that this prognostic/predictive accuracy outcome data is directly relevant to clinical practice and likely more informative than using the PlGF-based tests to establish a clinical diagnosis of pre-eclampsia alone. **We question why it is reported as "other" evidence because it does not fall within the "rule-in diagnosis"**	Use of the term “other” is not intended to negate the utility of the evidence to clinical practice. We have taken an inclusive approach and have reported as much of the available data as possible in our report. Hence, the report includes a a wide range of accuracy estimates ranging from diagnosis of pre-eclampsia to predication of pre-eclampsia requiring delivery at specified time points.

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				scope and request further consideration to ensure that the scope of the review adequately encompasses the way in which the tests are intended to be utilised.	
Quidel	14	177	8.2 Suggested research priorities	The report states that "Further evidence of the performance of the Triage and Elecsys, tests when used alongside standard clinical assessment to rule-in pre-eclampsia, is required. The current available evidence is of limited volume and relevance to current practice." 1. For the reasons given (intended use and applicability of the time-limited (delivery <14d, preterm) endpoints for which diagnostic or prognostic accuracy data has been generated for Triage), we disagree with this statement. The current evidence **supporting these time-limited delivery endpoints is of direct relevance to current practice**. 2. This, through consultation with clinical experts, is the basis of the intended use of the Triage test and how it is used in clinical practice. We believe that clinicians place more emphasis on tests which can identify **(rule-in, rule-out) disease which could deteriorate within a short timeframe**, might be missed by standard clinical assessment, and otherwise might cause an adverse maternal and/or fetal outcome. **3. However, we question the clinical utility of tests which help diagnose (rule-in) pre-eclampsia. These tests help to confirm a probable diagnosis of pre-eclampsia but do not convey information on an individual patient's prognosis. Hence, we raise a question about the clinical relevance of the endpoint being evaluated.**	We acknowledge these points. Our point is that there is a lack of evidence evaluating the clinician's use of the test results alongside standard clinical management to inform care decisions. Those decisions reflect the potential for the condition to deteriorate within a short timeframe (i.e. not just ruling in pre-eclampsia but pre-eclampsia requiring delivery at a specified time point).

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Quidel	15	138,139, 146	5.4.5 Key considerations when selecting a model structure	The report states that "It has been shown that there is a **correlation between the level of angiogenic biomarkers in women with suspected pre-eclampsia and the time from testing to delivery**.9,47 Therefore, a candidate model structure should be able to capture clinical risk stratification into low, intermediate and **high risk of pre-eclampsia**. It should also be able to adequately represent the clinical management algorithms for gestational hypertension and pre-eclampsia (with hypertension stratified by the level of severity), the management of delivery and the risk of maternal and neonatal adverse outcomes." Further, the report states "Figure 5 outlines the model structure, which includes four main components: [One component] Stratification of women into sub-cohorts depending on the risk of suspected PE (low, intermediate, or high) based on the results of standard clinical assessment with or without PlGF testing. Therefore, in the base-case analysis we assumed that women with PlGF of less than 12 pg/ml would be hospitalised while women with PlGF levels of ≥12pg/mL would be managed in outpatient settings except those with severe hypertension who can also be admitted for up to three days. The proportion of women with PlGF level of <12 pg/ml in the comparator arm who would be hospitalised within 24 hours was estimated from the risk ratio for diagnosis within 24 hrs (RR = 1.31) based on Duhig 2019.8". • We agree with the model structure. However, on p146 "Hospitalisation rates for these PlGF categories were not reported, but it was stated that the clinical management algorithm used by clinicians in PARROT (Appendix 8) **did not recommend routine admission for women with low** or very low PlGF (Duhig 202163)." • **The base-case analysis states "we assumed that women with PlGF of less than 12 pg/ml would be hospitalised." We question whether hospitalisation**	In response to this comment, we conducted a scenario assuming a lower proportion (90%) of women at high risk of pre-eclampsia in the test arm who would be hospitalised. This did not change the outcome, i.e. using Triage alongside standard clinical assessment remains less costly and more effective (see section 5 in Addendum).

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				rates might be over-estimated in the base-case analysis.	
Quidel	16	86,87	4.1.3.2 Predictive concordance	The report states that "McCarthy et al. compared the commercially recommended cut-offs for the Alere (now Quidel) Triage PlGF test (<100 pg/mL), Roche Elecsys test sFlt-1/PlGF ratio (>38) and an optimally derived cut-off for the Perkin Elmer DELFIA Xpress PlGF 1-2-3 test (<150 pg/mL). A trade-off was seen between sensitivity and specificity, with the Triage PlGF and DELFIA Xpress tests both having higher sensitivity, but lower specificity, than the Elecsys test. However, McCarthy et al. concluded that the tests' ability to predict delivery within 2 weeks did not differ significantly when using the specified cut-offs, with areas under the ROC curve being similar among the tests (full test accuracy statistics for the three tests are provided in the publication)." • Note that McCarthy further states that "the main outcome measure was detection of a difference of 0.05 in AUROC between tests for time to delivery within **14 days of testing**. They further state that "**using this [Triage] assay**, a PlGF ≥100 pg/ml is considered test negative (normal), suggestive of patients without placental dysfunction who are unlikely to progress to delivery within 14 days of the test." We request that consideration is made of the **intended use of each of these tests**. We are not aware of any PlGF-based test with the **same intended use as the Triage test** (i.e., for the endpoints used in this evaluation by McCarthy). Therefore, we question whether the COMPARE study provides a meaningful dataset/analysis given that the intended uses/endpoints of the available tests are different.	We note this point. Comparisons between tests will inevitably be problematic due to the different ways the tests are meant to be used. We have to be pragmatic and make use of comparative data when required.
Quidel	17	147, 148, 299 (T111)	5.4.7.3 Costs associated with	The report states that "Test costs were estimated from information provided by the test manufacturers to NICE, and from clinical experts and laboratory staff who use the Triage PlGF test and	QC costs were accounted for in two ways: (1) the costs of laboratory material and (2) the costs of staff required to perform QC.

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			PlGF-based tests	Elecsys sFlt-1/PlGF ratio test in clinical practice. Where information was unavailable for certain cost items, we made reasonable assumptions to inform our cost estimates." • The effect of QC testing frequency on cost-per-reportable in different patient volume scenarios has not been considered. Typically, wet-reagent platforms require daily 2-level QC testing and this, for low throughput testing scenarios such as is the case for pre-eclampsia, can significantly influence cost-per-reportable. • **Table 111 has inconsistent data reported across the manufacturers (cost per test, cost per reportable, costs for CaIs and QC controls) - it is not at all clear whether all of the correct costs are included for all of the tests.** • For example, for the Elecsys test the report reads "Assumption as informed by one of our experts" - yet **no separate cost is included for running controls and calibrators**. • **We question whether the effect of patient throughput of 365 tests per year (one of the scenarios listed) and the cost of QC testing frequency has been fully considered in the cost-per-reportable estimates for the Elecsys test.**	Costs of laboratory material: for the Triage test, these were informed by the manufacturer and an expert; for Elecsy, these were included in the cost per reportable test; for BRAHMS, these costs were provided by the manufacturer (see pages 294 and 296-297 of the EAG report). Costs of staff: "An estimate of 41 hours per year to quality control testing was used. This estimate was provided by Quidel. Therefore, we assumed twice the time is needed for the Elecsys and BRAHMS Kryptor sFlt-1/PlGF ratio tests" (see page 297 of the EAG report). Only Elecsys has been assigned with a cost per reportable test. The rationale for not applying the same approach for Triage and BRAHMS tests are explained in the EAG report, page 294: "The manufacturer further clarified that contracts included machine costs, cost of laboratory materials and consumables, maintenance, and training costs. This argument was supported by our experts (one of whom was a laboratory manager) who noted that machines and maintenance costs are not borne directly by providers but are typically paid for via a managed service agreement with manufacturers." "The other manufacturers did not refer to any such contractual arrangements in their submissions."

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					The cost per reportable test includes the costs for running controls and calibrators, as explained in EAG report, page 294: “Hence, we assumed that the cost of the Elecsys sFlt-1/PlGF ratio test includes capital, maintenance, and equipment costs.”. However, the costs of staff to perform QC was charged in addition to the cost per reportable test. We have run scenario analyses in which we varied the cost of the test across a broad range of costs and we concluded that changing the costs of the tests has a low impact on the model results (see EAG report, section 5.5.2.1). Therefore, the EAG considered that there is no reason to update the costs of the tests or run more scenario analyses
Quidel	18	232, 233	Table 86 Prediction of PE requiring delivery by time point	The report states "In the PELICAN study, Duckworth et al.21 reported that for women presenting between 20+0 and 34+6/7 weeks of gestation the AUC for PlGF <12 pg/mL for predicting pre-eclampsia requiring delivery in 14 days was 0.87 (95% CI 0.83-0.92)". • This is incorrect. The AUC does not relate to a single operating cutoff of 12 pg/mL. • Please include data for the 100pg/mL cutoff in Table 86 (Row "PELICAN, 22 270 Triage test, result concealed, 35+0 to 36+6 weeks") for delivery before 37 weeks. This data is reported in the Chappell Circulation paper (reference 270, Table 4. Test Performance Statistics for Low PlGF in Prediction of Adverse Outcomes). • Please include in Table 87 data for the **preterm delivery endpoint** and a cutoff of both 12pg/mL and 100pg/mL as	We have corrected the text as suggested. We are unable to add further data to the report due to time and resource limitations

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				reported in Triage product insert (Table 9) which uses data from the same PELICAN study analysis.	
Quidel	19	54-55,T4,T5	4.1.1.5 Approach to add-on test use	1. Test diagnostic cut-off(s) are reported in the Tables for the Triage test, but the endpoints evaluated are not consistently reported across the studies. The endpoints for the Triage test include prognostic use (prediction of required delivery; 14d, preterm).	We summarise the use of the tests in the respective studies. This is not intended to necessarily state the manufacturer's recommended use of the test unless the study in question explicitly mentions this.
Quidel	20	147	5.4.7.1 Parameterisation of the risk stratification phase of the model Triage PlGF test	The report states "We conducted an additional analysis for the **Elecsys** PlGF test using data from a comparative study of MAPPLE and PELICAN (Sharp et al 20189). In the analysis reported by Sharp and colleagues,9 clinical outcomes in women with singleton or twin pregnancies presenting prior to 35 weeks' gestation were compared, where possible, between revealed (MAPPLE) and concealed (PELICAN) cohorts. Data from Sharp9 are categorised by PlGF concentration: <12 pg/ml (very low), 12–100 pg/ml (low; representing <5th percentile of normal) and >100 pg/ml (normal)." • We believe that reference to the Elecsys test is an error and this should be the Triage test.	Corrected. Thank you.
		146	5.4.7.1 Parameterisation of the risk stratification phase of the model	The report states that "Women with a **serum** PlGF concentration of >100 pg/ml followed a care pathway involving outpatient management and routine surveillance unless clinical parameters such as severe hypertension indicated otherwise" and " Women with a **serum** PlGF concentration of >100 pg/ml followed a care pathway involving outpatient management and routine surveillance unless clinical parameters such as severe hypertension indicated otherwise." • The Triage tests uses an EDTA plasma sample.	Corrected. Thank you.
British Maternal Fetal Medicine Society	21			On the behalf of BMFMS, we would like to raise our concerns around the modelling of the two tests for PLGF and	Noted

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				conclusions / costing drawn from this modelling. Please see the points below – 1. The modelling for the two tests has used different base case data for the two main tests available (Quidel and Roche) and therefore the cost effectiveness analysis for the two tests has come out very differently. The model has concluded "*The EAG cost-effectiveness model estimates that the Triage PlGF test would have a cost saving of £1,746 and an increase of 0.20 QALYs per woman with suspected pre-eclampsia compared with current management only. Most of the savings in costs and improvement in QALYs were related to the long-term outcomes, which were based on the frequency of neonatal adverse outcomes. For the Elecsys test, there is an increase in cost of £621 per woman and a reduction of 0.14 QALYs with suspected pre-eclampsia compared with current management only.*"	
British Maternal Fetal Medicine Society	22			**2.** The modelling appears to have produced different outcomes because of the different RCTs which have been published assessing the tests. In the PARROT study (Quidel test), more detailed outcomes were reported in addition to a change in management based on a low, intermediate or normal result. In the cost effectiveness analysis performed as part of this trial a cost saving of £219 per pregnancy was demonstrated based on a cost utility analysis (admission bed days, NICU, scans, OP visits etc) compared using a direct comparison of cost utility between the arms of the trial.	Noted
British Maternal Fetal	23			**3.** The INSPIRE study (Roche test) did not include a formal cost utility analysis and also did not report the same	Noted. See also Addendum to the DAR

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Medicine Society				granular outcomes as the PARROT study. It was also a much smaller, single centre trial performed in a unit with expertise in the management of pre-eclampsia where the difference between management with and without the test may not be so representative of all UK hospitals (admission rates in the standard clinical care arm were lower than previous reported studies). There was also a chance imbalance in the rates of pre-eclampsia (ie number of women with a high ratio result) between the arms in the INSPIRE study, which means that the model appears to make the frequency of pre-eclampsia, and therefore its costly outcomes, more frequent in the group which had the test reported – this obviously doesn't make sense. The test itself doesn't increase the prevalence of the disease or its associated adverse outcomes. Had the imbalance been by chance in the other direction, it would have skewed the model in the opposite direction.	
British Maternal Fetal Medicine Society	24			**4.** The costs of management of 'suspected' pre-eclampsia are different in the EAG cost effectiveness analysis for the two tests which doesn't make sense. All the diagnostic accuracy studies and the COMPARE study have demonstrated comparable diagnostic accuracy between the test platforms. Clearly management pathways across UK hospitals are not affected by the test platform used (the clinical pathways recommended by NICE are identical), but by variation in clinical practice between hospitals – using different models (and therefore costs) of care to assess the utility of the different tests therefore doesn't make sense.	The management of suspected pre-eclampsia is based on NICE CG107. In line with that, the costs of managing suspected pre-eclampsia are dependent on the level of hypertension and gestational age of women (see EAG report, page 150). As both the level of hypertension and proportion of women with a gestational age < 35 weeks came from different RCTs – PARROT for Triage PlGF test and INSPIRE for Elecsys sFlt-1/PlGF ratio test – the costs of managing women with suspected pre-eclampsia are therefore dependent on the data reported in each of the RCTs. If the data is

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					different for PARROT and INSPIRE, then the costs of managing suspected pre-eclampsia will also be different.
British Maternal Fetal Medicine Society	25			**5.** Page 11- Rule in thresholds have been developed for Delfia 123 (Giblin et al).	We note this in section 4.1.3.2 of the DAR
British Maternal Fetal Medicine Society	26			**6.** Page 57 - "The population analysed in the COMPARE study does not fully match the NICE scope for the current review since it comprises women suspected of having pre-eclampsia as well as those suspected of having an SGA infant". COMPARE study included women suspected PE, with and without SGA foetuses, and as SGA is a fetus is a feature of pre-eclampsia, COMPARE study should be included within the NICE remit, as per the international definition of pre-eclampsia.	This sentenence has been removed to avoid confusion
British Maternal Fetal Medicine Society	27			**7.** The difference in prevalence of the disease in the studies (PARROT and INSPIRE) makes it difficult to compare the two, and may also explain the difference in modelling. However, it therefore makes it extremely difficult to draw tangible conclusions in the comparison.	Noted. Please see Addendum to the DAR where a scenario analysis has been reported.
British Maternal Fetal Medicine Society	28			In summary – the modelling is complex and following all the assumptions made is very challenging. For two tests which have previously been shown to have the same test performance, it doesn't seem logical to apply different cost assumption models in a cost effectiveness analysis which appear to have arisen from differences in the design of the two (very different) RCTs. It does not seem plausible that the tests could have such different costs associated (especially	Noted. Please see Addendum to the DAR where a scenario analysis has been reported.

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				as the cost of the tests themselves are the same). We would urge the panel to consider the plausibility of the models applied, studies included, and revise the conclusions drawn.	
Thermo Fisher Scientific	29	109	4.3	From DAR "The company studies for the BRAHMS Kryptor test which reported AIC data to the EAG for the purpose of this review (PRAECIS and REPORTS) were both excluded **on population**,". DAR Population - *The population of relevance to the decision problem is pregnant women, between gestation week 20 and gestation week 36 plus 6 days, who, on the basis of screening tests and clinical symptoms, are suspected of having pre-eclampsia. This is usually based on the presence of hypertension plus other signs or symptoms, including proteinuria, haematological abnormalities, frontal headache, severe pain just below the ribs, vision problems, vomiting, and/or sudden swelling of the face or hands.* PRAECIS Population (as shared in protocol) - *Pregnant women (≥18 years of age) and gestational age 23^{+}0 to 34^{+}6/7 weeks who are admitted to the hospital with (or develop while hospitalized) a hypertensive disorder of pregnancy (see Section 5.8) will be asked to participate in the study. This population is considered at risk for developing PE with severe features and is therefore the population that would benefit from the use of the sFlt-1/PlGF ratio test (in conjunction with clinical and laboratory factors) for risk-stratification. The upper limit of 34^{+}6/7 weeks' gestational age has specifically been chosen to allow for a 2 week window of observation for an outcome of interest to develop prior to the ACOG-recommended indication for delivery. That is, after this window (i.e., at 37^{+}0 weeks' gestation), delivery of the fetus is indicated per ACOG guidelines and could confound interpretation of the predictive ability of the sFlt-1/PlGF test results.*	Noted, thank you.

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				Unclear what substantial difference exists to exclude this study.	
Action On Pre-Eclampsia	30			Thank you for sending us the document on PLGF. As a pre-eclampsia charity we are very keen that as much choice as possible is available for women. We believe these tests will have important impact on the experience of women with suspected pre-eclampsia. We were surprised that The Perkin Elmer test was not recommended following the Compare study and the Giblin study demonstrating equivalence to the Quidel and Roche platforms and defining rule in and rule out thresholds. The Compare study evaluated women with suspected pre-eclampsia only (some who obviously had SGA) so we believe this does fulfil the scope of this review. https://obgyn.onlinelibrary.wiley.com/doi/full/10.1002/uog.19051 https://pubmed.ncbi.nlm.nih.gov/32388118/ Yours sincerely [redacted] [redacted] on behalf of APEC	In response to this commen, we have conducted an analysis for DELFIA Xpress PlGF 1-2-3 (PerkinElmer) assuming similar performance to that of Triage PlGF (Quidel). The outcomes and limitations of this analysis are reported in section 4 in the Addendum.
Perkin Elmer	31	7	Background	*The four tests specified in the NICE scope for this diagnostic assessment and evaluation, are: Triage® PlGF test (Quidel Cardiovascular Inc; San Diego, CA, USA); the DELFIA® Xpress PlGF 1-2-3 test (PerkinElmer, Wallac Oy, Turku, Finland); the Elecsys® sFlt-1 to PlGF ratio test (Roche Diagnostics GmbH, Mannheim, Germany) and the BRAHMS® sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio test (Thermo Fisher Scientific GmbH, Hennigsdorf, Germany).*	This has been corrected.

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				Why is the PerkinElmer DELFIA Xpress sFlt-1 kit not included in the list of reviewed tests? We believe this is an oversight as reviews were done for the other tests submitted which are comparable to DELFIA Xpress.	
Perkin Elmer	32	11	Results	*Evidence for the Elecsys test found that a test ratio cut-off of 85 had a PPV of 71% to rule-in pre-eclampsia within 4 weeks in women presenting between 24 and 37 weeks' pregnancy. The BRAHMS test using the same ratio cut-off of 85 had a PPV of 62% to rule-in pre-eclampsia within 4 weeks and a PPV of 46% to rule-in pre-eclampsia within 1 week in women presenting between 24 and 37 weeks' pregnancy (sensitivity and specificity were not reported). High NPVs were reported across the studies for the Elecsys test ratio cut-off of 38 so the evidence remains stronger for using the test to rule out pre-eclampsia. Other predictive accuracy evidence combined diagnosis of pre-eclampsia with other outcomes such as time to delivery, or requiring preterm delivery: the Triage test had a PPV of 100%§ (sensitivity 51%) to predict pre-eclampsia and a test to birth interval of 14 days using a test cut-off of <12pg/ml and a PPV of 87% (sensitivity 95%) using a test cut-off of <100pg/ml.* The COMPARE study provides similar information in identical women with suspected pre-eclampsia. The COMPARE study used prospectively collected samples in women with suspected pre-eclampsia and ran all assays on the same samples i.e. is the only study directly comparing the assays and shows they are similar. Therefore, why is the PerkinElmer's PlGF 1-2-3 assay excluded? Cut-off's and accuracy test statistics were available for PerkinElmer's DELFIA Xpress PlGF 1-2-3 (Giblin et al., 2020) – yet they were excluded. We believe it may be an oversight. "*Rule-in thresholds for DELFIA Xpress PlGF 1-2-3 test for suspected preeclampsia Lucie Giblin, Fergus P. McCarthy, Carolyn*	Noted. Please see Addendum to the DAR which includes an analysis of the DELIFA PlGF 1-2-3 assay

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				Gill, Paul T. Seed, Kate Bramham, Anna Brockbank, Lucy C. Chappell, Andrew H. Shennan - Women's Health Academic Centre, St Thomas' Hospital, King's College London, United Kingdom". Cut-off's and accuracy test statistics for PlGF alone approach and for sFlt-1/PlGF ratio are also presented in study report R01-17008 conducted at [redacted]. Comparison results performed at [redacted] between Elecsys sFlt-1/PlGF and DELFIA Xpress sFlt-1/PlGF showed a strong linear relationship between assays. This provides additional evidence that similar performance can be expected between the assays.	
Perkin Elmer	33	11	Results	*The EAG cost-effectiveness model estimates that the Triage PlGF test would have a cost saving of £1,746 and an increase of 0.20 QALYs per woman with suspected pre-eclampsia compared with current management only. Most of the savings in costs and improvement in QALYs were related to the long-term outcomes, which were based on the frequency of neonatal adverse outcomes. For the Elecsys test, there is an increase in cost of £621 per woman and a reduction of 0.14 QALYs with suspected pre-eclampsia compared with current management only. In the analysis for BRAHMS, assuming equal predictive accuracy to that of Elecsys, an increase in cost was £594.* An assumption was made for BRAHMS. The same process could have been adopted for the PerkinElmer PlGF-1-2-3 assay Predictive accuracy for PlGF 1-2-3 alone approach and for sFlt-1/PlGF ratio are presented in study report R01-17008 conducted in [redacted].	Please see our response to comment 30.
Perkin Elmer	34	31	1.2	*The **DELFIA Xpress PlGF 1-2-3 (Perkin Elmer)** can be used as a standalone test or in combination with the **Perkin Elmer DELFIA Xpress***	Noted

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				sFlt-1 test. *The DELFIA Xpress PlGF 1-2-3 test is intended for the quantitative determination of PlGF in maternal serum using the 6000 DELFIA® Xpress clinical random access screening platform. The kit is described as being an aid in screening pregnant women for pre-eclampsia in all trimesters of pregnancy. In the second and third trimester (which is relevant to this diagnostic assessment), the company states that PlGF can be used for screening for risk of pre-eclampsia together with other relevant clinical information.* The ability to utilize the same assay for prevention is an additional aspect showing how the kit can be considered as cost beneficial. Please see Cost analysis spreadsheet for illustration of impact on cost per reportable result when the same kit is used for pre-eclampsia prediction and aid in diagnosis.	
Perkin Elmer	35	31	1.2	*The **BRAHMS PlGF plus Kryptor test (ThermoFisher)** can be used as a stand-alone test or together with **ThermoFisher BRAHMS sFlt-1 Kryptor test.** The BRAHMS sFlt-1 Kryptor / BRAHMS PlGF plus Kryptor PE ratio is formed by combining the results from 2 automated 32 immunofluorescent sandwich assays, the BRAHMS sFlt-1 Kryptor and BRAHMS PlGF plus Kryptor assays. The assays are indicated for the quantitative determination of sFlt-1 and PlGF in serum samples and are compatible with the BRAHMS Kryptor compact plus analyser and the Kryptor Gold immunoanalyser. The BRAHMS sFlt-1 Kryptor / BRAHMS PlGF plus KRYPTOR PE ratio is intended to be used to confirm or exclude diagnosis of pre-eclampsia after 20 weeks gestation.* It is stated that "*The BRAHMS PlGF plus Kryptor test (ThermoFisher) can be used as a stand-alone test or together with ThermoFisher BRAHMS sFlt-1 Kryptor test.".* It should be stated for which trimester as it is stated for PerkinElmer (all 3 trimesters). It is our understanding that the BRAHMS PlGF	Noted

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				plus Kryptor test intended use, is as a stand-alone test for 1st trimester, which is not the scope of this report.	
Perkin Elmer	36	32	1.3	*NICE's guidance makes recommendations for further research to inform aspects of PlGF-based testing where evidence to inform guidance was lacking. These were:* *• The diagnostic accuracy and analytical validity of the DELFIA Xpress PlGF 1-2-3 test and BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio (Research recommendation 1.3). • Rule in pre-eclampsia using the Triage PlGF test, and the Elecsys immunoassay sFlt-1/PlGF ratio (Research recommendation 6.2)* *• Use of repeat PlGF-based testing for suspected pre-eclampsia (Research recommendation 6.1)* This recommendation is the same as 2016. Following a debrief meeting with NICE, the feedback was shared with Prof. Shennan and Prof. Chappell. The COMPARE study was designed by Prof. Andrew Shennan, Professor Lucy Chappell, Dr Fergus McCarthy to address the deficiencies identified in the previous NICE review. It was designed and powered (Dr Paul Seed) to demonstrate non-inferiority, with a difference of <0.05 in the AUROC as the endpoint. This was an Investigator led study. As communicated in the submission (R01-17008 study report, confidential), a new study (evaluate sFLT-1/PlGF ratio and PlGF alone) has been conducted [redacted] Study includes 23 Healthy controls, 174 Suspected PE (not confirmed) and 164 suspected PE (confirmed).	Noted. Please see Addendum to the DAR which includes an analysis of the DELIFA PlGF 1-2-3 assay

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Perkin Elmer	37	43	Table 1	Excludes the Giblin et al.,2020 publication. This analysis was conducted on women with suspected pre-eclampsia. "*Rule-in thresholds for DELFIA Xpress PlGF 1-2-3 test for suspected preeclampsia Lucie Giblin, Fergus P. McCarthy, Carolyn Gill, Paul T. Seed, Kate Bramham, Anna Brockbank, Lucy C. Chappell, Andrew H. Shennan - Women's Health Academic Centre, St Thomas' Hospital, King's College London, United Kingdom".* Rule-in cut-off being <50 pg/ml.	We discuss the Giblin publication in section 4.1.3 under assessment of test concordance. See also Addendum to the DAR.
Perkin Elmer	38	51	4.1.1.5	• ***Test cut-off values***. *All studies used the cut-offs recommended by the respective manufacturers. The Binder 202035 study additionally investigated ratio cut-offs of >80 and >67 and intermediate values of 38 to 80 and 38 to 67 as it was investigating different sFlt-1/PlGF ratio measures in twin pregnancies. However, only the cut-off of 38 in the Binder 202035 study is assessed in this review because the others do not match the cut-offs recommended by the manufacturer. Andersen 201948 used cut-offs of 33 and 85 with the BRAHMS Kryptor test: the cut-off of 85 is in keeping with the manufacturer recommendations that a measurement >85 is suggestive of pre-eclampsia and the patient should be delivered within two weeks; the cut-off of 33 correlates with the Roche Elecsys use of the sFlt-1/PlGF ratio to rule out pre-eclampsia in the short term.* We would like to highlight that there is an IP restriction on the use of sFlt-1/PlGF ratio to rule-out patients, this should be stated. EP2706359A1 Predictive accuracy for PlGF alone approach and for sFlt-1/PlGF ratio are presented in study report R01-17008 conducted at [redacted]	Noted

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Perkin Elmer	39	57	4.1.1.6	*An overview of the diagnostic test aspects of the standalone studies is in Table 5 below.* • ***Gestational age at testing**. Testing was performed from 20+0 weeks in three studies (PELICAN18 21, PETRA25 27, PROGNOSIS Asia43), and slightly later in other studies, from 22 weeks (Saleh 201654), and from 24 weeks (PROGNOSIS 36-42).* The COMPARE study is missing from the list of studies.	Noted
Perkin Elmer	40	57	4.1.1.6 table 5	There is a rule-in cut-off for DELFIA Xpress PlGF 1-2-3 kit which is missing from the table. It was validated in the publication "Rule-in thresholds for DELFIA Xpress PlGF 1-2-3 test for suspected preeclampsia Lucie Giblin, Fergus P. McCarthy, Carolyn Gill, Paul T. Seed, Kate Bramham, Anna Brockbank, Lucy C. Chappell, Andrew H. Shennan - Women's Health Academic Centre, St Thomas' Hospital, King's College London, United Kingdom". Rule-in cut-off <50 pg/ml. The new study data from [redacted] (Confidential) – previously described provides additional confirmatory data to support the diagnostic utility of the test for rule in, using the cut-off's described in the Giblin et al.,2020 publication Chapter 6.5 in R01-17008 report shows rule-in performance with different cut-offs.	Noted. We discuss the Giblin publication in section 4.1.3 under assessment of test concordance. See also Addendum to the DAR.
Perkin Elmer	41	81	4.1.2.1	*DELFIA Xpress PlGF test* *We did not identify any relevant add-on studies or standalone studies reporting on this* *outcome.* In the COMPARE study predicting delivery within 14 days from testing in women with suspected preterm pre-eclampsia before 35	Noted. See also Addendum to the DAR

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				weeks' gestation was studied. COMPARE is the same population as in PELICAN study, and for PELICAN study the predictive value is acknowledged. In addition, later on in the document (e.g. tables 90-91) there is data for predictive value. The new study report from [redacted] (R01-17008) data in shows the prognostic accuracy performance for both sFlt-1/PlGF ratio and PlGF alone approaches with DELFIA Xpress tests in chapters 6.3-6.4 and 6.5, respectively. Prognostic accuracy is presented with different cut-offs.	
Perkin Elmer	42	84	4.1.2.2	*DELFIA Xpress PlGF test* *No data were available from add-on studies, however, one standalone study, COMPARE30 reported NPVs >0.912 for a range of delivery-related outcomes.* In the NICE de-brief meeting, the primary criteria was to demonstrate equivalence to the existing assays. This has been fulfilled. COMPARE shows the results for DELFIA Xpress PLGF are near identical to those tests recommended. DELFIA Xpress PlGF 1-2-3 specificity (0,770); sensitivity (0,857); PPV (0,402); NPV (0,972). are reported in COMPARE study and in additional data that is provided. Testing to predict delivery is provided in the R01-17008 report from [redacted] for the sFLT-1/PlGF study. The report provides performance data for both PlGF alone (Chapter 6.5) and the sFLT-1/PlGF ratio (Chapter 6.3-6.4).	Noted. We discuss the Giblin publication in section 4.1.3 under assessment of test concordance. See also Addendum to the DAR.
Perkin Elmer	43	87	4.1.3.2	*A trade-off was seen between sensitivity and specificity, with the Triage PlGF and DELFIA Xpress tests both having higher sensitivity, but lower*	We have removed the reference to SGA to avoid confusuion

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				specificity, than the Elecsys test. However, McCarthy et al. concluded that the tests' ability to predict delivery within 2 weeks did not differ significantly when using the specified cut-offs, with areas under the ROC curve being similar among the tests (full test accuracy statistics for the three tests are provided in the publication). The results from the Triage PlGF and Elecsys ratio tests were similar to those previously reported. Note that the population analysed in the COMPARE study does not fully match the NICE scope for the current review since it comprises women suspected of having pre-eclampsia as well as those suspected of having an SGA infant. The samples chosen and used for the COMPARE study were taken from Peaches & Pelican sample cohorts previously used to validate the Triage PlGF assay. It is incorrect that there were women with isolated suspected SGA. All women had suspected pre-eclampsia. SGA is only included as an additional feature of pre-eclampsia as stated in international definitions of pre-eclampsia. As communicated in the submission (confidential), a new study (evaluate sFLT-1/PlGF ratio) has been conducted at [redacted] Study includes 23 Healthy controls, 174 Suspected PE (not confirmed) and 164 suspected PE (confirmed).	
Perkin Elmer	44	87	4.1.3.2	*Giblin et al. conducted a further secondary analysis of PlGF samples from women in the PELICAN and PEACHES studies who presented with suspected PE or a suspected SGA infant (as assessed in the COMPARE Study.* *Giblin et al. reported the test performance statistics (sensitivity, specificity, PPV, NPV and likelihood ratios) for PlGF or the sFlt-1/PlGF ratio for predicting delivery within 14 days using the Quidel Triage, Roche Elecsys and* *Perkin Elmer DELFIA Xpress tests. They concluded that the Quidel and Roche tests have slightly different sensitivities and specifies, but AUCs were similar and the test had similar clinical applicability for prediction*	Noted. We discuss the Giblin publication in section 4.1.3 under assessment of test concordance. See also Addendum to the DAR.

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				of delivery. That said, there was a 3-fold difference in the rule-in thresholds for the Triage and DELFIA Xpress tests, 12 pg/mL and 50 pg/mL respectively, and the authors recommended the assessments could be standardised across tests, e.g. by converting biomarker concentrations to multiples of the median, to reduce the possibility of confusion. In addition to the publication, study R01-17008 conducted in [redacted] provides evidence of the equivalency between the assays for PlGF alone approach and for sFlt-1/PlGF ratio. Comparison results performed in [redacted] between Elecsys sFlt-1/PlGF and DELFIA Xpress sFlt-1/PlGF showed strong linear relation between assays. Providing additional evidence that similar performance can be expected between the assays reporting the sFlt-1/PlGF ratios.	
Perkin Elmer	45	88	4.1.4	*No clinical outcome data is available for the BRAHMS Kryptor sFlt-1/PlGF ratio test or DELFIA Xpress PlGF tests.* Data provided in Chapter 6.3-6.4 in R01-17008 report shows clinical performance with sFlt-1/PlGF and Chapter 6.5 for PlGF alone on DELFIA Xpress	This is an issue of terminology What we mean is maternal/neonatal etc clinical outcomes from care decisions based on the use of the test to diagnose/predict pre-eclampsia. R01-17008 defines clinical performance of the tests as an aid to predict pre-eclampsia within specified timepoints.
Perkin Elmer	46	107-108	4.3	Diagnostic accuracy data will be provided with the additional data we are providing. Chapters 6.3-6.4 and 6.5 in R01-17008 report shows clinical performance with sFlt-1/PlGF and PlGF on DELFIA Xpress	Noted. See also Addendum to the DAR.

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				respectively. Diagnostic accuracy measures with 95% confidence intervals presented.	
Perkin Elmer	47	111	5.1.3	*The studies suggest that including diagnostic tests alongside usual care has the potential to reduce maternal adverse events and reduce the number of women who receive inappropriate treatment (mainly hospitalisation) due to false-positive diagnoses. Six studies98-100 102 103 106 reported a cost saving within a range of £94 to £2,896 per woman tested due to the introduction of a first PlGF test in addition to usual care versus usual care alone. Five studies100 101 103 105 106 reported a cost saving between £26 and £607 for women who have received a retest. The study by Myrhaug and colleagues104 reported £3,710 as the cost per additional correctly identified case of pre-eclampsia.* By demonstrating clinical equivalence for the PlGF 1-2-3 through the COMPARE study, the only additional data required for the DELFIA assay is the cost data, which has been provided. As illustrated by the attached spreadsheet, the costs per reportable result are highly competitive for a new customer and even more so, for an existing customer. To ensure that some costs are not double counted, additional clarification has been provided in the spreadsheet and an updated version of DP 23 EAG	The cost of DELFIA tests (PlGF 1-2-3 and ratio tests) was estimated by the EAG and provided as part of the Addendum to the DAR "Calculation of DELFIA testing costs" (section 4).
Perkin Elmer	48	129	5.2	*Four companies - Quidel Ireland, Roche Diagnostics Ltd, Thermo Fisher Scientific and PerkinElmer Health Sciences - participated in the current diagnostic assessment. The companies provided economic evidence, together with evidence on test accuracy. Although all companies reported the costs of their biomarker tests (as described in section 5.4.7.3), they did not provide economic models.* NICE had not indicated that an economic model would be required. If this information had been requested, PerkinElmer could have commissioned an external economic assessment.	No comment.

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Perkin Elmer	49	129	*5.3*	*We also conduct scenario analyses for the Triage and Elecsys tests using the 'next best' line of evidence from prospective observational comparisons of PlGF-based add-on tests versus usual care alone: the analysis of MAPPLE/PELICAN cohort studies16 for the Triage PlGF test; and the PreOS before/after prospective study34 for the Elecsys sFlt-1/PlGF ratio.* Why couldn't scenario analyses be performed for PerkinElmer and Brahms just like it was done for Triage and Elecsys tests.	Please see our response to comment 30.
Perkin Elmer	50	129	5.3	*Evidence for the BRAHMS Kryptor sFlt-1/PlGF ratio tests is weaker. Andersen and et al 48 estimated predictive accuracy for the BRAHMS test as an add-on to usual care from retrospective cohort data, but this is only reported in a conference abstract, and is of limited use for economic analysis because of a lack of comparison with usual care. Salahuddin and colleagues47 reported accuracy for prediction of adverse events within 2 weeks for both the BRAHMS and Elecsys tests by reanalysing frozen samples from the ROPE cohort study.45 They estimated an identical area under the curve (AUC) for the two tests, using a model that also accounted for systolic blood pressure and proteinuria.* ***We therefore present a simple cost-comparison analysis between BRAHMS and Elecsys, based on an assumption of equal predictive accuracy****. We note that this analysis is subject to uncertainty due to the context of the ROPE cohort study45 (standalone tests in a single US centre) and the study population (women with gestational age outside of 20 – 36-week range).* Cost-comparison analysis was performed for Triage, Elecsys and for BRAHMS platform making assumption of equal predictive accuracy. Why was PerkinElmer treated differently? See the next comment no. 21.	Please see our response to comment 30.
Perkin Elmer	51	130	5.3	*"A cost-effectiveness analysis for the DELFIA Xpress PlGF 1-2-3 test could potentially be informed by the COMPARE study, which compared the performance of three tests (standalone use) – Triage, Elecsys and*	Please see our response to comment 30.

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				DELFIA. (see Section 4.1.3). However, it has not been possible to conduct such an analysis in the time available" It is stated that DELFIA Xpress PlGF 1-2-3 cost-effectiveness analysis was not performed due to lack of time. With Brahms, an assumption was made for predictive assay., The COMPARE study has proven the equivalence of process between DELFIA and Elecsys and DELFIA and Triage, thus it can be very easy to do a comparable workflow and cost analysis. We consider it fair and equitable, for a similar workflow and cost analysis to be performed for DELFIA Xpress PlGF 1-2-3. Why there wasn't enough time to do the cost-effectiveness analysis for PerkinElmer's DELFIA products yet there was time to do the analysis for other products?	
Perkin Elmer	52	131	Table 51	**Table 51 Test accuracy and clinical effectiveness evidence included in the economic model** COMPARE is listed but excluded from evaluation in the economic modelling. We do not understand why this is the case.	Please see our response to comment 30.
Perkin Elmer	53	134	5.4.2	*In the base-case analysis, the relative effectiveness of Triage and Elecsys PlGF-based testing when used in addition to standard clinical assessment versus standard clinical assessment without PlGF-based testing was estimated from two clinical trials, the PARROT9 and INSPIRE32 RCTs (see section 5.1.3 above). We also present a simple cost-comparison for the BRAHMS ratio test based on similar estimates of predictive accuracy of the BRAHMS and Elecsys tests from the Salahuddin case-control study.47* Quidel state in their submission to NICE that the Triage PlGF test can be used in women presenting with signs and symptoms of pre-eclampsia prior to 35 weeks of gestation. However, the population in the PARROT trial, which informed the base-case analysis for this test was the same as in the NICE scope,(8)i.e. women with	Please see our response to comments 9 and 30.

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				gestational age from 20 weeks up to 36 weeks and 6 days (Duhig 2021). The population in the base-case analysis for the Elecsys immunoassay sFlt-1/PlGF ratio test (women with gestational age from 24+0 to 37+0 weeks, as shown in Table 52) is the same as that defined in the Roche's submission for the short-term prediction of pre-eclampsia. This is based on the study population in the INSPIRE RCT. For the BRAHMS test, the accuracy estimates were derived from the same source as for Triage - the PARROT trial,(9) with the population of women at gestational age of 20 - 36+6 (Table 52), which is in line with the population for which this test is suitable >20 weeks of gestation. PerkinElmer's DELFIA Xpress PIGF1-2-3 was again excluded, despite the fact that a similar comparative approach, afforded to Brahms could have been employed. Data from the new clinical study is provided. Chapters 6.3-6.4and 6.5 in R01-17008 report shows clinical performance with sFlt-1/PlGF and "PlGF alone" on DELFIA Xpress, respectively. Reporting is divided into two groups:20^{+0} – 33^{+6} and 34^{+0} – delivery	
Perkin Elmer	54	135	5.4.7	*The model parameters include test accuracy, clinical inputs (such as onset of labour, mode of delivery and birth outcomes) and costs (including the costs of testing, hospitalisation, ante-natal management, delivery and the costs of managing complications). Resource use assumptions for costing diagnostic and management strategies are presented in section 5.4.7.2. Unit costs were taken from UK sources for the most recent available year. Parameters included in the model are discussed in the following sections. An overview of all model parameters and model assumptions is provided in Appendix 10.*	Noted. Please see Addendum to the DAR which includes an analysis of the DELIFA PlGF 1-2-3 assay

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				PerkinElmer provided relevant model parameters to conduct analysis for the DELFIA assay. Additional supporting data has been provided in R01-17008	
Perkin Elmer	55	148	5.4.7.1	*In the cost-comparison between BRAHMS and Elecsys, based on the* ***assumption of equal predictive accuracy of these tests,*** *the clinical effectiveness evidence was the same as for the Elecsys test – the INSPIRE RCT (Cerdeira 201932) in the base-case (section 5.5.1) and PreOS (Klein 201679) in a scenario analysis (section 5.5.2).* Analysis performed for Brahms assay was based on "assumption of equal predictive accuracy"between BRAHMS and Elecsys Although the COMPARE study provides sufficient evidence to derive a similar conclusion between PerkinElmer's DELFIA Xpress PlGF 1-2-3 and Quidel's Triage, PerkinElmer's assay was not included to the cost comparison or any other assessments. The new data in R01-17008 report can be used to confirm the assumption of equal predictive accuracy supporting the conclusions from The COMPARE study.	Noted. Please see Addendum to the DAR which includes an analysis of the DELIFA PlGF 1-2-3 assay
Perkin Elmer	56	148	5.4.7.3	*In this economic evaluation we assumed there is no cost associated with standard clinical assessment as this is a component of both the intervention and the comparator. We do, however, estimate the incremental cost of the PlGF-based tests. Test costs were estimated from information provided by the test manufacturers to NICE, and from clinical experts and laboratory staff who use the Triage PlGF test and Elecsys sFlt-1/PlGF ratio test in clinical practice. Where information was unavailable for certain cost items, we made reasonable assumptions to inform our cost estimates.* *The estimation of the cost of the tests considered the following components:*	Noted. Please see Addendum to the DAR which includes an analysis of the DELIFA PlGF 1-2-3 assay

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				• *Cost of test kit (for Triage PlGF test and BRAHMS Kryptor sFlt-1/PlGF ratio test)* • *Charge per reportable test, includes capital, maintenance and equipment costs (for Elecsys sFlt-1/PlGF ratio test)* • *Machine costs* • *Service charges and maintenance costs* • *Equipment (laboratory materials and consumables)* • *Staff time for training* • *Staff time to perform and analyse test and staff time for quality control* • *Phone calls to communicate test results* All the data requested for the cost analysis for the DELFIA Xpress PlGF 1-2-3 test were provided, however, to our surprise, the calculation was not performed, and our assay is not included in the cost calculation model. PerkinElmer's DELFIA PlGF 1-2-3 and sFLT-1/ PlGF ratio was not included. To facilitate the cost analysis, a new spreadsheet has been prepared. Please be aware that most customers now request a "price per reportable result". For PerkinElmer this includes ALL components necessary to operate the instrument, service and consumables. Therefore, any shortfall in components required for analysis is covered by the manufacturer.	
Perkin Elmer	57	149	Table 54	*Table 54 Cost components and total cost of PlGF tests used in the base case analysis* PerkinElmer's DELFIA PlGF 1-2-3 and sFLT-1/ PlGF ratio was not included.	Please also see our response to comment 30.

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Perkin Elmer	58	149	5.4.7.4	*Where possible, we used data from PARROT9 for the Triage PlGF test and data from INSPIRE32 for the Elecsys sFlt-1/PlGF ratio test. For time to delivery, onset of delivery and mode of delivery parameters, we used data from PARROT9 for both tests since no information were reported by the studies for the Elecsys sFlt-1/PlGF ratio test. For the remaining missing data,* ***we have made some assumptions*** *based on the inputs used in the previous DAR,7 discussed below. For the BRAHMS Kryptor sFlt-1/PlGF ratio test, we assumed the same resource use and costs as for Elecsys sFlt-1/PlGF ratio test, with the exception of the cost of the test itself* The same process and assumption could have been made also for DELFIA, but this was not the case.	Please see our response to comment 30.
Perkin Elmer	59	162	5.5.1.2	*Table 61 Base-case: breakdown results for Elecsys sFlt-1/PlGF ratio test* Why are the standard assessment costs different from those in the Table 59. Base-case: breakdown results for Triage PlGF test are presented in table 59 p.161	The costs in the no testing arms in the base-case analyses for Triage and Elecsys were based on outcomes reported in different RCTs, PARROT and INSPIRE. Please see response to question 4D above.
Perkin Elmer	60	163	5.5.1.3	Why PerkinElmer breakdown results not performed as it is shown for other products in the document? For BRAHMS the breakdown was performed by using Roche's Elecsys numbers. Similarly, for DELFIA, Triage numbers could have been utilised.	Please see Addendum to the DAR which includes an analysis of the DELIFA PlGF 1-2-3 assay
Perkin Elmer	61	174	7.1.2	*The results of the cost-comparison analysis of the BRAHMS Kryptor sFlt-1/PlGF ratio, based on the assumption of equal predictive accuracy to that of the Elecsys sFlt-1/PlGF ratio test,47 were the same as for the cost-effectiveness analysis of the Elecsys test, that is, standard clinical assessment alone dominates use of testing alongside standard clinical assessment.*	Please see our response to comment 30.

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				The cost comparison analysis of the BRAHMS Kryptor sFlt-1/PlGF ratio was based on the assumption of equal predictive accuracy to that of the Elecsys sFlt-1/PlGF ratio test. The cost comparison analysis for DELFIA Xpress PlGF 1-2-3 could have been performed equally with assumptions based on equal predictive accuracy to that of the Triage PlGF assay	
Perkin Elmer	62	175	7.2.2	*It was not possible to meta-analyse the test accuracy and clinical effectiveness studies due to notable heterogeneity in study designs, scope and outcome measures.* *A fully incremental cost effectiveness analysis of the four PlGF tests relevant to the decision problem was not possible, due to the lack of data for because of available clinical effectiveness data limitations for the BRAHMS Kryptor sFlt-1/PlGF ratio and the BRAHMS Kryptor sFlt-1/PlGF ratio.* *It was not possible to compare the performance of the Triage and Elecsys tetsts directly because the clinical effectiveness evidence for these tests came from different studies. For the BRAHMS test we assumed similar effectiveness as for Elecsys based on Salahuddin et al.47 and the overall costs for these tests were assumed to be the same except for the cost of testing. This analysis, however, is subject to uncertainty due to the context of the ROPE cohort study45 which has the same caveats as the analysis for Elecsys.* The text states that a fully incremental cost effectiveness analysis of the four PlGF tests relevant to the decision problem was not possible, due to the lack of data for because of available clinical effectiveness data limitations for the BRAHMS Kryptor sFlt-1/PlGF ratio and the BRAHMS Kryptor sFlt-1/PlGF ratio, But it was performed by assuming similar effectiveness as for Elecsys Equally, the cost effectiveness analysis for DELFIA test could have been performed assuming similar effectiveness as for Triage.	Please see our response to comment 30.

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Perkin Elmer	63	208	Appendix 3.	*Tables of excluded studies with rationale* *Table 69 References excluded from the test accuracy review at full-text screening Reference* — *Exclusion reason: first reason identified* *Giblin 202071* — *(1) Not primary diagnostic research* Why has the supporting data been excluded? This was a peer reviewed paper, where the primary purpose was to develop cut-offs for the PIGF 1-2-3 assay. If this was an unacceptable approach, the paper would not have been published. This approach was considered valid by Prof. Andrew Shennan.	Giblin is a publication from the COMPARE study. Giblin's publication is discussed in section 4.1.3 of the DAR 'Concordance between tests'. See also Addendum to the DAR
Perkin Elmer	64	212	Appendix 4.	Appendix 4. Concordance studies Table 72 Predictive concordance studies **Study** — **Tests compared** — **Comments** **Triage PIGF** — **Elecsys ratio** — **BRAHMS Kryptor ratio** — **Delfia Xpress** Black 2019 72 — PIGF, sFlt-1 — ● a — ● — ● — ● — Screening at 19-22 weeks for developing PE and other adverse outcomes in a normal pregnancy population.	Noted

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				2019 74 PlGF, sFlt-1 ● a ● ● Tests were comparable in predictive capability but using test cut-offs not relevant to the current review. Screening at 19+0 to 24+6 weeks for PE development in a normal pregnancy population. Tests were comparable in predictive capability but based on a PE screening cut-off not relevant to the current review. Cheng 2019 70 PlGF, sFlt-1, sFlt-1 ratio ● ● ● Normal pregnancies, 20-39 weeks GA, Chinese population. There were	

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				notable inter-test differences in sensitivity and cross-reactivity to PlGF and sFlt-1 isoforms between the tests, meaning that rule-in and rule-out cut-offs for PE prediction are test-specific. McCarthy 2019 30 PlGF, sFlt-1/PlGF ratio • • • Women with suspected PE or suspected SGA before 35 weeks and between 35 and 36+6 weeks GA. Test cut-offs were relevant to the current review. The Alere, Roche and	

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				Perkin Elmer tests Regardless of the rule-in and rule-out cut-offs, which are concluded to be for PE prediction test-specific, the papers demonstrate equivalency between different manufacturer tests.	
Perkin Elmer	65	N/A	N/A	*2nd June 2021* ***Donna Barnes*** *Project Manager - Diagnostics Assessment Programme* *National Institute for Health and Care Excellence* *Level 1A, City Tower, Piccadilly Plaza, Manchester M1 4BT* *Dear Donna,* ***RE: PerkinElmer submission for the Placental growth factor (PlGF)-based testing to help diagnose suspected pre-eclampsia (update of DG23)*** *We have submitted the following documents for review by the Diagnostic Assessment committee:* • *Official response to the DAP23* [redacted]	

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				[redacted] • *Clarification of PerkinElmer price per reportable results for PIGF 1-2-3 and sFLT-1/PIGF ratio (spreadsheet)* • *Updated DP23 EAG Questions (additional clarification)* • *Supporting customer Letter ([redacted]), explaining the impact on PIGF 1-2-3 price per reportable result, when the instrument is already in-situ, with the instrumentation and service costs covered by routine aneuploidy screening.* [redacted] • *DAP 53 PIGF Checklist of confidential information* *Please accept our apologies for the delayed submission of the supporting [redacted] data. The original timeline for completion of this study, was December 2020, but it was postponed on several occasions as the study investigators were seconded to cover Covid-19 duties.* *We trust that the new evidence provided, will address the gaps previously identified. PerkinElmer has a long history in pre-eclampsia, having initiated research into Pre-eclampsia biomarkers in 2004 working with Professor Lucilla Position and Professor Andrew Shennan.* *We believe we are the only company who offers genuine choice to the customer and to the NHS. Our second generation PIGF 1-2-3 kit was validated in the ASPRE (EuFP7 funded) and SPREE (NIHR funded) studies for 1st Trimester prediction of pre-term Pre-eclampsia.* *PerkinElmer offers the PIGF 1-2-3 and sFLT-1 kits as separate kits. By offering separate kits a customer can choose to:*	

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				a) Use the PlGF 1-2-3 kit for 1st Trimester prediction of pre-term PE and aid in diagnosis for all suspected PE in the 2nd and 3rd Trimester *b) If prediction testing is not offered in 1st T, use for aid in diagnosis for all suspected PE in the 2nd and 3rd T* *c) Use the PlGF 1-2-3 kit for 1st Trimester prediction of pre-term PE and the sFLT-1 kit & the same PlGF 1-2-3 kit as the sFLT-1/PlGF ratio for aid in diagnosis for all suspected PE in the 2nd and 3rd T* *d) If prediction testing is not offered in 1st Trimester, use the sFLT-1 kit and the PlGF 1-2-3 kit for the sFLT-1/PlGF ratio for aid in diagnosis for all suspected PE in the 2nd and 3rd T* *Using the same PlGF assay which has been designed and optimised for all trimesters, as the name PlGF 1-2-3 (1st, 2nd, 3rd Trimester) implies, the customer can benefit from increased volumes of tests, when combining prediction and aid in diagnosis. This reduces the impact of the instrumentation on the cost per reportable result, improving the effective price per patient assessment.* *PerkinElmer has demonstrated clinical efficacy and flexibility in product offering, to ensure maximum potential access to all women, at an affordable price for the NHS.* *Yours sincerely,* *Yvonne Parker*	

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				Yvonne Parker MSc MBA ***Vice President, Market Development, Reproductive Health***	
Perkin Elmer	66	N/A	N/A	[redacted] 2, June 2021 Diagnostics Assessment Programme National Institute for Health and Care Excellence Level 1A, City Tower, Piccadilly Plaza, Manchester M1 4BT **To whom it may concern,** **RE: Placental growth factor (PlGF)-based testing to help diagnose suspected pre-eclampsia (update of DG23)** [redacted]	

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				[redacted]	

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				[redacted]	

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				[redacted]	

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				[redacted]	
Perkin Elmer	66	N/A	N/A	Ref: DMF_PlGF 26th May 2021 [redacted]	

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				[redacted] To whom it may concern, Perkin Elmer PlGF-123 Analysis I am writing to support the approval of the Perkin Elmer PlGF-123 assay for use in the diagnosis of Pre-eclampsia. [redacted]NHS Trust has run a successful Trisomy Screening service for over 25 years, covering the population of [redacted]. The laboratory also offers a private Non-Invasive Prenatal Testing (NIPT) testing service. In order to continue to provide the highest quality prenatal care for our population the laboratory now aims to develop a Pre-eclampsia testing service for the diagnosis of this condition in the Third Trimester with the ultimate aim of developing a First Trimester Pre-eclampsia screening service. Based on our initial costing projections the introduction of a Pre-eclampsia First-Trimester Screening service would result in an annual saving of £1,527,400 (based on a predicted reduction of 1400 bed days as stated in the ASPRE study in the Neonatal Unit). We have fully validated the PlGF-123 assay in our laboratory and our clinical teams have approved a one year pilot project to introduce this assay into our service. Full ethical approval of our study has been attained from the HRA and Care Research Wales (HCRW) Research Authority as all parties have concluded that the introduction of this assay will be clinically significant but also cost-effective. The laboratory validation has been successfully submitted and approved in principal as an extension to scope by the United Kingdom Accreditation Service (UKAS) and we are awaiting final documentation for this. Placental Growth Factor (PlGF) testing has been demonstrated to rule-out the diagnosis of suspected pre-eclampsia, as endorsed by the National Institute for Health and Care Excellence (NICE	

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Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
				Diagnostics Guidance 2016). The introduction of PlGF has been demonstrated to be cost-effective (reducing cost per patient by £945 (Hadker et al, (2010)) by improving resource targeting and avoiding inappropriate patient hospitalisation. The difference in costing strategies between manufacturers was not insignificant in our decision to introduce the Perkin Elmer PlGF-123 assay. Perkin Elmer current pricing strategies ([redacted]) compared to alternative manufacturers (£94.00 per reportable test) will allow the introduction of this clinically important test. Upon removal of the ITP funding our laboratory would not be in the position to offer PlGF-123 testing from alternative manufacturers as the costs could not be adsorbed by clinical team budgets without negatively impacting other services. As the majority of screening laboratories already have Perkin Elmer technology the approval of the Perkin Elmer PlGF-123 assay would allow this test to be more accessible as additional instrumentation would not be required in order to provide this service and there would be no requirement for further maintenance contracts and electronic interfaces which all require additional funding. As pre-eclampsia typically affects 3% of pregnancies and is one of the leading causes of maternal and perinatal morbidity and mortality it is a well-recognised but treatable condition. Perkin Elmer is currently the only manufacturer to offer a standalone PlGF assay which has been clinically validated with the Compare Study. Approval of this assay would allow laboratories to introduce a validated, more cost-effective service for Pre-eclampsia diagnosis. My concern is that if alternative, more cost-effective assays, are not considered for approval PlGF will not be widely available to all pregnant women and this will lead to significant inequality in the standard of care provided. As it is envisaged that the introduction of PlGF-123 testing for the rule-out of pre-eclampsia will allow women at low risk to return to community care this will ensure more effective use of NHS resources, ultimately providing a better patient pathway.	

PlGF-based testing to help diagnose suspected pre-eclampsia (update of DG23)

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
				Thank you for your time concerning this matter. Kind regards [redacted]	

1. National Institute for Health and Care Excellence (NICE). Diagnostics Assessment Programme manual. Manchester: National Institute for Health and Clinical Excellence 2011.
2. de Almeida FA, Al MJ, Koymans R, et al. Impact of hospitalisation on health-related quality of life in patients with chronic heart failure. *Health Qual Life Out* 2020;18(1)
3. Cerdeira AS, O'Sullivan J, Ohuma EO, et al. Randomized Interventional Study on Prediction of Preeclampsia/Eclampsia in Women With Suspected Preeclampsia: INSPIRE. *Hypertension* 2019;74(4):983-90. doi: 10.1161/HYPERTENSIONAHA.119.12739 [published Online First: 2019/08/14]
4. Duhig KE, Myers J, Seed PT, et al. Placental growth factor testing to assess women with suspected pre-eclampsia: a multicentre, pragmatic, stepped-wedge cluster-randomised controlled trial. *The Lancet* 2019;393(10183):1807-18. doi: 10.1016/s0140-6736(18)33212-4

NICE National Institute for Health and Care Excellence

PlGF-based testing to help diagnose suspected pre-eclampsia (update of DG23)

Model - Comments

Stakeholder	Comment	Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	EAG response
Roche Diagnostics Limited	1	The problems we have identified with the economic model are conceptual rather than mechanical so they are detailed in the table above.	We would recommend redeveloping the model using a linked evidence approach so that improved diagnostic test accuracy leads to better outcomes for patients.	We expect both tests would be dominant if this is done.	
Perkin Elmer	2	Cost per test analysis could have been done to DELFIA Xpress PlGF 1-2-3	Cost per test analysis could have been done to DELFIA Xpress PlGF 1-2-3	Can be utilized when DELFIA Xpress PlGF 1-2-3 is fully included to the DRAFT assessment with additional data provided.	
Perkin Elmer	3	The diagnostic assessment report excluded DELFIA Xpress PlGF 1-2-3 from many parts and such assessments were not perfomed which would have been the basis to create the economic model.	Economic model to be created for DELFIA Xpress PlGF 1-2-3. There is enough data to create the model-	A fair inclusion of the DELFIA Xpress PlGF 1-2-3assay to the assessment	

COMPARISON OF SFLT-1/PLGF ASSAYS

OBJECTIVE

A comparison study between two platforms, Roche Cobas e411 and PerkinElmer DELFIA Xpress, providing sFlt-1 and PlGF assays was performed at the [redacted]

A total of 285 pregnancy samples (GA>20) were analysed using both platforms and the correlation between platforms and sFlt-1/PlGF ratio results were evaluated. The samples analysed were including both fresh and stored pregnancy serum samples.

The objective of the comparison was to compare the assays of the two platforms and show the relationship between the platforms.

SAMPLE POPULATION, SAMPLE RUNS AND OBTAINED DATA

All samples were from women who presented with signs or symptoms of preeclampsia in the 3rd trimester of pregnancy; and where an sFlt-1/PlGF ratio was requested as part of standard clinical management.

Samples were run from the same primary sample tube or aliquot using both platforms during the time-period January 2019 to May 2021. The validity of each run was assured using quality control material; DELFIA Xpress using PlGF Controls (prod no 3090-0010) and sFlt-1 Controls (prod no 3246-0010) and Cobas PreciControl Multimarker (prod no 05341787190).

The obtained ratio values ranged over the entire clinically relevant range. Appendix 1 displays the results for individual samples as concentrations and the sFlt-1/PlGF ratio for both platforms.

PLATFORMS AND KITS USED

Samples were run using two different platforms, the Cobas e 411 immunoassay analyzer (Roche Diagnostics, Germany) and the 6000 DELFIA® Xpress clinical random access screening platform (PerkinElmer Health Sciences, US).

The assay reagents used for analysis were the Elecsys sFlt-1and Elecsys PlGF kits (prod no 05109523190, 05144671190 respectively) from Roche Diagnostics and DELFIA Xpress sFlt-1 and DELFIA Xpress PlGF 1-2-3 kits (prod no 6009-0010 and 6007-0030, respectively) from PerkinElmer Health Sciences.

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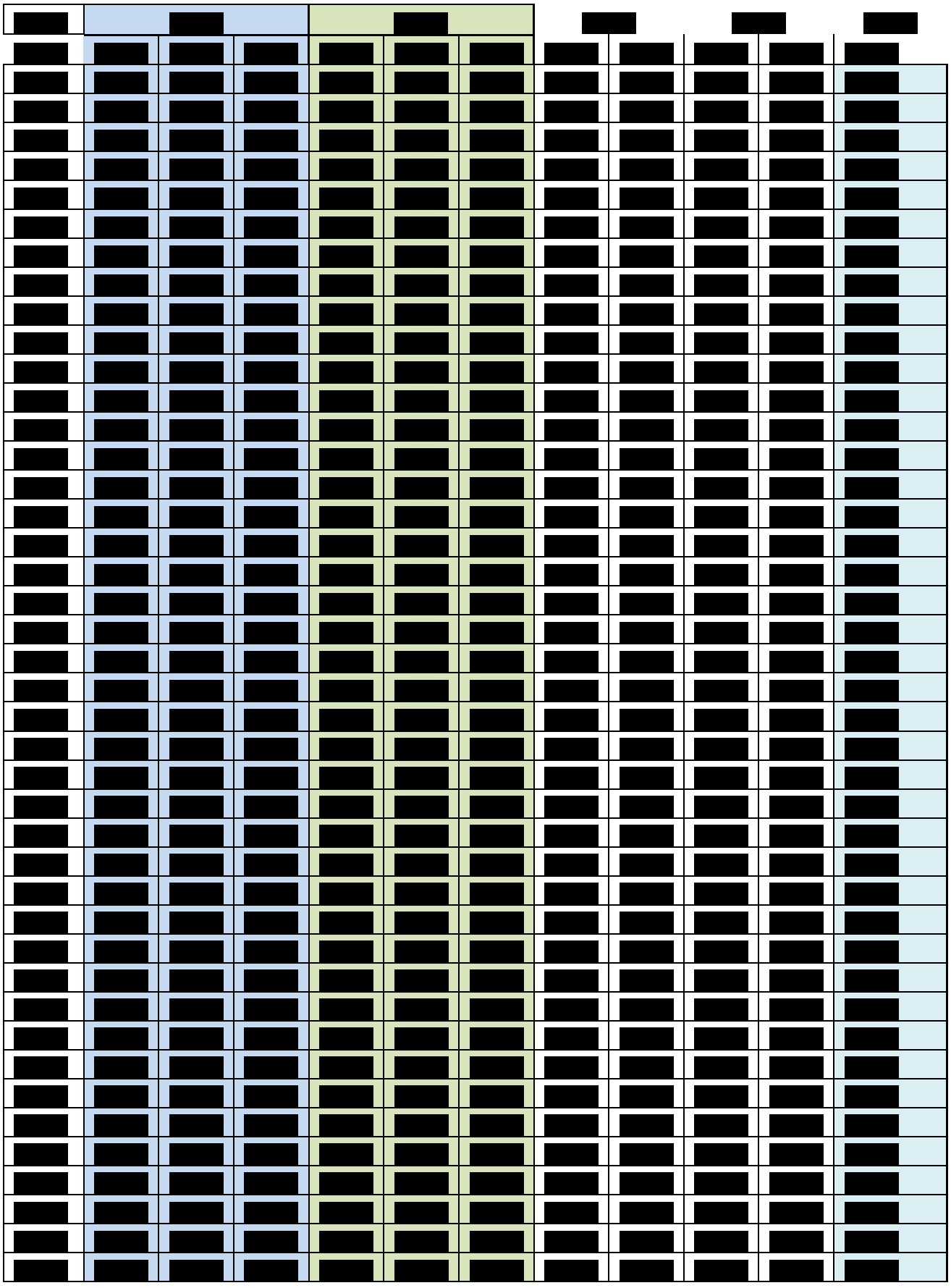

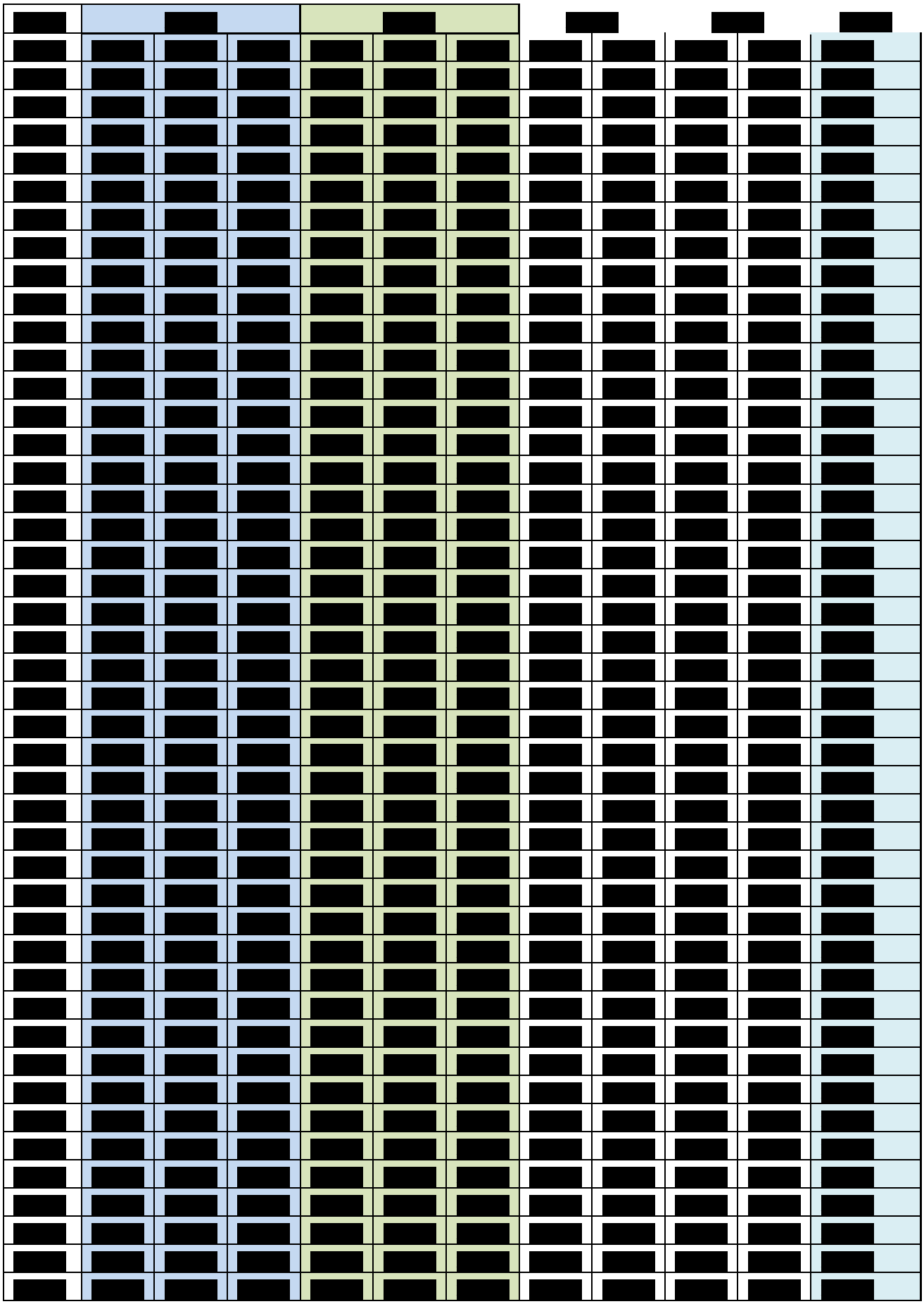

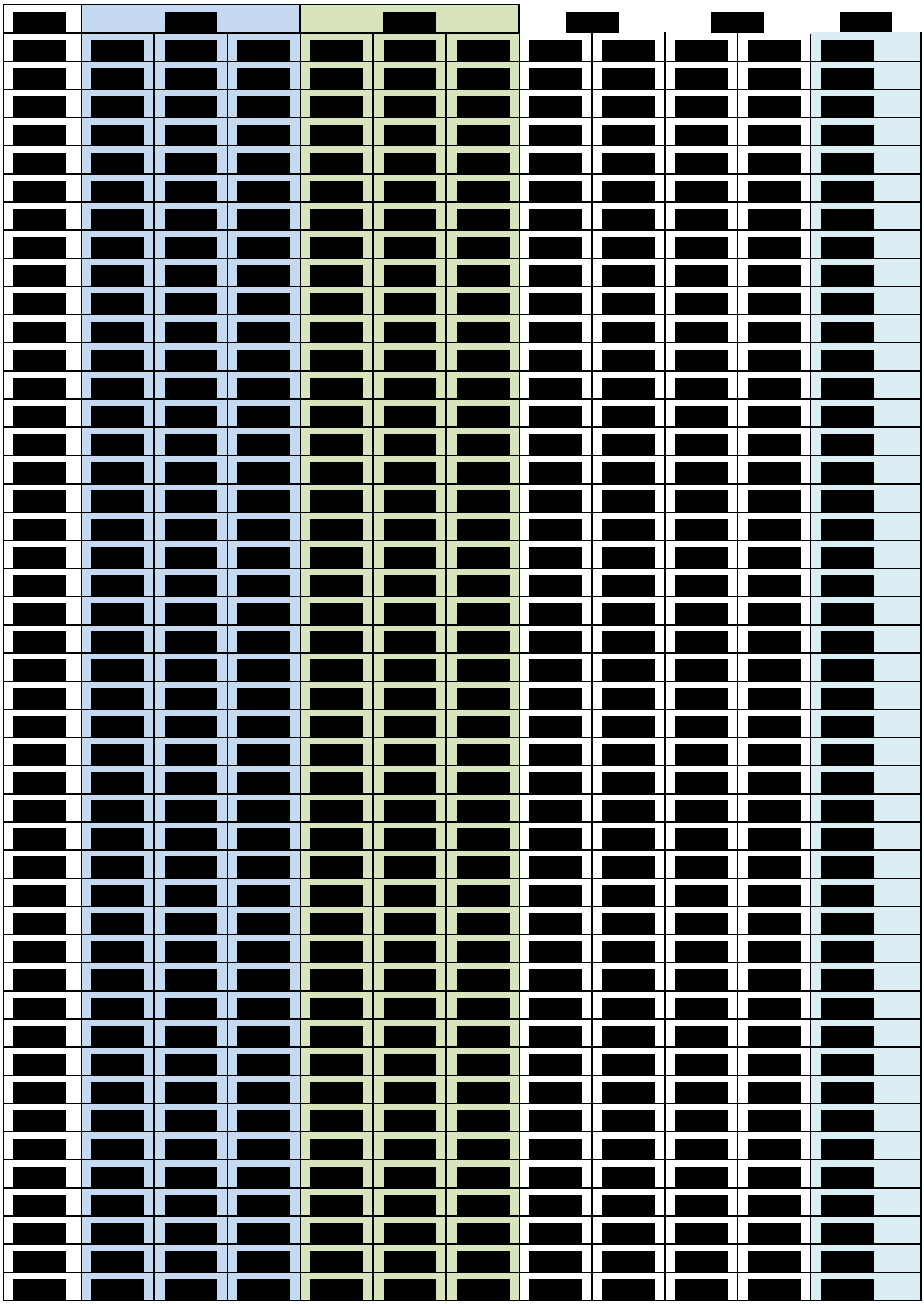

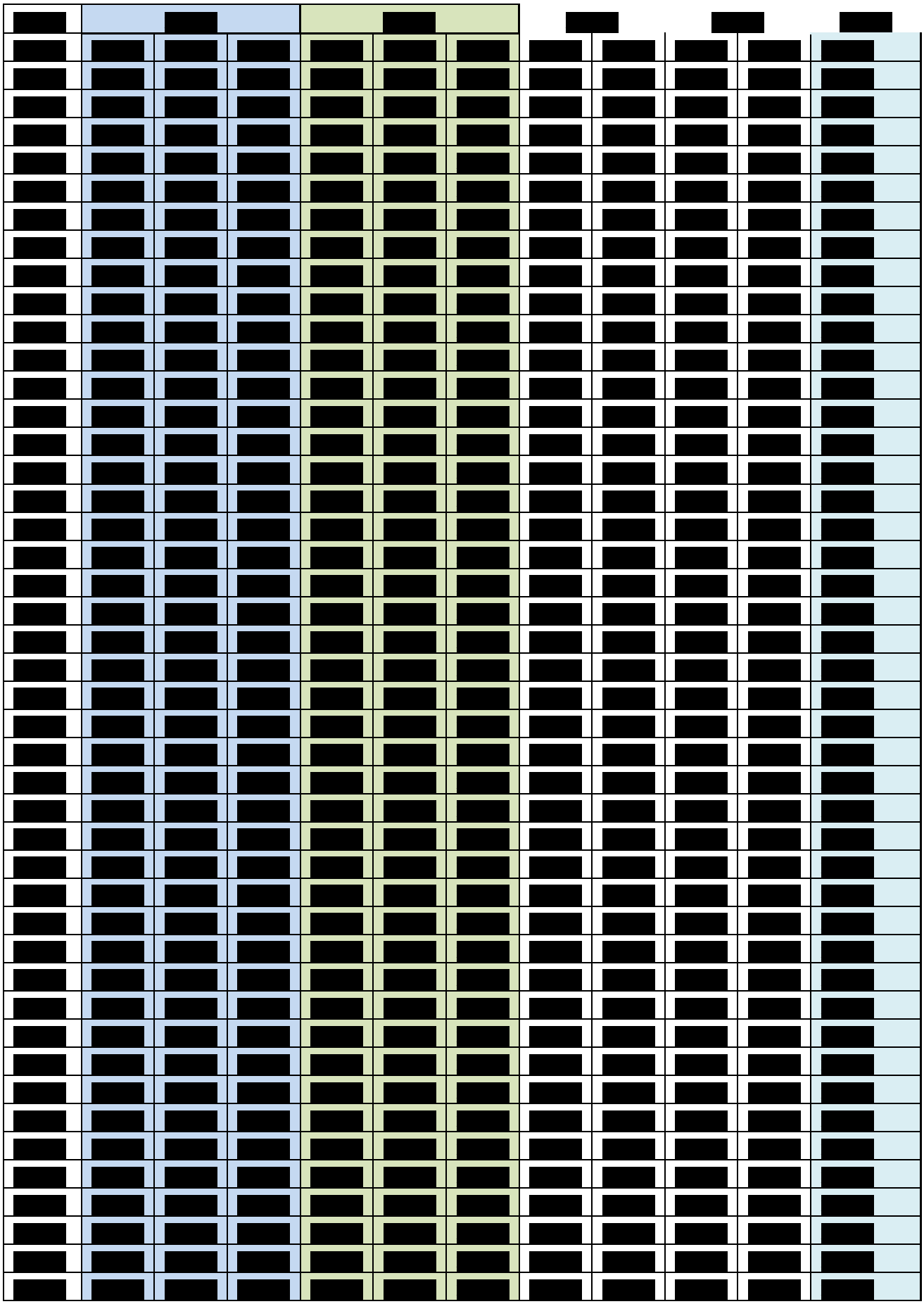

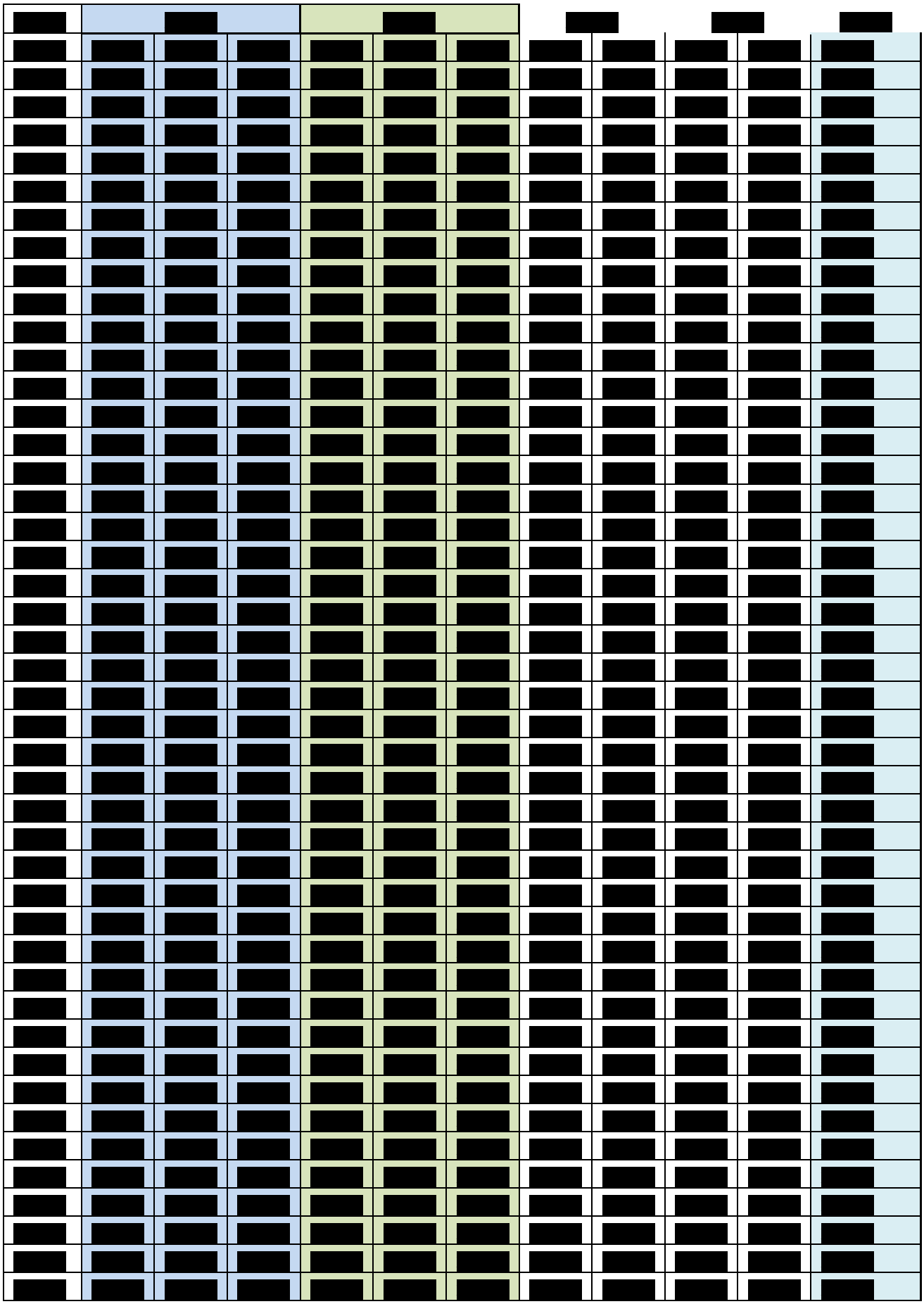

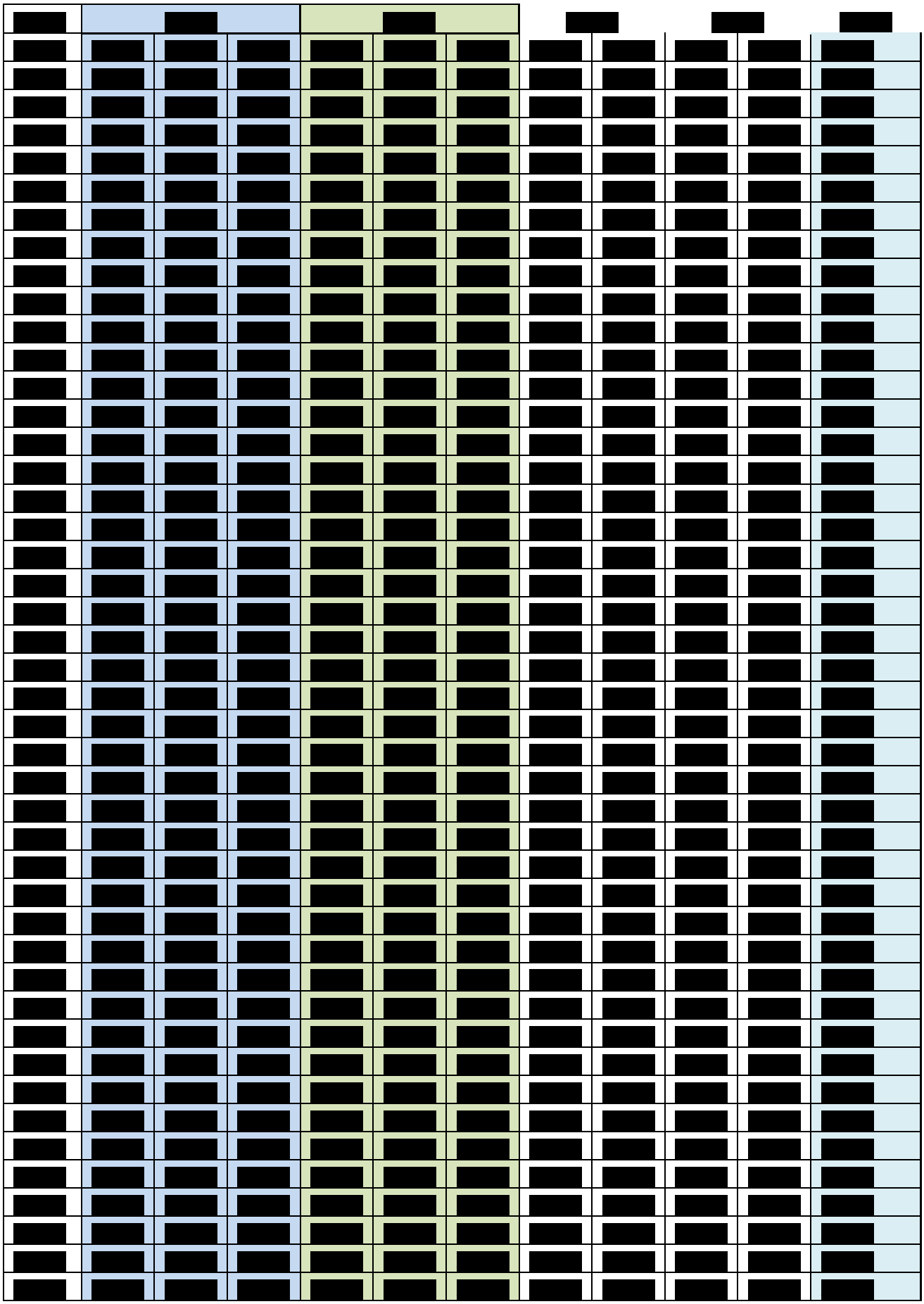

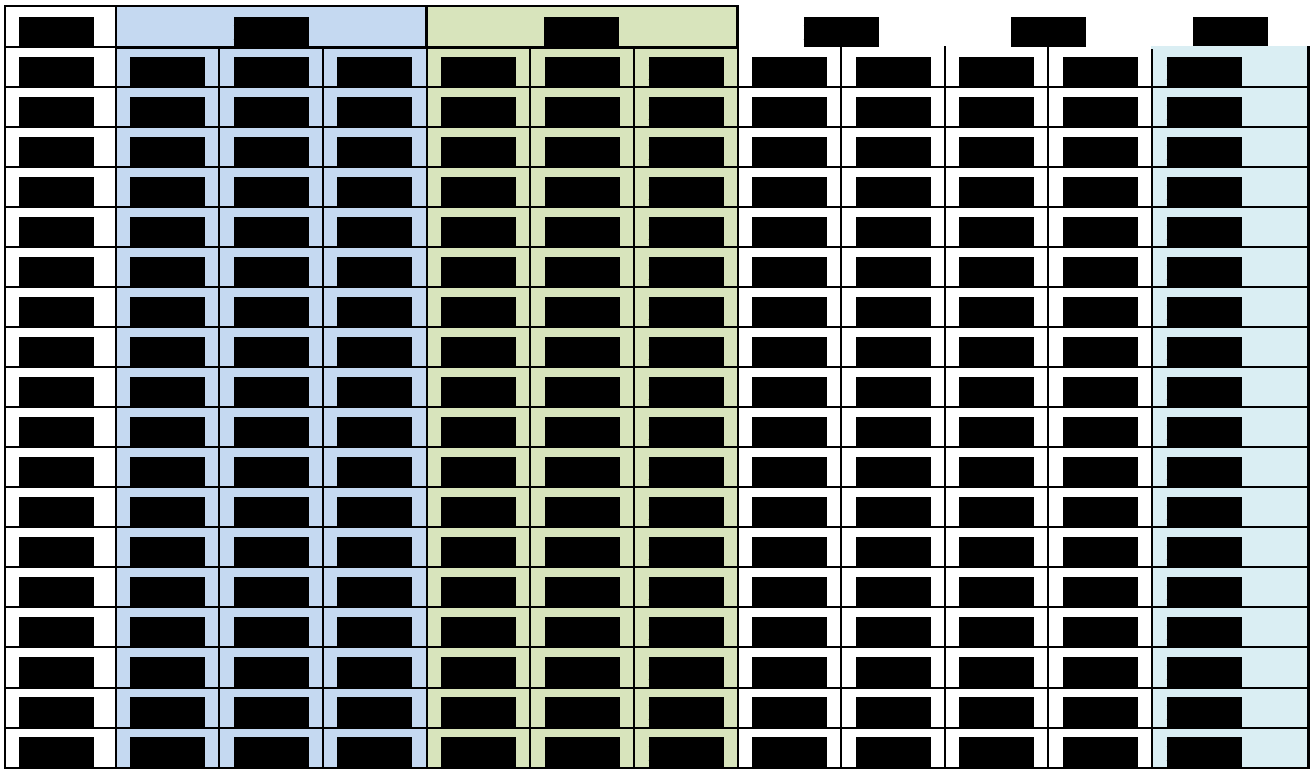

Info previously provided

Quotes have been provided as price per sample, on a five year reagent rental basis to include:

Instrument

1x DELFIA Xpress instrument	6001-0010
Platinium Service Contract including 2 preventive maintenance visits	SVC-DX

Assay kits

DELFIA Xpress PlGF 1-2-3 assay kit	6007-0030
PlGF controls	3090-0010
DELFIA Xpress sFlt-1 kit	6009-0010
sFlt-1 kit controls	3246-0010

Consummables

Inducer	3027-0010
Wash concentrate	3014-0010

Testing with PlGF 1-2-3 only

Quote	Samples / Year	Price / Sample
A	500	£58.30
B	1000	£50.00
C	6000	£13.00

Testing with PlGF 1-2-3 and sFlt-1

Quote	Samples / Year	Price / Sample
A	500	£100.00
B	1000	£70.00
C	6000	£19.00

Pricing reviewed and updated
Minor changes for 500 and 1000 samples per year
Assumption for 6000 incorrect (6000 PlGF and 1000 sFLT-1)

PlGF 1-2-3

Assumption: Price per reportable result = instrumentation, service, PlGF 1-2-3 kits, controls, inducer, wash solution, carryover material, all consumables

	Existing Customer	New Customer	Comment
Aneuploidy customer	Yes	No	
Instrument Cost List Price £36,990 +VAT	N/A covered by Aneuploidy screening	Assume depreciated over 5 years and factored into price per reportable result	
Service Contract per annum £4439 + VAT (1st year FOC)	N/A covered by Aneuploidy screening	Factored into price per reportable result	
List Price PlGF kit (96 wells) + VAT	£722	£722	
PlGF only / price per reportable result 500 samples/ year for Aid in Diagnosis at list price (assumes 1-2 samples /day plus 3 controls per day).	£26	£58.30	Includes all instrumentation /service for new customer and consumables/ controls/ kits necessary for all customers to provide results for 500 patients. Assumes 18 kits of PlGF. Assumes List Price for PlGF kit. Assumes calibration in duplicate each change in lot number
PlGF only / price per reportable result 1000 samples/ year for Aid in Diagnosis (assumes 2-3 samples/day plus 3 controls per day NHS guidance (morning/middle of day and evening)	£16.60	£50.00	Includes all instrumentation /service for new customer and consumables/ controls/ kits necessary for all customers to provide results for 1000 patients. Assumes 23 kits of PlGF. Assumes List Price for PlGF kit. Assumes calibration in duplicate each change in lot number (quarterly)
PlGF only/ price per reportable result 6000 samples/ year (assumes 5000 1st T pre-term PE prediction and 1000 Aid in Diagnosis), plus 3 controls per day	£9.15	£13.00	Includes all instrumentation /service for new customer and consumables/ controls/ kits necessary for all customers to provide results for 6000 patients. Assumes 76 kits for PlGF. Assumes List Price for PlGF kit
Technician time / calibration & daily maintainence	Maintainence/ carry-over process already covered for Aneuploidy screening. Including QC for PlGF (5 mins) Calibration once per quarter (1 hour)	Maximum 1.5 hour per day / 1 hour (morning) 30 minutes (late afternoon). Calibration (standard curve in duplicate) once per quarter (1hour)	Reagents are loaded at the beginning of the day for tests. Kit required for calibration included in cost per reportable result
Technician time to run the test (post centrifugation)	15 minutes to load sample/ reagents and 10 minutes to read result /check QC	15 minutes to load sample/ check reagents and 10 minutes to read result/ check QC	

sFLT-1 PlGF ratio

Assumption: Price per reportable result = instrumentation, service, PlGF 1-2-3 kits, controls, inducer, wash solution, carryover material, all consumables

	Existing Customer	New Customer	Comment
Aneuploidy customer	Yes	No	
Instrument Cost List Price £36,990 +VAT	N/A covered by Aneuploidy screening	Assume depreciated over 5 years and factored into price per reportable result	
Service Contract per annum £4439 + VAT (1st year FOC)	N/A covered by Aneuploidy screening	Factored into price per reportable result	
List Price PlGF kit (96 wells) + VAT	£722	£722	
List Price sFLT-1 kit (96 wells) + VAT	£944	£944	
sFLT-1/PlGF ratio price per reportable result 500 samples/ year at list price (assumes 1-2 samples /day plus 3 controls per day).	£60	£93.00	Includes all instrumentation /service for new customer and consumables/ controls/ kits necessary for all customers to provide results for 500 patients. Assumes 18 kits of PlGF and 18 Kits of sFLT-1. Assumes List Price for PlGF kit and sFLT-1 kit. Assumes calibration in duplicate each change in lot number (quarterly)
sFLT-1/PlGF ratio price per reportable result 1000 samples/ year (assumes 2-3 samples/day plus 3 control)	£38.32	£71.71	Includes all instrumentation /service for new customer and consumables/ controls/ kits necessary for all customers to provide results for 1000 patients. Assumes 23 kits of PlGF and 23 Kits of sFLT-1. Assumes List Price for PlGF kit. Assumes calibration in duplicate each change in lot number (quarterly)
sFLT-1/PlGF ratio price per reportable result 6000 samples/ year (assumes 5000 1st T Pre-term PE prediction tests and 1000 Aid in Diagnosis analyses in 2nd/3rd T) plus 3 controls per day (as per NHS guidance)	£30.86	£34.72	Includes all instrumentation /service for new customer and consumables/ controls/ kits necessary for all customers to provide results for 6000 patients. Assumes 76 kits of PlGF and 23 kits of sFLT-1. for Assumes List Price for PlGF kit
Technician time / calibration & daily maintainence	Maintainence/ carry-over process already covered for Aneuploidy screening. Calibration once per quarter (1 hour)	Maximum 1.5 hour per day / 1 hour (morning) 30 minutes (late afternoon). Calibration (standard curve in duplicate) once per quarter (1hour)	Reagents are loaded at the beginning of the day for tests. Kit required for calibration included in cost per reportable result
Technician time to run the test (post centrifugation)	15 minutes to load sample/ reagents and 10 minutes to read result /check QC	15 minutes to load sample/ check reagents and 10 minutes to read result /check QC	

STUDY REPORT

Version 3.0

[redacted]

Product number (s) and name (s)
6009-0010/-001C DELFIA Xpress sFlt-1 kit and 3246-0010 sFlt-1 Controls

Project number	2008495
Project name	sFlt-1
Identifier	Performance evaluation study for 6009-0010 DELFIA Xpress sFlt-1 kit and 3246-0010 sFlt-1 Controls

CONTENTS

1. STUDY TYPE AND DESIGN

The study type and design are described in the Study Protocol (**Error! Reference source not found.**) [redacted]. Pre-eclampsia was defined according to International Society of Study of Hypertension in Pregnancy guidelines (2020)(3). Women were excluded if they had chronic kidney disease due to reduced PlGF clearance and pre-existing angiogenic imbalance (4).

2. SAMPLE SIZE CONSIDERATIONS

The sample size considerations are presented in the Study Protocol (**Error! Reference source not found.**).

3. STUDY ACCEPTANCE CRITERIA

The study acceptance criteria are described in the Design Validation Plan and have been formulated to match the Study Objectives.

Acceptance criteria for clinical performance:

- The tested method has predictive value for outcome of intended use (aid in diagnosis of pre-eclampsia). When constructing a ROC curve from the case-control study data the AUC-value should be higher than 0.5.

The data is regarded to support the intended use when the sFlt-1/PlGF ratio has a predictive value (with case-control setting) for pre-eclampsia during pregnancy weeks 20–33^{+6} (PER-16), to rule-out and to rule-in pre-eclampsia.

There are not any acceptance criteria for the study for clinical performance relating to the secondary objective (short term prediction of pre-eclampsia).

4. DATA MANAGEMENT

4.1. Data collection

The report includes anonymized amalgamated data from [redacted] and no patient identifying information (e.g. name, address, social security number) will be transferred to PerkinElmer.

All result files generated by the instruments (Exported *.txt files from DX) have been transferred from the study site to PerkinElmer using a Cloud-based service (OneDrive).

Signed and dated paper printouts have been produced for each run of DELFIA Xpress.

The instrument and Workstation log files were transferred from the study site to PerkinElmer when undesired events during the runs occurred and were examined and resolved.

The demographic information are presented as defined in the Study Protocol.

4.2. Data Storage

Data and backup log files are stored in dedicated study folder under correct study number. Original external evaluation study data files are write-protected. Data will be also archived as signed and dated printouts at the study site.

4.3. Statistical Data Management

Received raw data files were imported into statistical software package, STATA, with statistical scripts. Each script included an information section which describes the function of the script.

The imported data were combined and modified to create the analysis datasets. All of these steps are performed with statistical scripts which are the documentation of the performed steps with the following modifications.

- Calculation of sFlt-1/PlGF ratio from individual concentration results
- Combining demographic information to sample results
- Categorization of test positive/negative samples

The sample size flow description/report accounts for all sample results assayed during the external evaluation study.

4.4. Data Review

4.4.1. Raw Data Review

Instrument raw data was randomly double-checked against the paper printouts by PerkinElmer using 10% sampling. No errors were identified.

The integrity of the demographic information was monitored by study site.

- 20% sampling for correct identification of confirmed positive samples was confirmed.

In addition, the following data integrity checks were undertaken:

- Final analysis data listings compared to the raw data listings
- Using data summaries to check for variable inconsistencies (e.g. 0-fields, missing information)
- Checking for correct kit lot, calibrator and control target information
- Checking for correct calibration curve fitting and other default configurations

4.4.2. Acceptance of assay runs

Controls were used to validate the sFlt-1 and PlGF 1-2-3 assay runs as advised in the kit inserts.

The quality control (QC) acceptance criteria include the derivation of QC acceptance limits and QC acceptance rules for control results of each study assay run.

The control results of the familiarization period and the Main Study were submitted to PerkinElmer for review, familiarization study undertaken and acceptance criteria were met.

The familiarization study QC acceptance criteria is that all the control replicate results should be within the target ±3SD limits, where target is the QC certificate/QC Data Sheet target value and SD is total SD from product specifications. The total mean values of the controls during the familiarization period must be within the range for target values stated in the QC certificate or QC Data Sheet.

Site specific mean values and acceptance ranges for DELFIA Xpress sFlt-1 and PlGF assays for the Main Study were established during the familiarization period.

The quality control target values for the Main Study were the familiarization mean values and the acceptance limits were derived from the specification of within lot variation. The target and SD for QC acceptance was defined before the main study started.

A simple Westgard QC acceptance rule was used for DELFIA Xpress. An assay run is rejected if one replicate is outside 3SD (1_{3s} rule).

The Table 1 summarizes how the study QC acceptance criteria are defined for familiarization and the Main study.

Table 1. *Summary of the QC acceptance criteria*

	Familiarization	**Main Study**
	Tested method	**Tested method**
Target	QC certificate	Familiarization mean
SD	Total SD from product specifications	Within-lot SD from product specifications
Acceptance rules	All results within ±3SD	By manufacturer

5. STATISTICAL METHODS

5.1. Data sets to be analyzed

All eligible specimens (checked for inclusion/exclusion criteria) with valid analyte results were used, and only those with complete time to pre-eclampsia diagnosis were included in the data analysis for clinical performance.

5.2. General Statistical Considerations

5.2.1. Significance and Confidence Levels

The point estimates are presented together with the two-sided 95% confidence intervals when applicable. Statistical significance level of 0.05 is used.

5.2.2. Subgroups

Results are presented for subgroups according to gestation, and in women without chronic kidney disease (CKD).

5.2.3. Outliers

Graphical methods with visual inspection for outliers was performed and none identified.

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CONFIDENTIAL UNTIL PUBLISHED

Technology Assessment Report commissioned by the NIHR Evidence Synthesis Programme on behalf of the National Institute for Health and Care Excellence (NICE)

Placental growth factor (PlGF)-based testing to help diagnose suspected pre-eclampsia (update of DG23)

ADDENDUM

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
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Correspondence to	Dr Jonathan Shepherd
Date completed	11th June 2021

Please note that: content highlighted in [redacted] is 'academic in confidence' (AIC).

Contents

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Introduction

Following submission of the Diagnostic Assessment Report (DAR) on 11th May 2021, NICE identified issues requiring further investigation by the Extremal Assessment Group (EAG), to inform the Diagnostic Advisory Committee's discussion of this topic on 15th June 2021.

In this document we provide a response to each of the above issues raised by NICE, including updated cost-effectiveness analyses where necessary. This addendum should be read in conjunction with the DAR of 11th May.

1 Cost-effectiveness analyses assuming the same prevalence of pre-eclampsia in the intervention and comparator arms

In the base case reported in the DAR, the prevalence of pre-eclampsia was modelled as observed in the PARROT and INSPIRE RCTs.

This current scenario analysis, requested by NICE, assumes no difference in the proportion of women with pre-eclampsia in the intervention and comparator arms. Expert clinical advice to the EAG is that this assumption is clinically justifiable.

- Setting the proportion of women with pre-eclampsia to be the same in both the intervention and comparator arms does not change the outcomes (see Table 1).

Table 1 Scenario analyses with equal prevalence of pre-eclampsia in the intervention and comparator arms

Test	Arm	Costs	QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Triage	**Comparator**	£13,090	16.99	-£1,785	0.2081	Dominant
	Intervention	£11,305	17.20			
DELFIA	**Comparator**	£13,090	16.99	-£1,797	0.2081	Dominant
	Intervention	£11,293	17.20			
Elecsys	**Comparator**	£10,321	17.08	£297	-0.0956	Dominated
	Intervention	£10,617	16.99			
BRAHMS	**Comparator**	£10,321	17.08	£270	-0.0956	Dominated
	Intervention	£10,591	16.99			

2 Cost-effectiveness analyses excluding neonatal outcomes

This scenario excludes the impact of the use of testing on neonatal outcomes. There was substantial uncertainty around the impact of PlGF testing on neonatal outcomes, and these outcomes were among the key drivers of the model results.

- Excluding neonatal outcomes has a large impact on the results, reducing the incremental costs and QALYs substantially, with ICERs for all tests lying in the south-west quadrant of the cost-effectiveness plane (Table 2). Note that the incremental QALYs for all the test are less than 0.001.

Table 2 Scenario analyses excluding neonatal outcomes

Test	Arm	Costs	QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Triage	**Comparator**	£5,940	0.42	-£80	-0.0004	£187,040
	Intervention	£5,860	0.42			
DELFIA	**Comparator**	£5,940	0.42	-£92	-0.0004	£215,484
	Intervention	£5,848	0.42			
Elecsys	**Comparator**	£5,587	0.42	-£112	-0.0005	£210,959
	Intervention	£5,475	0.42			
BRAHMS	**Comparator**	£5,587	0.42	-£139	-0.0005	£261,848
	Intervention	£5,448	0.42			

3 Cost-effectiveness analyses for the Elecsys and BRAHMS tests assuming the same neonatal outcomes as for the Triage test

Neonatal outcomes such as neonatal death and the incidence of Respiratory Distress Syndrome [RDS] and intraventricular hemorrhage [IVH] were not reported in the INSPIRE RCT. Therefore, in the base-case analysis for the Elecsys and BRAHMS ratio tests they were assumed to be the same in both test and comparator arms and were set to the average values across the arms in PARROT.

On request from NICE, we conducted scenario analyses for Elecsys and BRAHMS with the neonatal outcomes parameterised from PARROT data,[1] effectively assuming that the neonatal outcomes for all tests would be the same as those for the Triage test.

- Using the PARROT trial arm-specific rates of neonatal outcomes in the analyses for Elecsys and BRAHMS had a large impact on the model results. The ICERs move into the south-east quadrant of the cost-effectiveness plane signifying dominance of use of testing over standard clinical assessment only (Table 3).

Table 3 Scenario analyses for Elecsys and BRAHMS ratio tests with neonatal outcomes (IVH, RDS and neonatal death) assumed to be the same as those for the Triage PlGF test

Test	Arm	Costs	QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Elecsys	**Comparator**	£10,451	17.06	-£320	0.1291	Dominant
	Intervention	£10,131	17.19			
BRAHMS	**Comparator**	£10,451	17.06	-£347	0.1291	Dominant
	Intervention	£10,104	17.19			

4 DELFIA Xpress PlGF 1-2-3 test with or without DELFIA Xpress sFlt-1 test

PerkinElmer's submission states that the DELFIA Xpress PlGF 1-2-3 test used alone or in combination with DELFIA Xpress sFlt-1 (for sFlt-1/PlGF ratio) is recommended to be used as aid in diagnosis and for short term prediction for pregnant women presenting with symptoms related to pre-eclampsia after 20 weeks of gestation and before 35 weeks of gestation.
The recommended cut-offs for the DELFIA Xpress PlGF 1-2-3 test are:

- > 150 pg/ml: rule out
- 150-50 pg/ml: follow up
- < 50 pg/ml: rule in and deliver within 14 days (50% of women).

When using DELFIA Xpress 1-2-3 in combination with DELFIA Xpress sFlt-1, each laboratory must validate their own cut-offs for management of suspected pre-eclampsia. The published cut-offs can only be used as guidance. For aid in diagnosis and for short term prediction of pre-eclampsia using the cut-offs validated in the laboratory, the sFlt-1/PlGF ratio results may be categorized to:

- Low: rule out
- Intermediate: follow-up
- Increased: rule in

An overview of the publications evaluating the DELFIA tests are presented in Table 4. Two of these publications, COMPARE[2] and Giblin et al.,[3] were identified in our systematic review of test accuracy and clinical effectiveness (see section 4.1.3 of the DAR). The Gilbin et al publication is a secondary report of the COMPARE study, with the focus of establishing an

optimal rule in cut off for the DELFIA PlGF 1-2-3 test. The third study, R01-17008 (Table 4), was provided by PerkinElmer after the submission of the DAR (see section 6).

As reported in COMPARE,[2] at the commercially recommended cut-offs for Triage and Elecsys and the cut-off of 150 pg/ml for DELFIA Xpress PlGF 1-2-3 (determined to give an optimal test performance, with the same overall proportion of positive tests as Triage), the tests' ability to predict delivery within 2 weeks did not differ significantly before 35 weeks' gestation in AUC, sensitivity, PPV and NPV; Elecsys had significantly higher specificity than did DELFIA and Triage. The authors argued, however, that high sensitivity is a more useful attribute in the early detection of pre-eclampsia than specificity because consideration of benefits, harms and costs indicates a much greater preference for minimizing false negatives than false positives. When comparing the performance of the tests for a wider population of women with gestational age of up to 37 weeks, no significant differences were observed.

Giblin et al.[3] used the established rule-in thresholds requiring delivery within 2 weeks of <12 pg/ml for Triage and >85 for the Elecsys sFlt-1/PlGF ratio test to calculate an optimal rule-in threshold for PerkinElmer DELFIA Xpress PlGF 1-2-3 with an equivalent specificity. A threshold of 50 pg/ml for PlGF 1-2-3 Test was equivalent to <12 pg/mL (Triage) and >85 (Elecsys).

Table 4 Test accuracy evidence for DELFIA Xpress PlGF 1-2-3 with or without DELFIA Xpress sFlt-1 test

Study (type)	Setting (n)	Study period	Source	Gestational age (weeks)	Pregnancy type (n)	Cut-offs considered
DELFIA Xpress PlGF 1-2-3						
COMPARE (standalone, retrospective analysis of samples from PEACHES,[4] PELICAN-1[60] and PELICAN-2 [5])	PEACHES - two London academic health science centres; PELICAN-1 and PELICAN-2 -18 maternity units in the UK and Ireland	PEACHES – 2009 – 2017, PELICAN-1 and PELICAN-2 – 2011 - 2013	McCarthy et al.[2]	24-37	Singleton (396 plasma samples and 244 serum samples)	ROC analysis to rule out delivery within 2 weeks with the cut-offs: - 100 pg/ml for Triage PlGF - 38 for Elecsys sFlt-1/PlGF ratio - An optimally derived cut-off of 150 pg/ml for the DELFIA Xpress PlGF 1-2-3[a]
Giblin et al 2020 (standalone, analysis of samples from PEACHES,[4] PELICAN-1[60] and PELICAN-2 [5])	PEACHES - two London academic health science centres; PELICAN-1 and PELICAN-2 -18 maternity units in the UK and Ireland	PEACHES – 2009 – 2017, PELICAN-1 and PELICAN-2 – 2011 - 2013	Giblin et al.[3]	<35	Singleton (305 plasma samples)	Cut-offs for diagnosis of preterm PE requiring delivery within 2 weeks: - <12 pg/ml for Triage PlGF - >85 for Elecsys sFlt-1/PlGF ratio - An optimally derived rule-in cut-off of <50 pg/ml for PerkinElmer DELFIA Xpress PlGF 1-2-3
Study R01-17008 (standalone, analysis of frozen samples from PEACHES[4])	King's College London	NR	Unpublished study report provided by PerkinElmer	[redacted] (median), 95% CI = [redacted]	NR	Rule out: - 12 pg/ml[b] - 100 pg/ml[b] - 150 pg/ml
DELFIA Xpress PlGF 1-2-3 sFlt-1/PlGF ratio						
Study R01-17008 (standalone, analysis of frozen samples from PEACHES[4])	King's College London	NR	Unpublished study report provided by PerkinElmer	[redacted] (median), 95% CI = [redacted]	NR	- Rule out: ≤27 - Rule in: o >69 for GA of 20^{+0} – 33^{+6} o >89 for GA of 34^{+0} – delivery

GA, gestational age; NR, not reported; PE, pre-eclampsia; ROC, receiver operating characteristic

[a] A concentration of <150 pg/ml was determined to give an optimal test performance, with the same overall proportion of positive tests as Triage PlGF.

[b] Not among the cut-offs recommended by PerkinElmer in their submission

Based on these findings, we conducted a simple cost-comparison analysis for the DELFIA Xpress PlGF 1-2-3 test assuming equivalence in effectiveness to that of the Triage PlGF test. The resource use and costs for DELFIA PlGF 1-2-3 were assumed to be the same as for Triage with the only exception of the cost of testing. The results are presented in

Table 6 and Table 7 below.

A caveat of this analysis is the intended use of the tests: PARROT[6] was a pragmatic RCT where the Triage test was used as part of a clinical management algorithm (shown in Figure 10, Appendix 8 in the EAG report), while McCarthy[2] and Giblin[3] compared the performance of DELFIA Xpress PlGF 1-2-3 and Triage to predict delivery within 2 weeks. This analysis also has the same limitation as that of the analysis of the Triage test (discussed in section 7.2.2 of the DAR); that the maternal and neonatal outcomes taken from PARROT were for women with gestational age of up to 37 weeks, whereas the Triage test is only recommended for women with <35 weeks gestation.

4.1 Calculation of the cost of testing for DELFIA

The approach taken to calculate the cost of the DELFIA PlGF 1-2-3 test was the same as that used to estimate the cost of the Elecsys sFlt-1/PlGF ratio test (see DAR Appendix 15 for further details). The manufacturer of DELFIA PlGF 1-2-3 provided the cost per reportable test based on the volume of tests per year (up to 500, 1000 and 5000), including capital, maintenance, and equipment costs. The costs of staff for training, performing the test and interpreting results and for quality control as well as the costs of phone calls to communicate test results were added to the cost per reportable test.

An updated cost per reportable test was provided by the company as part of the stakeholder comments to the EAG report and model. We have considered the cost per reportable test valid for up to 500 tests per year and charged to existing customers in the base case, and the cost charged to new customers in a scenario analysis. The company also informed that technician time for maintenance is already covered by aneuploidy screening for existing customers but not for new customers. As we assumed the same for the current purpose, a higher staff cost for maintenance and quality control was applied to new costumers (£33.66 per test; scenario analysis) versus existing customers (£7.51 per test; base case). The cost of testing with DELFIA PlGF 1-2-3 is detailed in Table 5.

Table 5 Breakdown costs for DELFIA PIGF 1-2-3 test

Cost component	Price	Cost per test	Rationale/Formula
Cost per reportable test	NA	£26	As informed by the manufacturer
Training			
Standard training	£0.00	£0.00	Perkin Elmer provides training for free
Staff time	£17.43	£0.43	Salary of a healthcare scientist per hour = £17.43 Time spent in training per year: 3h*3 persons = 9h Cost of training per year (£17.43*9h)/number of tests per year (n=365)
Staff			
Staff who process samples in lab	£17.43	£7.32	Salary of healthcare scientist per hour/time spent per test (0.42h)
Staff who perform device QC	£17.43	£0.19	Time spent per device QC per year: 4h Cost of device QC per year (£17.43*4h)/number of tests per year (n=365)
Other costs			
Phone calls	£3.47	£3.47	Proportion of tests processed in labs: 100% (100%*365=365 tests) Cost per year (£3.47*365)/number of tests per year (n=365)
TOTAL		**£37.41**	
NA, not applicable; QC, quality control			

Scenario analyses

Scenario analyses for the minimum and maximum costs of testing using DELFIA PIGF 1-2-3 were conducted in the same manner as those for the other tests (see EAG report section 5.5.2.1). The minimum cost corresponds to the price of the test kit only (£8) and the maximum cost is based on the cost for new customers as explained above (£96). Results of these scenario analyses are shown in Table 8.

4.2 Cost-effectiveness results for the DELFIA PIGF 1-2-3 test

The cost-effectiveness results for DELFIA PIGF 1-2-3 test used alongside standard clinical assessment versus standard clinical assessment alone are presented in

Table 6. In the base case, total costs are £11,293 for the DELFIA PIGF 1-2-3 test and £13,051 for standard clinical assessment. Total QALYs are 17.20 and 16.99 in the test and comparator arms, respectively. The strategy including the test gives a cost reduction of £1,758 and a QALY gain of 0.204. The base-case results indicate that using the DELFIA PIGF 1-2-3 test in the assessment of pre-eclampsia is more effective and less costly when compared to standard clinical assessment alone.

The breakdown results are presented in Table 7. The main drivers of the base-case results are the long-term costs and QALYs. The rate and costs of neonatal care have a large impact in the results as well.

Table 6 Base-case results for DELFIA PIGF 1-2-3 test

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Standard assessment	£13,051	16.99			
DELFIA PIGF test	£11,293	17.20	-£1,758	0.204	Dominant
QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio					

Table 7 Base-case breakdown results for DELFIA PIGF 1-2-3 test

Components	Triage PIGF test	Standard assessment	Incremental
Costs			
First testing	£37	£0	£37
Management	£1,561	£1,791	-£230
Delivery	£3,880	£3,740	£140
Maternal care	£370	£410	-£40
Neonatal care	£3,969	£4,661	-£692
Neonatal care - long term	£1,476	£2,450	-£974
Total	£11,293	£13,051	-£1,758
QALYs			
Management	0.000	0.000	0.000
Delivery	0.035	0.035	0.000
Maternal - short term	0.384	0.384	0.000
Neonatal - short term	-0.001	-0.001	0.000

Components	Triage PIGF test	Standard assessment	Incremental
Maternal - long term	17.289	17.267	0.022
Neonatal - long term	-0.511	-0.694	0.183
Total	17.1961	16.9918	0.2043
QALYs, quality-adjusted life-years			

4.3 Scenario analyses

To test the uncertainty around the estimates for DELFIA PIGF 1-2-3 test, we conducted the same scenario analyses as for the other tests in the DAR (see section 5.5.2.1); the results are presented in Table 8. Additional scenario analyses for DELFIA PIGF 1-2-3 test, conducted in response to stakeholders' comments are described in section 7, and the results are shown in Table 10 and Table 11.

Clinical assessment alongside use of the DELFIA PIGF 1-2-3 is less expensive and yields more QALYs than the standard clinical assessment alone in all the scenarios except two: when the time horizon is changed to 6 months post-partum, and when stillbirth is excluded.

Table 8 Scenario analyses for DELFIA PIGF 1-2-3 test

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY) vs. standard assessment
Base case	**-£1,758**	**0.204**	**Dominant**
MAPPLE/PELICAN inputs	-£3,148	0.394	Dominant
Time horizon: 6 months post-partum	-£784	-0.0005	£1,725,592
Management of women with suspected PE: NG133	-£1,750	0.204	Dominant
Level of hypertension: stratified by level of risk of PE	-£1,751	0.204	Dominant
Gestational age <35 weeks: 0%	-£1,692	0.204	Dominant
Gestational age <35 weeks: 100%	-£1,976	0.204	Dominant
Immediate delivery: up to 24 hours	-£1,758	0.204	Dominant
Death in neonates: excluding stillbirth	-£1,665	-0.018	£92,231
Cost of testing: low value	-£1,788	0.204	Dominant

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY) vs. standard assessment
Cost of testing: high value	-£1,699	0.204	Dominant
Long-term costs: cost of pre-term babies applied to all admitted neonates	-£1,768	0.204	Dominant
QALY decrement for mothers whose child died: applied for 10 years	-£1,758	0.1855	Dominant
QALY decrement for mothers whose child had complications: applied for 10 years	-£1,758	0.1776	Dominant
NG133, NICE Guideline 133; PE, pre-eclampsia; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio			

5 Hospital admission of women at high risk of pre-eclampsia in the test arm: Triage PlGF

A stakeholder commented that, hospitalisation rates might be over-estimated in the test arm in the base-case analysis for Triage where it was assumed that all women with low (<12 pg/ml) PlGF are admitted.

In response to this comment we conducted a scenario assuming a lower proportion (90%) of women at high risk of pre-eclampsia in the test arm who would be hospitalised.

- This did not change the outcome, i.e. using Triage alongside standard clinical assessment remains less costly and more effective (see Table 9).

Table 9 Scenario analysis for hospital admission in the test arm: Triage PlGF

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Standard assessment	£13,051	16.99			
Triage PlGF test	£11,270	17.20	-£1,781	0.2043	Dominant
QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio					

6 Additional stakeholder evidence for the DELFIA Xpress PlGF 1-2-3 test and the DELFIA Xpress sFlt-1 test

6.1 Study R01-17008

In their stakeholder comments on the DAR, Perkin-Elmer provide details of new data from a study carried out at Kings College, London, study R01-17008. [redacted]

The R01-17008 study is the only study the EAG is aware of that reports test accuracy estimates for the DELFIA sFlt-1/PlGF ratio. The study also reports test accuracy estimates for the DELFIA PlGF 1-2-3 test, but there is no comparison between these DELFIA tests and any other test in this study.

The only other study the EAG is aware of that evaluates DELFIA is the aforementioned COMPARE study. That study reports accuracy estimates for the DELFIA PlGF 1-2-3 test but not for the DELFIA sFlt-1/PlGF ratio. With R01-17008 and COMPARE, the EAG now has two sources of test accuracy estimates for the DELFIA PlGF 1-2-3 test. However, as mentioned above in section 4, we have chosen the COMPARE study to inform our cost effectiveness analysis of the DELFIA PlGF 1-2-3. We have not been able to perform a thorough assessment and critical appraisal of R01-17008, as certain key information, such as participant characteristics and methodology, are not given in the study report. The report refers to the study protocol for this information, however the protocol does not appear to be in the public domain. Furthermore, the study report does not appear to have been peer reviewed.

In summary, whilst the EAG considers this study to be relevant to this appraisal (with the caveat that it is a standalone rather than an add-on study) we are currently uncertain about aspects of its methodology and risk of bias.

6.2 Comparison study of the Roche Cobas e411 and PerkinElmer DELFIA Xpress, providing sFlt-1 and PlGF assays

Perkin Elmer mention a study based at the [redacted] In their stakeholder comments on the DAR. The study reports a comparison study between two platforms, Roche Cobas e411 and PerkinElmer DELFIA Xpress, providing sFlt-1 and PlGF assays.

[redacted]

The EAG considers this study to be potentially relevant to this appraisal (with the caveat that it is a standalone rather than an add-on study) but due to limited details provided, we are currently uncertain about aspects of its methodology and risk of bias.

7 Additional scenarios

7.1 Management of women at intermediate risk of pre-eclampsia

In the EAG's model, we assumed that women at intermediate risk of pre-eclampsia are managed in the same way as low-risk patients.

As there is uncertainty about the way intermediate-risk patients are managed in clinical practice, we tested this assumption in a scenario analysis assuming that intermediate-risk patients are managed in the same way as patients at high risk of pre-eclampsia.

- This assumption changes the incremental costs only slightly and does not change the outcomes (Table 10).

Table 10 Scenario analyses with women at intermediate risk of pre-eclampsia managed as high-risk patients

Test	Arm	Costs	QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Triage	**Comparator**	£13,645	16.99			Dominant
	Intervention	£11,642	17.20	-£2,004	0.2043	
DELFIA	**Comparator**	£13,645	16.99			Dominant
	Intervention	£11,630	17.20	-£2,016	0.2043	
Elecsys	**Comparator**	£10,536	17.08	£515	-0.1403	Dominated

Test	Arm	Costs	QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
	Intervention	£11,051	16.94			
BRAHMS	**Comparator**	£10,536	17.08			Dominated
	Intervention	£11,024	16.94	£488	-0.1403	

7.2 Level of blood pressure severity

In response to a comment provided by Dr Manu Vatish, we used the baseline blood pressure measurements from PARROT[6] reported as the "*highest blood pressure in the 48h before study entry, mmHg"* to allocate patients across hypertension levels for Triage and DELFIA PIGF tests. Taking a baseline systolic blood pressure of 144 +/- 20 mmHg from the RCT and assuming a standard normal distribution, the proportion of patients with normal/mild, moderate and severe hypertension is 62%, 17% and 21%, respectively.

- The assumptions made by the EAG to allocate women across hypertension severity levels have only a marginal impact on the model results. In this analysis, the incremental costs increased only marginally while QALYs remained the same as in the base case (Table 11).

Table 11 Scenario analyses with blood pressure at baseline used to allocate patients across the levels of hypertension in the analyses for Triage PIGF and DELFIA PIGF 1-2-3 tests

Test	Arm	Costs	QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Triage	Comparator	£12,890	16.99			
	Intervention	£11,125	17.20	-£1,765	0.2043	Dominant
DELFIA	Comparator	£12,890	16.99			
	Intervention	£11,113	17.20	-£1,777	0.2043	Dominant

8 References

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CONFIDENTIAL UNTIL PUBLISHED

Technology Assessment Report commissioned by the NIHR Evidence Synthesis Programme on behalf of the National Institute for Health and Care Excellence (NICE)

Placental growth factor (PlGF)-based testing to help diagnose suspected pre-eclampsia (update of DG23)

ERRATUM replacement pages

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SCIENTIFIC SUMMARY

Background

Pre-eclampsia affects approximately 6% of pregnant women, usually from around 20 weeks of gestation, with severe cases affecting 1-2% of pregnant women. If the condition is undetected or left untreated it can result in serious, potentially fatal, maternal and neonatal complications, such as stroke or organ dysfunction or eclampsia or fetal growth restriction or intrauterine death. The only cure for pre-eclampsia is to deliver the placenta (and therefore the baby) so women are monitored until the optimum time for delivery.

Pre-eclampsia can be asymptomatic, and it can be difficult to detect in women with pre-existing hypertension, therefore assessment for pre-eclampsia is incorporated into routine antenatal assessments. Women are suspected of having pre-eclampsia if they have high blood pressure and/or proteinuria. Further signs and symptoms of suspected pre-eclampsia include swelling of the feet, ankles, face and hands, severe headache, vision problems, pain just below the ribs, and suspected fetal compromise.

If pre-eclampsia is suspected, current practice is to assess the person for blood pressure, proteinuria, other symptoms such as oedema or neurological disturbances, and abnormal laboratory results in order to diagnose the condition or decide whether and how to continue to monitor the pregnancy. In addition, blood tests have been developed that measure levels of two proteins in the blood: placental growth factor (PlGF), which occurs in abnormally low levels in women with pre-eclampsia; and soluble fms-like tyrosine kinase 1 (sFlt-1), which occurs in abnormally high levels in women with pre-eclampsia. Two of these tests (Triage and Elecsys) were recently incorporated into clinical practice to aid in predicting a diagnosis of pre-eclampsia. A further two tests which measure these proteins (BRAHMS and DELFIA) are now available for use which have not yet been evaluated for diagnostic or prognostic/predictive accuracy and cost-effectiveness for the NHS.

The four tests specified in the NICE scope for this diagnostic assessment and evaluation, are: Triage® PlGF test (Quidel Cardiovascular Inc; San Diego, CA, USA); the DELFIA® Xpress PlGF 1-2-3 test and the DELFIA Xpress sFlt-1 test (PerkinElmer, Wallac Oy, Turku, Finland); the Elecsys® sFlt-1 to PlGF ratio test (Roche Diagnostics GmbH, Mannheim, Germany) and the BRAHMS® sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio test (Thermo Fisher Scientific GmbH, Hennigsdorf, German

Our analysis shows that the Triage PlGF test is likely to be cost effective, based on the outcomes from the PARROT trial. The test is cost saving and would improve QALYs compared to standard clinical practice only. In contrast, the Elecsys would not be cost-effective, based on the INSPIRE trial. However, data were not available for maternal and neonatal outcomes so results should be treated with caution. The analysis for BRAHMS suggests that standard clinical practice would be dominant. This analysis, however, is subject to uncertainty due to the context of the ROPE cohort study (standalone tests in a single US centre) which provided samples for an area-under-the-curve (AUC) analysis for BRAHMS and Elecsys, and has the same caveats as the cost-utility analysis for Elecsys.

Further research to compare more than one of the PlGF-based tests used as add-ons to the standard clinical assessment within the same trial would be useful, although there might be practical limitations. There is uncertainty around clinical utility of the BRAHMS and DELFIA tests, and the impact on maternal and neonatal outcomes of the use of Elecsys test in addition to standard clinical practice for diagnosis of pre-eclampsia. The clinical effectiveness systematic review identified limited evidence on the use of repeat testing which precluded a thorough economic evaluation of this testing strategy. Further research is needed to address the long-term impact of pre-eclampsia in women, for example future complications that could emerge and the related costs and utilities. More research is also needed on the impact of adverse maternal and neonatal outcomes on long-term quality of life and costs for mother and neonates, in particular the life-time costs related to intraventricular haemorrhage.

PLAIN ENGLISH SUMMARY

Pre-eclampsia is a condition that affects some pregnant women and, if not detected or left untreated, can result in serious complications for the mother and/or the baby.

Four tests are now available (Triage, Elecsys, BRAHMS and DELFIA) that measure the level of certain proteins in the blood that can be abnormal in women with pre-eclampsia. We investigated the use of these tests in addition to clinical assessment to help diagnose pre-eclampsia. These blood tests can help determine whether pregnant women suspected of having pre-eclampsia require admission to hospital or if they can be safely monitored as outpatients, potentially improving care and saving money.

We carried out expert medical evidence searches to update our knowledge of the accuracy and cost of these tests and to evaluate the impact on delivery-related outcomes for mother and baby. From the evidence we found we developed an economic model that estimated

costs and benefits to predict whether or not the tests would be good value for money for the NHS.

Our model results suggest the Triage test is likely to reduce costs and improve health outcomes compared with standard clinical management only. In contrast, the Elecsys is likely to increase costs and reduce health outcomes compared to standard clinical management only, although the results for this test varied depending on the clinical study used. There is uncertainty around use of the BRAHMS and DELFIA tests, and on the usefulness and costs of repeat testing because of limited evidence, and research recommendations are made to reduce this uncertainty.

in Appendix 9 is two weeks for low risk pre-eclampsia, and one or two weeks for intermediate risk. Repeat testing would usually be considered at two weeks after the first test, and the proportion of women undergoing repeat testing could vary between 20% up to 50% depending on local clinical practice protocols. Repeat testing of women at a later gestation would be less likely, although this would depend on local practice.

Repeat testing was reported in just one study included in the systematic review of test accuracy and clinical effectiveness, the prospective observational standalone study PROGNOSIS study (Elecsys sFlt-1/PlGF ratio).[36]

When testing is repeated, it is likely that there is conditional dependence between the first and subsequent tests, that is, the sensitivity (or specificity) of the subsequent test would not be independent of the outcome of the first test.[148] Therefore, the overall sensitivity and specificity of the repeat testing strategy should be calculated taking into account the effect of test covariance. This would require additional evidence on pairwise test results for the first and subsequent tests. Such evidence was not available in clinical effectiveness studies informing this economic evaluation. For this reason we were unable to conduct scenario analyses of repeat testing.

5.4.4 Comparator

The comparator in this economic evaluation no further clinical assessment (beyond assessments already done, such as blood pressure measurement, urinalysis and fetal monitoring) to diagnose pre-eclampsia and inform subsequent decisions about care.

The 2010 NICE guideline on managing hypertension and pre-eclampsia (CG107)[59] was replaced in 2019 by the NICE guideline on hypertension in pregnancy: diagnosis and management (NG133).[3] The key differences between the CG107[59] and NG133[3] guidelines are discussed below. NICE guideline NG133[3] incorporates the recommendation from the NICE DG23[6] on the use of the Triage PlGF test and the Elecsys immunoassay sFlt-1/PlGF ratio test in addition to standard clinical assessment and subsequent clinical follow-up, to help rule-out pre-eclampsia in women presenting with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation. NG133[3] also includes the use of online risk assessment tools (fullPIERS and PREP-S) to estimate the risk of adverse events in women diagnosed with pre-eclampsia.

assumptions for costing diagnostic and management strategies are presented in section 5.4.7.2. Unit costs were taken from UK sources for the most recent available year. Parameters included in the model are discussed in the following sections. An overview of all model parameters and model assumptions is provided in Appendix 10.

5.4.7.1 Parameterisation of the risk stratification phase of the model

The clinical effectiveness study outcomes, as parameterised for risk stratification in the base-case model are shown in Table 103 (Appendix 13) and for scenario analyses in Table 106 (Appendix 14).

Triage PlGF test

The risk stratification in the base-case model for Triage was parameterised, where possible, from the outcomes in the PARROT RCT.[63] In this pragmatic trial, women presenting with suspected preeclampsia were randomized to management by Triage PlGF test in conjunction with standard clinical assessment versus standard clinical assessment alone:

- Women with a plasma PlGF concentration of >100 pg/ml followed a care pathway involving outpatient management and routine surveillance unless clinical parameters such as severe hypertension indicated otherwise.
- Women with low PlGF concentrations were advised to increase surveillance with a greater frequency of antenatal care visits and fetal ultrasound scanning.
- Women with very low PlGF were assessed as pre-eclampsia, which included consideration for admission, intensive monitoring, and fetal ultrasound scanning.

The clinical management algorithm used in this trial is shown in Figure 10 (Appendix 8).

In PARROT, the outcomes (including the characteristics of labour and delivery for women with suspected pre-eclampsia, maternal and neonatal outcomes and the use of corticosteroids in both trial arms) were stratified by PlGF level: <12 pg/ml, 12-100 pg/ml and >100 pg/ml (Duhig et al. 2021[63]). Hospitalisation rates for these PlGF categories were not reported, but it was stated that the clinical management algorithm used by clinicians in PARROT (Appendix 8) did not recommend routine admission for women with low or very low PlGF (Duhig 2021[63]). Therefore, in the base-case analysis we assumed that women with PlGF of less than 12 pg/ml would be hospitalised while women with PlGF levels of ≥12 pg/ml would be managed in outpatient settings except those with severe hypertension who can also be admitted for up to three days. The proportion of women with PlGF level of <12 pg/ml in the comparator arm who would be hospitalised within 24 hours was estimated from the

risk ratio for diagnosis within 24 hrs (RR = 1.31) based on Duhig 2019.[8] The impact of uncertainty in the hospitalisation rate was assessed in a one-way sensitivity analysis.

We conducted an additional analysis for the Triage PlGF test using data from a comparative study of MAPPLE and PELICAN (Sharp et al 2018[9]). In the analysis reported by Sharp and colleagues,[9] clinical outcomes in women with singleton or twin pregnancies presenting prior to 35 weeks' gestation were compared, where possible, between revealed (MAPPLE) and concealed (PELICAN) cohorts. Data from Sharp[9] are categorised by PlGF concentration: <12 pg/ml (very low), 12–100 pg/ml (low; representing <5th percentile of normal) and >100 pg/ml (normal).

Elecsys immunoassay sFlt-1/PlGF ratio test

The accuracy estimates for predicting the development of preeclampsia within 7 days for the cut-off of 38, and the clinical outcomes from the INSPIRE RCT (including the rates of hospital admissions within 24 hours)[32] were used in the base-case analysis for Elecsys immunoassay sFlt-1/PlGF ratio test. In this pragmatic trial, women presenting with suspected preeclampsia were randomized to management by sFlt-1/PlGF
ratio test incorporated into standard clinical care versus standard clinical care alone.

The trial reported the number of women in the reveal and conceal arms who were admitted following clinical assessment (with or without PlGF testing). Treatment decision was based on a clinical management algorithm used in INSPIRE (shown in Figure 11, Appendix 8). The criteria for admission in the reveal arm were a high sFlt-1/PlGF ratio and blood pressure of more than 150/100. Admission was also considered if a woman had a high sFlt-1/PlGF ratio and blood pressure of less than149/99. In the conceal arm, the decision to admit was based on the NICE guideline CG107.[59] The proportion of women who would be managed on Stage 1 clinical pathway (see Figure 11, Appendix 8) was not reported in INSPIRE and, therefore, was approximated by outcomes reported in PreOS (another study of Elecsys). A scenario with an alternative assumption on the proportion of patients managed according to Stage 1 clinical pathway parameterised from PARROT was also conducted.

Outcomes from the PreOS study were used in another scenario analysis where the risk stratification part of the model was parameterised from the number of hospitalised women with the ratio of <33, from 33 to <85 and ≥85 before and after Elecsys test results were revealed (Klein 2016[79]).

for the Elecsys sFlt-1/PlGF ratio test and £10,321 for standard clinical assessment. Total QALYs vary between 16.94 for the Elecsys sFlt-1/PlGF ratio test and 17.08 for standard clinical assessment. The strategy including the test is more expensive (+£621) and produces less QALYs (-0.140) than standard clinical assessment. The breakdown results are presented in Table 61. The main drivers are again the long-term costs and QALYs and also the costs of neonatal care. For the long-term outcomes (child death, respiratory distress syndrome and intraventricular haemorrhage), it was assumed that there is no difference between the intervention and comparator arms (see section 5.4.7.5). A possible explanation for the incremental costs and QALYs can be the higher prevalence of women with pre-eclampsia and also higher number of women categorised as high-risk of pre-eclampsia in the Elecsys sFlt-1/PlGF ratio test arm, which are more costly and also incur high loss in QALYs.

Table 60 Base-case: results for the Elecsys sFlt-1/PlGF ratio test

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Standard assessment	£10,321	17.08			
Elecsys sFlt-1/PlGF ratio test	£10,942	16.94	£621	-0.140	Dominated
QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio					

Table 61 Base-case: breakdown results for Elecsys sFlt-1/PlGF ratio test

Components	Elecsys sFlt-1/PlGF ratio test	Standard assessment	Incremental
Costs			
First testing	£79	£0	£79
Retesting	£0	£0	£0
Management	£1,185	£1,492	-£308
Delivery	£3,912	£3,751	£161
Maternal care	£299	£344	-£45
Neonatal care	£2,935	£2,679	£256
Neonatal care - long term	£2,532	£2,055	£477
Total:	£10,942	£10,321	£621
QALYs			

Components	Elecsys sFlt-1/PlGF ratio test	Standard assessment	Incremental
Management	-0.0001	-0.0002	0.0001
Delivery	0.0347	0.0353	-0.0006
Maternal - short term	0.3841	0.3841	0.0000
Neonatal - short term	-0.0006	-0.0004	-0.0001
Maternal - long term	17.250	17.277	-0.0267
Neonatal - long term	-0.727	-0.614	-0.1130
Total:	16.94	17.08	-0.1403
QALYs, quality-adjusted life-years			

5.5.1.3 Cost-effectiveness results for BRAHMS Kryptor sFlt-1/PlGF ratio test

The cost-effectiveness results for BRAHMS Kryptor sFlt-1/PlGF ratio test versus standard clinical assessment are presented in Table 62. Those are assumed to be similar to the results for Elecsys sFlt-1/PlGF ratio test, with the only difference being the cost of the test itself which leads to a total cost of £10,915 for the BRAHMS Kryptor sFlt-1/PlGF ratio test. Total QALYs are the same as the ones reported for Elecsys sFlt-1/PlGF ratio test. Therefore, the strategy including the test is more expensive (+£594) and produces less QALYs (-0.14) than standard clinical assessment. The breakdown results are presented in Table 63.

Table 62 Base-case: results for BRAHMS Kryptor sFlt-1/PlGF ratio test

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Standard assessment	£10,321	17.08			
BRAHMS ratio test (ThermoFisher)	£10,915	16.94	£594	-0.14	Dominated
QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio					

Table 63 Base-case: breakdown results for BRAHMS Kryptor sFlt-1/PlGF ratio test

Components	Elecsys sFlt-1/PlGF ratio test	Standard assessment	Incremental
Costs			
First testing	£52	£0	£52
Retesting	£0	£0	£0
Management	£1,185	£1,492	-£308

Components	Elecsys sFlt-1/PlGF ratio test	Standard assessment	Incremental
Delivery	£3,912	£3,751	£161
Maternal care	£299	£344	-£45
Neonatal care	£2,935	£2,679	£256
Neonatal care - long term	£2,532	£2,055	£477
Total:	£10,915	£10,321	£594
QALYs			
Management	-0.0001	-0.0002	0.0001
Delivery	0.0347	0.0353	-0.0006
Maternal - short term	0.3841	0.3841	0.0000
Neonatal - short term	-0.0006	-0.0004	-0.0001
Maternal - long term	17.250	17.277	-0.0267
Neonatal - long term	-0.727	-0.614	-0.1130
Total:	16.94	17.08	-0.1403
QALYs, quality-adjusted life-years			

5.5.2 Sensitivity analyses

This section provides an overview of how uncertainties associated with test diagnostic accuracy, costs and utilities was incorporated into the decision analysis.

5.5.2.1 Scenario analyses

The following scenario analyses were performed:

- **Alternative study sources of test accuracy data:** MAPPLE/PELICAN for Triage and PreOS for Elecsys
    - **Inputs from MAPPLE/PELICAN**: we used inputs from the MAPPLE/PELICAN[16] trials where available (including time to delivery, maternal outcomes and neonatal incidence of respiratory distress syndrome and intraventricular hemorrhage). We applied this scenario to the Triage PlGF test arm only.
    - **Inputs from PreOS**: we used inputs from the PreOS[34] trial where available. We applied this scenario to the Elecsys sFlt-1/PlGF ratio test arm only.

Cost of PlGF-based tests: the EAG explored the uncertainty around the main assumptions of the cost of tests. Here we present the assumptions corresponding to the minimum and maximum cost per test only. These are (1) using the price of test kits only (see Appendix 13)

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY) vs. standard assessment
Base case	**-£1,746**	**0.204**	**Dominant**
Gestational age <35 weeks: 0%	-£1,680	0.204	Dominant
Gestational age <35 weeks: 100%	-£1,964	0.204	Dominant
Immediate delivery: up to 24 hours	-£1,746	0.204	Dominant
Death in neonates: excluding stillbirth	-£1,652	-0.018	£91,557
Cost of testing: low value	-£1,755	0.204	Dominant
Cost of testing: high value	-£1,725	0.204	Dominant
Long-term costs: cost of pre-term babies applied to all admitted neonates	-£1,756	0.204	Dominant
QALY decrement for mothers whose child died: applied for 10 years	-£1,746	0.1855	Dominant
QALY decrement for mothers whose child had complications: applied for 10 years	-£1,746	0.1776	Dominant
NG133, NICE Guideline 133; PE, pre-eclampsia; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio			

Scenario analyses for Elecsys sFlt-1/PlGF ratio test

The cost-effectiveness results for Elecsys sFlt-1/PlGF ratio test versus standard clinical assessment based on PreOS[34] inputs are presented in Table 66. Using the inputs from PreOS[34] (where available) has a significant impact on the results. In contrast to the base case results, the Elecsys sFlt-1/PlGF ratio test produces lower costs (-£595) than standard clinical assessment. This is mainly driven by savings in the neonatal costs, both short- and long-term, compared to base case. Moreover, the difference in QALYs is negligible as there are no differences between arms related with long-term outcomes. As stated in the previous DAR,[7] given that the utility data, particularly the short-term utility data, have a high degree of uncertainty as a result of being derived from mapping from SF-36, the differences in HRQoL are not likely to be clinically significant.

Table 66 Scenario analysis (PreOS): results for Elecsys sFlt-1/PlGF ratio test

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Standard assessment	£9,378	17.27			

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Elecsys sFlt-1/PlGF ratio test	£8,783	17.27	-£595	-0.0006	£1,081,112
QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio					

The Elecsys sFlt-1/PlGF ratio test is more expensive and produces fewer QALYs than standard clinical assessment in all the scenarios presented below (Table 67).

Table 67 Scenario analyses: results for Elecsys sFlt-1/PlGF ratio test

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY) vs. standard assessment
Base case	**£621**	**-0.1403**	**Dominated**
Time horizon: 6 months post-partum	£144	-0.0007	Dominated
Management of women with suspected PE: NG133	£686	-0.1403	Dominated
Level of hypertension: stratified by level of risk of PE	£677	-0.1403	Dominated
Gestational age <35 weeks: 0%	£685	-0.1403	Dominated
Gestational age <35 weeks: 100%	£575	-0.1403	Dominated
Time to delivery: based on PROGNOSIS	£620	-0.1404	Dominated
Immediate delivery: up to 24 hours	£621	-0.1403	Dominated
Neonatal admission to critical care units: based on PARROT	£305	-0.1403	Dominated
Death in neonates: excluding stillbirth	£621	-0.0565	Dominated
Cost of testing: low value	£608	-0.1403	Dominated
Cost of testing: high value	£652	-0.1403	Dominated
Long-term costs: cost of pre-term babies applied to all admitted neonates	£655	-0.1403	Dominated
QALY decrement for mothers whose child died: applied for 10 years	£621	-0.1304	Dominated
QALY decrement for mothers whose child had complications: applied for 10 years	£621	-0.1763	Dominated
NG133, NICE Guideline 133; PE, pre-eclampsia; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio			

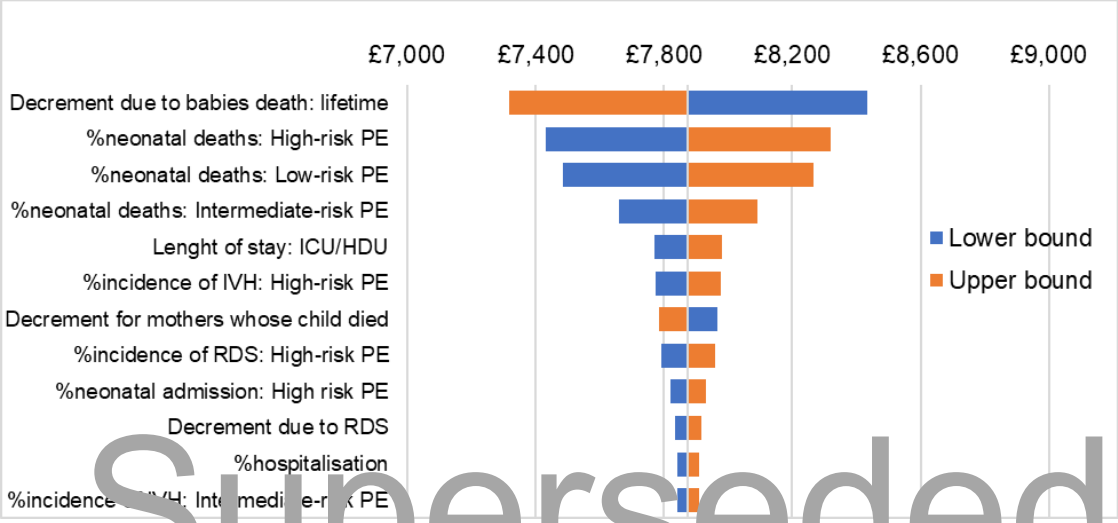

Figure 8 Tornado diagram: Net monetary benefit of Triage PlGF test versus standard clinical assessment

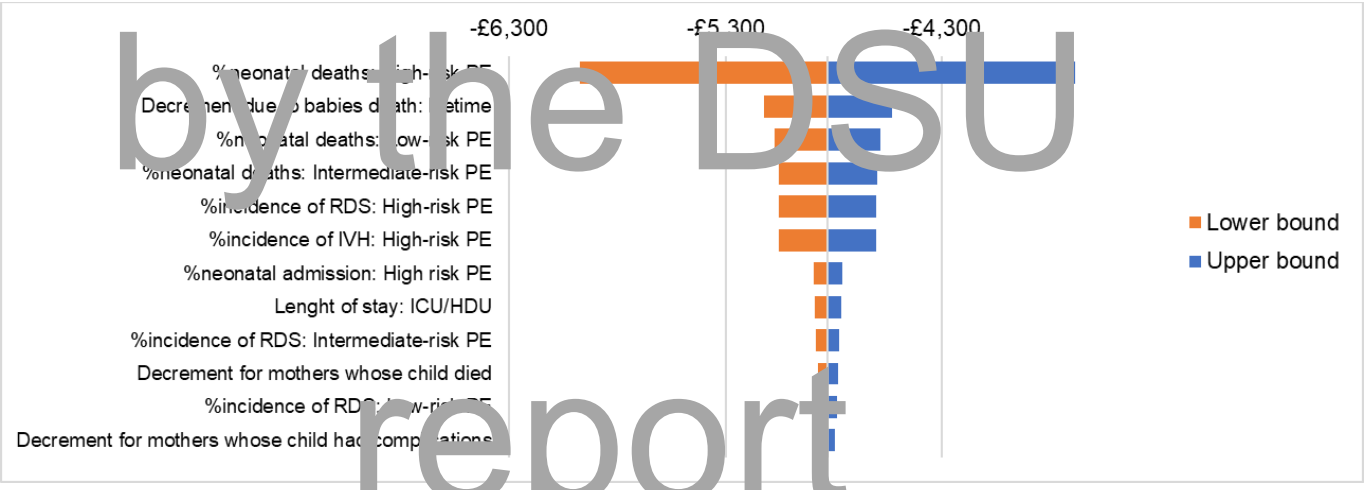

Figure 9 Tornado diagram: Net monetary benefit of Elecsys sFlt-1/PlGF ratio test versus standard clinical assessment

5.5.2.3 Comparison with the results of other economic evaluations

None of the studies in our review of cost-effectiveness searches included long-term costs and QALYs. For the Triage test, Duckworth and colleagues[98] reported a cost saving per woman tested of £635 and Duhig and colleagues[99] reported a cost saving of £149 per woman tested. We estimated a similar saving of £772 per woman tested for the time period to hospital discharge. For the Elecsys test, comparison is more difficult as the studies

	Low-risk PE	PE	0.5%	0%		
		No PE	0.2%	0%		
Elecsys (scenario based on PreOS)						
Cohort size (n)	<33		75	75	Pre	
	33 to <85		22	22		
	≥85		21	21		
PE prevalence in hospitalised women (%)	<33		20.9%	9.3%		Prevalence in hospitalised and non-hospitalised women in the comparator arm are assumed to be the same as the prevalence for the respective PlGF category reported in PreOS,[34] whereas prevalence in the test arm was based on changes in decision regarding hospitalisation with knowledge of test results (Klein 2016[34] p. 11).
	33 to <85		28.1%	28.1%		
	≥85		42.2%	40.5%		
PE prevalence in non-hospitalised women (%)	<33		6.4%	9.3%	PreOS[34]	
	33 to <85		28.1%	28.1%		
	≥85		38.6%	40.5%		

PLGF-BASED TESTING TO HELP DIAGNOSE SUSPECTED PRE-ECLAMPSIA (UPDATE OF DG23)

REPORT BY THE DECISION SUPPORT UNIT

28 January 2022

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ABOUT THE DECISION SUPPORT UNIT

The Decision Support Unit (DSU) External Assessment Centre is based at the University of Sheffield with members at York, Bristol, Leicester and the London School of Hygiene and Tropical Medicine. The DSU is commissioned by The National Institute for Health and Care Excellence (NICE) to provide a research and training resource to support the Institute's Centre for Health Technology Evaluation Programmes. Please see our website for further information www.nicedsu.org.uk.

The production of this document was funded by the National Institute for Health and Care Excellence (NICE) through its Decision Support Unit. The views, and any errors or omissions, expressed in this document are of the authors only. NICE may take account of part or all of this document if it considers it appropriate, but it is not bound to do so.

This report should be referenced as follows:

Kearns B., Wailoo A., Abdullah P., PLGF-Based Testing to Help Diagnose Suspected Pre-Eclampsia (Update of DG23). NICE DSU Report 2022.

EXECUTIVE SUMMARY

An economic model has been produced by an external assessment group (EAG) for the ongoing National Institute for Health and Care Excellence (NICE) diagnostics assessment programme assessment of PLGF-based testing to help diagnose suspected pre-eclampsia (PE).

After submission of the final diagnostics assessment report and model by the EAG, several concerns were raised by the NICE team, stakeholders, and the NICE diagnostics advisory committee about the model and approach to modelling taken by the EAG. As such, the committee did not agree draft recommendations at the first committee meeting, and requested additional modelling work. This additional work was carried out by the NICE Decision Support Unit and is described in this report.

Key aspects of the updated work were to ensure that all PLGF-based tests have the same comparator (standard assessment), to use the same patient-population for all comparisons, and gain expert clinical opinion on how the use of PLGF-based tests influenced the decision to admit a woman to hospital for suspected PE.

The original EAG model may be viewed as essentially providing a within-trial evaluation. When evaluating the Triage PLGF Test, evidence is primarily taken from the PARROT UK study. For the Elecsys immunoassay sFlt-1/PlGF ratio, evidence is primarily taken from the INSPIRE study. This approach makes it difficult to ensure that both the comparator (standard assessment) and populations considered are consistent across tests (as both vary by trial). Instead, for the updated DSU model a single ‘baseline’ trial was used, to which relative treatment effects are applied. Two baselines were considered: PARROT UK and INSPIRE. This approach ensures consistency in both the modelled population and the modelled assessment methods. The primary disadvantage of this approach is the heterogeneity across trials, both with regards to the definition of a test outcome and the patient populations considered. Due to this heterogeneity evidence synthesis was not undertaken, and the results of the economic evaluation should be treated with caution.

The use of relative treatment effects meant that the original EAG model required restructuring. Originally, outcomes were primarily driven by the trial (and arm) specific observed distributions of risk categories. During committee discussions it was noted that some of these differences were due to chance, and during stakeholder comments a stakeholder highlighted that cost-effectiveness results were to a degree driven by trial baseline imbalances. In the updated DSU model, a single population is modelled, with a distribution of hypertension severity and conditional upon this a prevalence of PE (as PE is more common amongst women with more severe hypertension). Differences in assessment method (use of PLGF-based tests, or standard assessment) are then reflected by differences in the identification of PE and subsequent management decisions. This is based on the sensitivity and specificity of the assessment method. Sensitivity and specificity were used in preference to other measures of test performance as these are independent of the prevalence of PE.

For the updated DSU model, evidence on test performance was taken from comparative studies that reported on the sensitivity and specificity of at least two assessment methods. Four studies were identified which collectively covered all four PLGF-based tests as well as standard assessment. Standard assessment was included in two studies, both of which compared it with Elecsys. Relative effects were very different between the two studies. Hence two different estimates of standard assessment were included in the model (one for each study). Of the four studies, only one provided evidence on the performance of a test when used in conjunction with clinical judgement (add-on Elecsys). All other studies reported on the stand-alone use of tests. Hence add-on Elecsys was included in addition to stand-alone Elecsys. This resulted in seven assessment methods:

- Standard assessment (from INSPIRE)
- Standard assessment (from DG23)
- Triage PlGF Test (hereafter ‘Triage test’)
- Elecsys immunoassay sFlt-1/PlGF ratio (hereafter ‘Elecsys’)
- Elecsys immunoassay sFlt-1/PlGF ratio (used as an add-on to standard assessment; hereafter ‘Elecsys add-on’)
- DELFIA Xpress PlGF 1-2-3 test (hereafter ‘DELFIA’)

- BRAHMS sFlt-1 Kryptor / BRAHMS PlGF plus Kryptor PE ratio (hereafter ‘BRAHMS’)

As clinical outcomes are driven by sensitivity and specificity, there were two mechanisms by which PLGF-based testing may lead to improved health economic outcomes:

1. Increase in the rate of true positive diagnoses (correct identification of women with PE).
2. Increase in the rate of true negative diagnoses (correct identification of women without PE).

An additional limitation of the original EAG model noted during the committee discussion was the assumption that all women with a high-risk test result would be admitted, and no other women would be admitted (apart from women with severe hypertension). For the updated DSU model, evidence on the decision to admit was obtained from a short survey. This asked clinical experts about the proportion of admitted (or not admitted) women for which the decision to admit would vary, dependent on the outcomes of a PLGF test. Five usable responses were obtained. All agreed that for a woman who would be admitted in the absence of a test, a high-risk test result would still result in an admission. For women with a high-risk test result who would not originally be admitted, three respondents stated that these women would never be admitted, one stated that half (50%) would be admitted, and one stated that all (100%) would be admitted. There was variation in how the other test results would alter the decision to admit. As such, a variety of scenarios were considered to assess the impact of test result on the clinical decision to admit. These can be broadly classified as either using tests to rule-out a suspicion of PE or using tests to both rule-out and rule-in a suspicion of PE.

For the base-case cost-effectiveness analysis, PLGF-based tests were used to rule-out PE, baseline test accuracy and hypertension severity were both taken from PARROT UK, all neonatal outcomes were included, and true positive test results were assumed to incur the same clinical management costs as false negative results. These assumptions were tested in scenario analyses. Due to a lack of robust comparative

evidence, PLGF-based tests were not compared to each other but were instead compared with standard assessment.

Cost-effectiveness results for the PLGF-based tests were found to vary depending on the choice of standard assessment (from INSPIRE or DG23), if testing were used to rule-out or both rule-out and rule-in PE, and the inclusion or exclusion of neonatal outcomes.

When used as rule-out tests (with neonatal outcomes included), all tests produced higher quality-adjusted life years (QALYs) and higher costs than both types of standard assessment. ICERs ranged from £637 (DELFIA vs standard assessment from INSPIRE) to £47,393 (Triage vs standard assessment from DG23) per QALY. Incremental costs and QALYs were always very small, with incremental costs always less than the cost of the test and incremental QALYs always less than 0.006. Excluding all neonatal outcomes led to all ICERs (compared with either standard assessment) exceeding £20,000.

When used to both rule-out and rule-in PE, PLGF-based tests always dominated standard assessment as used in DG23. This dominance remained when excluding all neonatal. When compared with standard assessment from INSPIRE, results became sensitive to the clinical management decisions used as which neonatal outcomes were included.

Results from scenario analyses showed that, in general, PLGF-based testing to rule-out and rule-in PE dominated both types of standard assessment. When used to just rule-out PE, use of the hypertension distribution from PARROT Ireland (representing less severe hypertension than the base-case) led to an increase in ICERs, as did use of the INSPIRE trial for both baseline test performance and standard assessment. Allowing true positive test results to cost more than false negative results had little impact on results.

Across analyses, incremental QALY gains for PLGF-based tests were always very small. The largest cost-savings were always associated with clinical management of suspected PE, followed-by short-term neonatal costs. The largest cost increases were

always the cost of the test. Amongst the PLGF-based tests, cost-effectiveness results were generally the most favourable for the Elecsys test when used as an add-on to standard assessment. For all of the other PLGF-based tests evidence was only available for their use as stand-alone tests. In practice they would be used as add-on tests, so the cost-effectiveness results reported here are likely to under-estimate the value of PLGF-based tests.

To conclude, use of PLGF-based tests to rule-out and rule-in PE has the potential to provide improved outcomes at reduced cost when compared with standard assessment. However, results are limited by heterogeneity in the evidence, particularly with regards to outcomes assessed by PLGF-based test. In addition, any estimated QALY-benefits associated with PLGF-based tests were very small, and there was a lot of uncertainty about the impact of PLGF-based tests on improving neonatal outcomes, the accuracy of standard assessment, the population that would receive these tests, and how PLGF-based tests influence decision-making. These uncertainties could each have a negative impact on the incremental estimates of cost and QALYs for PLGF-based tests.

CONTENTS

TABLES

FIGURES

ABBREVIATIONS AND DEFINITIONS

DAC	Diagnostics Advisory Committee
DAR	Diagnostics Assessment Report
DSU	Decision Support Unit
EAG	External Assessment Group
GA	Gestational Age
ICER	Incremental Cost-Effectiveness Ratio
NICE	National Institute for Health and Care Excellence
PE	Pre-Eclampsia
PLGF	Placental Growth Factor
QALY	Quality Adjusted Life Year

1. INTRODUCTION

An economic model has been produced by an external assessment group (EAG) for the ongoing NICE diagnostics assessment programme assessment of PLGF-based testing to help diagnose suspected pre-eclampsia.

After submission of the final diagnostics assessment report (DAR) and model by the EAG, several concerns were raised by the NICE team, stakeholders, and the NICE diagnostics advisory committee (DAC) about the model and approach to modelling taken by the EAG. This ultimately led to the committee not being able to produce draft recommendations at a committee meeting on 15th June 2021. Amendments to the model were requested by the committee, as follows:

- Standard assessment should be the same for all tests (that is, the comparator against which tests are compared with). This should represent current care in the NHS (without use of PLGF-based tests) and a population that the test would be used on in practice. If the characteristics of a trial population are used in the model, rationale should be provided to support the case that this is a good representation of wider NHS practice (for example, discussion with clinical experts and consideration of UK studies that assessed populations with suspected pre-eclampsia, potentially beyond INSPIRE and PARROT).
- The same population should be also used in the models for standard assessment (the comparator) and standard assessment plus use of PLGF-based test (the intervention).
- Clinical experts highlighted that PLGF-based test results would not be the only criterion used to make decisions about hospitalisation; therefore, assumptions that 100% of women with a positive result would be admitted and 0% of women with a negative result would not be admitted (excepting those with severe hypertension) will not reflect clinical practice. The committee requested amendment to the model to reflect this (using expert opinion to inform estimates) and exploration of uncertainty related to this.
- Model results to be provided with and without neonatal outcomes included, that is:

    - Full inclusion of neonatal outcomes (as per the EAG's original base case). The committee's view was that the assumption in the original base case of no impact of the Elecsys test use on neonatal outcomes (mortality, RDS, IVH; in contrast to the Triage test) was not appropriate.
    - Removal of all neonatal outcomes (as per addendum)
    - Removal of short-term neonatal outcomes only: IVH, RDS and neonatal death.
- A probabilistic sensitivity analysis to be done.
- Estimated costs and QALYs per person to be provided by pre-eclampsia status (present or not present) and test result (true/false positive/negative or high/intermediate/low risk of pre-eclampsia).
- Analyses should be provided for all 4 tests included in the scope of this assessment.

In addition, the DSU were requested to identify any additional relevant studies that have become available since the EAG DAR. For any identified studies a quality assessment should be provided and, if relevant, model analyses using these data.

This review

This report describes the work carried out by the DSU. It includes details of the changes made to the original EAG model, cost-effectiveness results from the updated model, and an overview of the recently published PARROT-IRELAND study.

2. METHODS: DSU CHANGES TO THE EAG MODEL

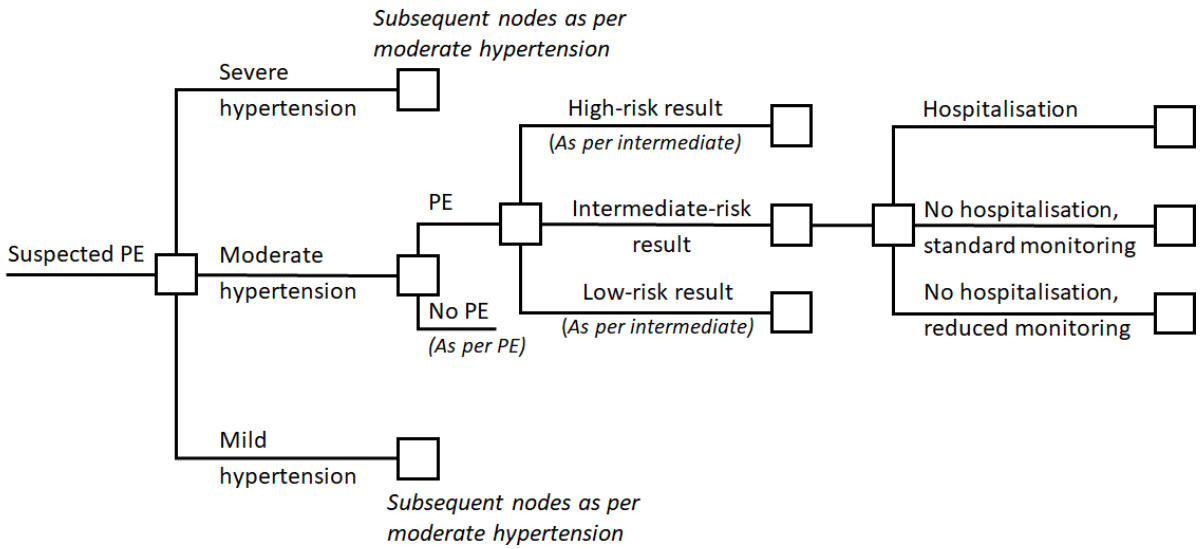
An overview of the inputs used for the updated and restricted DSU model is provided in Appendix A.1. Clinical effectiveness parameters are given in Table 27, resource use evidence is provided in Table 28, whilst utility values are displayed in Table 29. The methods used to obtain these inputs, along with additional details and justification, are provided in the following sections.

2.1. CLINICAL EFFECTIVENESS

The original EAG model used trial-specific evidence. For example, the economic evaluation of the Triage test mainly used evidence from the PARROT UK trial,[1] whilst INSPIRE[2] was the main evidence source for the Elecsys evaluation. This approach meant that patient populations and definitions of standard assessment (the approach taken in the absence of PLGF-based tests) varied by test and so health economic outcomes could not be compared across tests. To allow for a comparison across tests, the health economic model was re-structured to use estimates of relative test performance (sensitivity and specificity) which were applied to a single baseline population. This ensured that the same population was used for all evaluations and a consistent definition of standard assessment was used (although, as will be seen, two separate estimates of standard assessment were used in the model).

An overview of the updated risk stratification and pregnancy management is provided in Figure 1. The modelling of maternal and neonatal outcomes uses the same structure as the original EAG model.

Figure 1: Updated model structure (risk stratification and pregnancy management)



The updated DSU model required information on the following clinical effectiveness parameters:

- Distribution of hypertension categories.
- Prevalence of PE by hypertension category.
- Test sensitivity and specificity.
- Clinical management decisions conditional on the original decision to admit, and the test result.

These are discussed in turn. Throughout, information on the steps taken to make the model probabilistic are also provided. For probabilistic analyses 10,000 iterations were used.

2.1.1. Distribution of hypertension categories

For their addendum, the EAG used evidence from PARROT UK[1] to derive distributions of hypertension categories. This reported an average highest systolic blood pressure of 143.56 (standard deviation 20), which was assumed to follow a Normal distribution, with hypertension categories based on cut-offs of >160 for severe hypertension, 150 to 160 for moderate hypertension, and <150 for mild hypertension. This source and approach was retained for the updated base-case for two reasons:

- As a large, multi-centre UK study, evidence from PARROT UK is of relevance to the NHS.
- Compared to the original EAG base-case (which combined evidence from PARROT UK and PELICAN),[1,3] this approach is more consistent as all the evidence is from a single source.

It is possible to derive distributions of hypertension categories from a variety of other sources. Three were selected for scenario analyses as collectively they provide a range of different distributions. Resulting categories are provided in Table 1. Categories were derived from PARROT IRELAND[4] (mean 136.29, standard deviation 18.38) using the same approach as for the base-case. For PELICAN[3,5] and 'EAG, Triage test (PE)' values by category were directly available.

For probabilistic analyses a Dirichlet distribution was used.

Table 1: Distributions of hypertension categories considered in the economic evaluation

Hypertension category	PARROT UK	PARROT IRELAND	PELICAN	EAG (Triage test, PE)
Severe	20.56%	9.85%	5.32%	42.00%
Moderate	16.82%	12.93%	58.40%	43.00%
Mild	62.62%	77.21%	36.27%	15.00%

2.1.2. Prevalence of pre-eclampsia by hypertension status

The PELICAN study was the only identified evidence to report on the distribution of pre-eclampsia by hypertension status. This is reproduced in Table 2. For probabilistic analyses a Dirichlet distribution was used, with the total counts set to 60 (the number of participants in PELICAN[5]).

Table 2: Distribution of pre-eclampsia by hypertension status (from Figure 1 of PELICAN)[5]

Hypertension category	Pre-eclampsia (PE) status	Percent of whole sample	Percent of hypertension category

Mild	No PE	29.0%	74.70%
Mild	PE	7.3%	25.30%
Moderate	No PE	38.1%	66.65%
Moderate	PE	20.3%	33.35%
Severe	No PE	2.8%	26.75%
Severe	PE	2.5%	73.25%

2.1.3. Test sensitivity and specificity

Based on the studies identified in the EAG report, four studies were identified that reported on the sensitivity and specificity of at least two assessment methods (PLGF-based or standard assessment), and so could be used to obtain relative estimates of test accuracy. Relative treatment effects were used as it was assumed that these would generalise across studies (that is, unlike absolute estimates of test accuracy, relative estimates would not be affected by differences in trial populations). These relative effects were then applied to baseline (absolute) sensitivity and specificity values for a single test, to generate absolute estimates of sensitivity and specificity for each test (including standard assessment).

An overview of the four studies is provided in Table 3, and the available comparisons is illustrated in Table 4: Quality assessment of Simon and COMPARE studies: risk of bias

	Simon	**COMPARE**
Patient selection		
1. Was a consecutive or random sample of patients enrolled?	Yes	Yes
2.Was a case-control design avoided?	No	Yes
3. Did the study avoid inappropriate exclusions?	Yes	Yes
Could the selection of patients have introduced bias?	High	Low
Index test		
1. Were the index test results interpreted without knowledge of the results of the reference standard?	N/A	N/A
2. If a threshold was used, was it pre-specified?	Yes	No (DELFIA)
Could the conduct or interpretation of the index test have introduced bias?	Low	High
Reference standard		
1. Is the reference standard likely to correctly classify the target condition?	Yes	Yes
2. Were the reference standard results interpreted without knowledge of the results of the index test?	Yes	Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?	Low	Unclear
Flow and Timing		
1. Was there an appropriate interval between index test(s) and reference standard?	N/A	Yes
2. Did all patients receive a reference standard?	Yes	Yes
3. Did patients receive the same reference standard?	Unclear	Yes
4. Were all patients included in the analysis?	Yes	Yes
Summary of Q 1 to 4: Could the patient flow have introduced bias?	Unclear	Low

Table 5: Quality assessment of Simon and COMPARE studies: applicability

	Simon	COMPARE
Patient selection		
Is there concern that the included patients and settings do not match the review question?	High	Low
Index test		
Is there concern that the index test, its conduct, or interpretation differ from the review question? i.e. used/followed decision tool	Low	Low
Reference standard		
Is there concern that the target condition as defined by the reference standard does not match the review question?	High	Low

Table 6: Additional details for the Simon study

Design	Case-control study (participants selected from a previous prospective cohort study). Matching by parity and body mass index.
Total population analysed	Total: 42 (21 cases, 21 controls)
Test diagnostic cut-offs	Same cut-offs for both tests: >38 (suspicion of PE), ≥85 (aid in PE diagnosis)
Use of the test	Fresh blood samples tested for Elecsys, frozen samples tested for BRAHMS within three years
Reference standard diagnostic criteria	PE: National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Fetal growth restriction: when an estimated fetal weight by ultrasound was<3rd centile, or when an estimated fetal weight of <10th centile was detected together with abnormal fetal Doppler (umbilical artery pulsatility index>95th centile, middle cerebral artery pulsatility index<5th centile or cerebroplacental ratio<5th centile)
Reasons for suspected pre-eclampsia	Maternal factors and uterine artery Doppler resistances

Figure 2. The list of studies that were ongoing at the time of the EAG DAR (Appendix 6) was also checked. Studies that did not use the test cut-offs recommended in the final scope for DG23 were excluded.

Within the EAG DAR there was no quality assessment for the Simon and COMPARE studies. This is provided in Table 4 for risk of bias and Table 5for applicability. The main concerns for the Simon study are the non-UK setting, and the definition of a case (which includes fetal growth restriction as well as PE, with measurements restricted to 24 to 28 weeks gestation). For the COMPARE study the main concern was the lack of a pre-specified threshold for the BRAHMS test. The EAG DAR did not provide study details for the Simon study; these are provided in Table 6.

Table 3: Characteristics of studies providing comparative test accuracy estimates (sensitivity and specificity)

Study	Tests evaluated	Locations	Population	Median baseline gestational age (GA), weeks	Proportion with pre-eclampsia (PE)*	Test outcome
INSPIRE	Elecsys (add-on) Elecsys (stand-alone) Standard assessment	Clinical trial. Single site (Oxford, UK)	Women with GA 24 to 37 weeks	34	23%	Admission driven by the test (or standard assessment) within 24 hours (within 7 days or by delivery also considered)
COMPARE	Triage test (stand-alone) Elecsys (stand-alone) DELFIA (stand-alone)	Retrospective analysis of three prospective cohorts. Multiple UK and Ireland sites	Women with GA up to 37 weeks	28 (Baseline GA < 35) 36 (Baseline GA 35 to 36[+6])	16%	Delivery within 14 days secondary to suspected PE
Simon	Elecsys (stand-alone) BRAHMS (stand-alone)	Case-control study. Single site (Madrid, Spain)	Women with GA 24 to 28[+6] weeks	Not reported	N/A (case-control study)	Diagnosis of PE or fetal growth restriction
Schnettler	Elecsys (stand-alone) Standard assessment	Prospective cohort. Single site (Boston, USA)	No restriction by GA	31	34%	Adverse maternal and fetal outcomes within two weeks

Table 4: Quality assessment of Simon and COMPARE studies: risk of bias

	Simon	**COMPARE**
Patient selection		
1. Was a consecutive or random sample of patients enrolled?	Yes	Yes
2.Was a case-control design avoided?	No	Yes
3. Did the study avoid inappropriate exclusions?	Yes	Yes
Could the selection of patients have introduced bias?	High	Low
Index test		
1. Were the index test results interpreted without knowledge of the results of the reference standard?	N/A	N/A
2. If a threshold was used, was it pre-specified?	Yes	No (DELFIA)
Could the conduct or interpretation of the index test have introduced bias?	Low	High
Reference standard		
1. Is the reference standard likely to correctly classify the target condition?	Yes	Yes
2. Were the reference standard results interpreted without knowledge of the results of the index test?	Yes	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low	Unclear
Flow and Timing		
1. Was there an appropriate interval between index test(s) and reference standard?	N/A	Yes
2. Did all patients receive a reference standard?	Yes	Yes
3. Did patients receive the same reference standard?	Unclear	Yes
4. Were all patients included in the analysis?	Yes	Yes
Summary of Q 1 to 4: Could the patient flow have introduced bias?	Unclear	Low

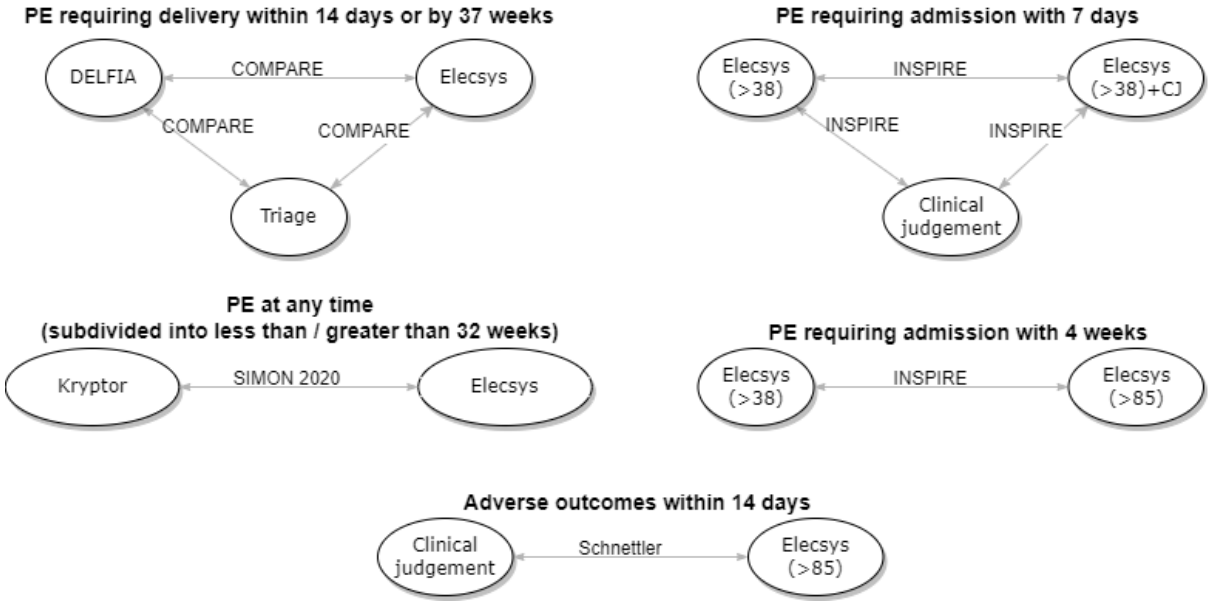
Table 5: Quality assessment of Simon and COMPARE studies: applicability

	Simon	COMPARE
Patient selection		
Is there concern that the included patients and settings do not match the review question?	High	Low
Index test		
Is there concern that the index test, its conduct, or interpretation differ from the review question? i.e. used/followed decision tool	Low	Low
Reference standard		
Is there concern that the target condition as defined by the reference standard does not match the review question?	High	Low

Table 6: Additional details for the Simon study

Design	Case-control study (participants selected from a previous prospective cohort study). Matching by parity and body mass index.
Total population analysed	Total: 42 (21 cases, 21 controls)
Test diagnostic cut-offs	Same cut-offs for both tests: >38 (suspicion of PE), ≥85 (aid in PE diagnosis)
Use of the test	Fresh blood samples tested for Elecsys, frozen samples tested for BRAHMS within three years
Reference standard diagnostic criteria	PE: National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Fetal growth restriction: when an estimated fetal weight by ultrasound was<3rd centile, or when an estimated fetal weight of <10th centile was detected together with abnormal fetal Doppler (umbilical artery pulsatility index>95th centile, middle cerebral artery pulsatility index<5th centile or cerebroplacental ratio<5th centile)
Reasons for suspected pre-eclampsia	Maternal factors and uterine artery Doppler resistances

Figure 2: Overview of studies providing comparisons of test performance



As can be seen from Table 3, these studies vary with regards to the population included (in particular, gestational age), tests considered, how tests were used (as stand-alone or add-ons to standard assessment), and the definition of a positive result.

An overview of the test sensitivity and specificity values is provided in Table 7. When estimating and applying relative treatment effects, sensitivity and specificity values were first converted from probabilities to rates (and converted back afterwards). This ensures that any values obtained from relative effects are constrained to the interval [0, 1]. In some instances, sensitivity values were reported as 100%. When this occurred, a continuity correction was applied by adding 0.5 to the number of cases that were correctly identified, and 1 to the overall sample size. An example of deriving the sensitivity of Elecsys relative to the Triage test (from COMPARE[6]) and applying this to the PARROT UK[1] baseline is shown below.

Sensitivity of Elecsys (high-risk result, from COMPARE): 0.65

Above sensitivity, as a rate: $-\ln(1-0.65) = 1.06$

Sensitivity of Triage (high-risk result, from COMPARE): 0.54

Above sensitivity, as a rate: $-\ln(1-0.54) = 0.77$

Relative sensitivity of Elecsys (based on rates): 1.37

Baseline sensitivity (Triage high-risk result, from PARROT UK): 0.74

Above sensitivity, as a rate: $-\ln(1-0.74) = 1.36$

Absolute sensitivity of Elecsys: $1 - exp(-1.36 * 1.37) = 0.85$

When deriving sensitivity and specificities, logical constraints were included to ensure that high-risk thresholds never have better sensitivity or worse specificity than intermediate-risk thresholds.

Of note, the approach of using relative estimates of sensitivity and specificity meant that evidence for the BRAHMS (Kryptor) can be easily incorporated, using the Simon study.[7] Evidence from the two PARROT trials (UK and Ireland) was not used as these studies did not report on the sensitivity and specificity of standard assessment.[1,4] Evidence from PROGNOSIS[8] includes Elecsys and standard assessment (use of the ACOG criteria) but this was not included as it was assumed to be superseded by the INSPIRE trial,[2] for which standard assessment was based on observed clinical decision-making. Similarly, it was assumed that the PELICAN trial[3] was superseded by PARROT UK[1].

As illustrated in Table 4: Quality assessment of Simon and COMPARE studies: risk of bias

	Simon	**COMPARE**
Patient selection		
1. Was a consecutive or random sample of patients enrolled?	Yes	Yes
2.Was a case-control design avoided?	No	Yes
3. Did the study avoid inappropriate exclusions?	Yes	Yes
Could the selection of patients have introduced bias?	High	Low
Index test		
1. Were the index test results interpreted without knowledge of the results of the reference standard?	N/A	N/A
2. If a threshold was used, was it pre-specified?	Yes	No (DELFIA)
Could the conduct or interpretation of the index test have introduced bias?	Low	High
Reference standard		
1. Is the reference standard likely to correctly classify the target condition?	Yes	Yes
2. Were the reference standard results interpreted without knowledge of the results of the index test?	Yes	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low	Unclear
Flow and Timing		
1. Was there an appropriate interval between index test(s) and reference standard?	N/A	Yes
2. Did all patients receive a reference standard?	Yes	Yes
3. Did patients receive the same reference standard?	Unclear	Yes
4. Were all patients included in the analysis?	Yes	Yes
Summary of Q 1 to 4: Could the patient flow have introduced bias?	Unclear	Low

Table 5: Quality assessment of Simon and COMPARE studies: applicability

	Simon	COMPARE
Patient selection		
Is there concern that the included patients and settings do not match the review question?	High	Low
Index test		
Is there concern that the index test, its conduct, or interpretation differ from the review question? i.e. used/followed decision tool	Low	Low
Reference standard		
Is there concern that the target condition as defined by the reference standard does not match the review question?	High	Low

Table 6: Additional details for the Simon study

Design	Case-control study (participants selected from a previous prospective cohort study). Matching by parity and body mass index.
Total population analysed	Total: 42 (21 cases, 21 controls)
Test diagnostic cut-offs	Same cut-offs for both tests: >38 (suspicion of PE), ≥85 (aid in PE diagnosis)
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Reference standard diagnostic criteria	PE: National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Fetal growth restriction: when an estimated fetal weight by ultrasound was<3rd centile, or when an estimated fetal weight of <10th centile was detected together with abnormal fetal Doppler (umbilical artery pulsatility index>95th centile, middle cerebral artery pulsatility index<5th centile or cerebroplacental ratio<5th centile)
Reasons for suspected pre-eclampsia	Maternal factors and uterine artery Doppler resistances

Figure 2, comparative evidence was used from four different studies. Two of these studies provided evidence for standard assessment, with both comparing it to the Elecsys test. Relative effects were very different between the two studies. When applied to the PARROT UK trial, standard assessment from INSPIRE (used in the EAG DAR) had sensitivity and specificity values of 0.74 and 0.72, respectively. In contrast, standard assessment from Schnettler[9] (as used in the original DG23 report) had values of 0.98 and 0.25, respectively. During stakeholder comments on the EAG DAR, a stakeholder noted that the INSPIRE trial may not be representative of many UK hospitals, particularly those which have limited accessibility or less experience of managing suspected PE. Hence, they suggested that standard assessment as used in DG23 may be more representative. For this economic evaluation both estimates of standard assessment were included and presented as separate assessment methods.

Of the four studies providing comparative evidence, only one provided evidence on the performance of a test when used in conjunction with clinical judgement (add-on Elecsys). All other studies reported on the stand-alone use of tests. Hence add-on

Elecsys was included in addition to stand-alone Elecsys. This resulted in seven assessment methods:

1. Standard assessment (from INSPIRE)
2. Standard assessment (from DG23)
3. Triage test
4. Elecsys
5. Elecsys (add-on)
6. DELFIA
7. BRAHMS

As with the original EAG analysis, PARROT UK and INSPIRE were considered to be the most relevant sources of trial evidence. Hence two analyses were considered, one where absolute test performance values (sensitivity and specificity) were derived from PARROT UK[1], and one where INSPIRE[2] was used. Resulting values are provided in Table 7, along with details of how they were derived. Base-case analyses use the PARROT UK trial population, as this was deemed to be more relevant to the NHS than INSPIRE (PARROT UK is a multi-centre trial, whilst INSPIRE is a single-centre trial). The ROPE study[10] provided estimates of the sensitivity and specificity of the BRAHMS test. Whilst there were no estimates of relative test accuracy, this study could have been used as a source of absolute test performance values. This approach was not pursued as the ROPE study is US-based, and the relevance to the UK NHS is unclear.

A full overview of model inputs is provided in Appendix A.1.

Table 7: Sensitivity and specificity values used in the updated economic model

Baseline = PARROT UK	Sensitivity	Specificity	Notes
Triage <100	0.95	0.53	Absolute values from PARROT UK[1]
Triage <12	0.74	0.84	Absolute values from PARROT UK[1]
Elecsys >38	0.91	0.72	Relative to Triage <100, from COMPARE[6]
Elecsys >85	0.85	0.84	Relative to Triage <12, from COMPARE[6]
DELFIA >150	0.97	0.53	Relative to Triage <100, from COMPARE[6]
DELFIA >50	0.85	0.83	Relative to Triage <12, from COMPARE[6]

BRAHMS >38	0.96	0.67	Relative to Elecsys >38, from Simon 2020[7]
BRAHMS >85	0.92	0.77	Relative to Elecsys >85, from Simon 2020[7]
Elecsys+CJ >38	0.95	0.70	Relative to Elecsys >38, from INSPIRE 2019[2]
Elecsys+CJ >85	0.90	0.82	Assume can use same relative effect as above
Clinical judgement (INSPIRE)	0.74	0.72	Relative to Elecsys >38, from INSPIRE 2019[2]
Clinical judgement (Schnettler)	0.98	0.25	Relative to Elecsys >85, from Schnettler 2013[9]
Baseline = INSPIRE	**Sens**	**Spec**	**Notes**
Triage <100	0.98	0.61	Relative to Elecsys >38, from COMPARE[6]
Triage <12	0.90	0.80	Relative to Elecsys >85, from COMPARE[6]
Elecsys >38	0.96	0.80	Absolute values from INSPIRE 2019[2]
Elecsys >85	0.71	0.80	Relative to Elecsys >38, from INSPIRE 2021[11,12]
DELFIA >150	0.99	0.61	Relative to Elecsys >38, from COMPARE[6]
DELFIA >50	0.90	0.79	Relative to Elecsys >85, from COMPARE[6]
BRAHMS >38	0.99	0.75	Relative to Elecsys >38, from Simon 2020[7]
BRAHMS >85	0.82	0.75	Relative to Elecsys >85, from Simon 2020[7]
Elecsys+CJ >38	0.98	0.78	Relative to Elecsys >38, from INSPIRE 2019[2]
Elecsys+CJ >85	0.79	0.78	Assume can use same relative effect as above and apply to Elecsys >85
Clinical judgement (INSPIRE)	0.83	0.80	Relative to Elecsys >38, from INSPIRE 2019[2]
Clinical judgement (Schnettler)	0.92	0.22	Relative to Elecsys >85, from Schnettler 2013[9]

Within the economic evaluation the test sensitivity and specificity were assumed to be independent of hypertension severity. This assumption was informed by an analysis of published data from the PELICAN study,[3] which showed very similar performance for the Triage test by hypertension category, as shown in Table 8.

Table 8: Sensitivity and specificity by hypertension status[5]

Parameter	Sensitivity	Specificity
PLGF <100		

Severe hypertension	95.45%	54.60%
Moderate hypertension	95.90%	56.77%
Mild hypertension	93.33%	58.82%
PLGF <12		
Severe hypertension	61.36%	88.51%
Moderate hypertension	63.11%	91.27%
Mild hypertension	60.00%	88.24%

2.1.4. Clinical management decisions

One area of uncertainty highlighted at the first committee meeting was the impact PLGF test results might have on management decisions for women. In particular, the role of PLGF test results on the decision for women to be hospitalised or not, which is a key part of the economic model, was questioned.

The original EAG model classifies women according to clinical risk stratification into low, intermediate, and high risk of pre-eclampsia. Women assessed as being at high risk of pre-eclampsia are admitted and managed as inpatients, while those at low and intermediate risk of pre-eclampsia are managed in an outpatient setting. This is the initial management decision only: admission at a later stage is possible where symptoms of pre-eclampsia develop. Similarly, women who have been admitted to hospital but do not develop disease are assumed to be discharged at some point and managed as outpatients up to delivery.

According to the EAG report, for the Triage test and comparator, evidence on this initial management decision was drawn from the PARROT UK trial.[13] Where the test was classified as low or intermediate risk, 0% of patients were hospitalised. For high-risk, 100% of patients were hospitalised. This is based on the clinical management algorithm in PARROT UK. For the comparator group, again 0% of the low and moderate groups were hospitalised. 72% of patients that would have been high risk PLGF are assumed to be hospitalised. This was estimated from RR=1.31 for the number of patients in test and comparator arms in PARROT diagnosed within 24 hours.[1]

During the committee discussion of the EAG report, it was reported that the committee heard from clinical experts that these estimates did not reflect clinical practice. Clinical experts highlighted that PLGF-based test results would not be the only criterion used to make decisions about hospitalisation. As such, the committee concluded that assumptions that 100% of women with a positive result would be admitted and 0% of women with a negative result would not be admitted (excepting those with severe hypertension) will not reflect clinical practice. The committee requested amendment to the model to reflect this (using expert opinion to inform estimates) and exploration of uncertainty related to this.

The DSU contacted seven clinical experts from specialist committee members appointed for the committee, and from other relevant clinical contacts in this area. A short survey was developed that focussed on the following estimates:

- The proportion of women that would be admitted to hospital, if they were assessed as high risk on the basis of clinical assessment, conditional on the result of a PLGF test.
- The proportion of women that would be admitted to hospital if they were assessed as low or moderate risk on the basis of clinical assessment, conditional on the result of a PLGF test.

Six responses were received but not all of these provided direct results to the survey. It was noted that the questions were difficult to answer because they were not directly related to clinical practice. Two respondents also stated that published evidence should be used.

One respondent stated that a clinical assessment to admit a patient would not be changed by the result of a PLGF test. They also stated that they would not admit a patient on the basis of a PLGF test but would use closer surveillance for those testing moderate and high risk and lower the surveillance for those testing low risk.

One respondent referred to audit data showing that 79% of women with an abnormal test result were admitted. Quantitative responses to the survey are provided in Table 9.

Table 9: Survey responses

Respondent ID	Clinical decision: hospital			Clinical decision: not hospital		
	High	Mod	Low	High	Mod	Low
1	100	20	0	0	0	0
2	100	50	20	50	0	0
3	100	70	30	100	30	0
4				0	0	0
5	100	100	100	0	0	0

The following issues were also highlighted during responses to the survey:

- Several respondents indicated that women assessed as needing to be admitted to hospital that then had a PLGF test indicating either moderate or low risk would not then be admitted to hospital for management of pre-eclampsia, but they may be admitted for other reasons. These costs should not be included in the economic model.
- Several respondents also indicated that whilst they would not admit women on the basis of a high-risk PLGF test alone, they would monitor them more closely outside of the hospital setting. They may also reduce surveillance of those whose test results are low-risk.

Due to the heterogeneity in responses, three different options for clinical management decisions were derived from the survey responses. For all three options, for women in whom the original decision was to admit, the proportion who are subsequently admitted was based on an average of the values provided in Table 9.

1. Testing is only used to rule-out PE. That is, for women in whom the original decision was not to admit, the decision is unchanged.
2. Testing for rule-out and rule-in. For women in whom the original decision was not to admit, 100% of those with a high-risk test result are admitted, and 30% of those with an intermediate-risk test result are admitted.
3. Testing for rule-out and cautious rule-in. For women in whom the original decision was not to admit, 50% of those with a high-risk test result are admitted.

In addition to this survey, evidence on how the results of a PLGF-test influence the decision to admit was available in the PreOS study[14] and is reproduced in Table 10.

Table 10: Numbers admitted before and after testing, by test result

Numbers admitted	High risk	Intermediate risk	Low risk
Before test result			
Admit	9	8	23
Don't Admit	12	14	52
After test result			
Admit	11	8	15
Don't Admit	10	14	60

This was used to derive evidence from the model based on the following assumptions:

- The 11 admitted following a high-risk test result includes the nine who would have been admitted without testing.
- The eight admitted following an intermediate-risk test result are the same eight who would have been admitted without testing.
- The 15 admitted following a low-risk test result are a subset of the 23 who would have been admitted without testing.

Table 11 provides the four clinical management decisions considered. Of note, in the economic model the decision without a test is based on hypertension severity (with only severe hypertension being admitted), and subsequent hospitalisation decision influenced by the use of tests. These could be PLGF-based tests, or tests used as part of standard assessment.

Table 11: Proportion of women hospitalised based on previous decision and test result

Decision based on hypertension severity	Test result	Rule-out	Rule-out and rule-in	Rule-out and cautious rule-in	PreOS
Admit	High risk	100%	100%	100%	100%
Admit	Int. risk	60%	60%	60%	100%
Admit	Low risk	38%	38%	38%	65%
Don't admit	High risk	0%	100%	50%	17%
Don't admit	Int. risk	0%	30%	0%	0%

Don't admit	Low risk	0%	0%	0%	0%

For women who are not admitted, it is assumed that under standard assessment resource use follows the expectant management pathway (stratified by hypertension severity), as described in the EAG DAR (Table 100). Resource use with PLGF-based tests was the same as for standard assessment, with the one difference that women with moderate hypertension and a low-risk test result were managed the same as women with mild hypertension. This assumption was based on discussions with clinical experts.

2.1.5. Errors identified with the EAG model

In addition to structural changes, some errors were also identified with the EAG model. These were not anticipated to have a large impact on estimates of cost-effectiveness and they were fixed for the updated DSU model.

- Women between 35 to 37 weeks gestational age with severe hypertension and either low or intermediate risk of hypertension were assigned the cost of two fetal assessments. Table 100 of the EAG DAR states that these women would receive one fetal assessment, so the model was changed to assign the cost of one assessment.
- Clinical management costs when using a test for women with a high-risk test result and mild hypertension had a typo whereby the resource use for corticosteroids was added to its unit cost. This was fixed so that resource use was multiplied by unit cost.
- On sheets ‘cTriage’ and ‘uTriage’ the cells R35:R36 are both hard-coded. These were changed to use the correct formulae.

2.2. RESOURCE USE AND COSTS

2.2.1. Clinical management

Resource use for the clinical manage varied by both time to delivery and gestational age. Hence these are discussed first, before describing other aspects of resource use and costs.

2.2.1.1. Time to delivery

Evidence on time to delivery by gestational age were taken from the PARROT UK study,[13] which provided evidence by trial arm and PLGF category. There was some evidence that time to delivery was shorter for the PLGF-revealed group amongst women with very low PLGF (< 12 pg/ml); with values of 12 days (gestational age <35 weeks) and 4 days (gestational age 35+0 to 36+6 weeks), compared with respective values of 17 and 8 amongst the usual care arm. For the remaining PLGF categories, time to delivery was very similar between trial arms. As rates of PE are more common amongst the very low PLGF group there is the potential that this is confounding results. When comparing tests with different performances this could create illogical results (with a woman's time to delivery varying depending upon which test is used). Hence for the updated model time to delivery instead varied by both gestational age and the woman's true PE status. The only identified study that reported evidence on time to delivery by both factors was PELICAN[3]. This reports delivery times of 19 and 5 days for women with PE and gestational ages of less than 35 and 35 to 37 weeks (respectively). Values for women without PE were estimated to be 45 and 8 days, respectively. In probabilistic analyses these times were varied using a normal distribution assuming that the standard error was 10% of the mean. Sampled values were capped to not be less than two days. As with the original model, it was assumed that admitted women with a gestational age greater than 35 weeks and severe hypertension had a time to delivery of two days (this time was not varied). This same assumption was also expanded to also include women with a gestational age greater than 35 weeks and PE who were admitted.

2.2.1.2. Gestational age

In the original EAG model, data on the proportion of women with a gestational age less than 35 weeks was derived from either the PARROT UK or INSPIRE trials.[1,2] For the former, this proportion varied by risk category and was derived via assumptions. For the latter there was no variation by risk, and data were from a confidential analysis. For the updated basecase evidence from the PELICAN study[3] was used as this provided the proportion of women with a gestational age less than 35 weeks (287/625 =) 46%. This proportion was varied via a beta distribution.

In the original EAG model, hospitalised women (those with a high-risk test result) were assumed to remain in hospital for the duration of their treatment. Evidence from PARROT UK shows that the average number of inpatient nights was very similar across trial arms (7.43 in the revealed group and 7.26 in the concealed group).[1] Hence in the updated a weighted average of 7.36 was used for admitted women (with the exception of admitted women with PE or severe hypertension and a gestational age greater than 35 weeks, for whom two days was used). The corresponding cost for this admission is taken from the NHS Payment by Results Tariff 2020/21 (NZ18A)[15], which is a fixed cost for stays of up to eight days. Hence variation in length of stay was not modelled.

2.2.2. Delivery, maternal and neonatal resource use

Information on the onset of delivery, mode of delivery, use of magnesium sulphate, use of neonatal healthcare resources, maternal and neonatal outcomes were all reported for the PARROT UK trial.[1,13] This evidence was used to make the original EAG calculations probabilistic. There was some evidence to suggest a difference by test arm in both maternal outcomes and short-term neonatal healthcare resources, so these outcomes were specific to if a test was used (but did not vary by type of test due to a lack of evidence). There was no evidence that testing led to an improvement in long-term neonatal costs. However, discussions during the first committee meeting noted that whilst there was no direct evidence, both PARROT UK[1] and INSPIRE[2] provided evidence to suggest that decisions about care may be improved with PLGF-based testing and this may impact on long-term outcomes. Hence a change in long-

term neonatal costs was incorporated. This was derived by applying the relative differences in costs (between testing and no testing) for short-term neonatal costs. In PARROT UK there was evidence to suggest that onset of delivery, mode of delivery, and use of magnesium sulphate did not differ between the Triage test and standard assessment arms.[13] Hence delivery costs were the same regardless of if a test was used, and based on PARROT UK data pooled across both arms.[1] This differs from the original EAG approach, for which these costs varied by arm. The change in approach was to avoid estimates of incremental cost-effectiveness being driven by trial imbalances.

For neonatal healthcare resource use (use of intensive care, high-dependency units or special baby care unit), a gamma distribution was used. Published standard deviations were converted to standard errors using the number of neonatal admissions as the denominator (this is a subset of the overall sample).

2.2.3. Unit costs

The majority of unit costs were taken from standard national sources (such as NHS reference costs and NHS Payment by Results), as detailed in Table 104 of the EAG report. These were sampled using a gamma distribution, assuming that the standard error was 10% of the mean. The following logical constraints were also applied:

- The cost of a spontaneous birth with assistance was constrained to never be less than the cost of a spontaneous birth without assistance.
- The cost of an induced birth with assistance was constrained to never be less than the cost of an induced birth without assistance.
- The cost of an emergency caesarean section was constrained to never be less than cost a planned caesarean section.

Long-term neonatal costs were taken from the literature.[16,17] There was insufficient reported evidence to obtain estimates of uncertainty, so the standard error was assumed to be 10% of the mean, and a gamma distribution was used.
The following costs were assumed to not vary:

- The tests under evaluation.

- Labetalol, magnesium sulfate, corticosteroids.

2.3. UTILITIES

As with the original EAG model, the lifetime discounted disutility for a child's death was derived from the publication by Ara and Brazier[18] (Figure 2, formula for general population), assuming that 50% of births were male. As this publication does not provide estimates of uncertainty about model coefficients, they were assumed to follow a normal distribution, with standard error set to 10% of the mean.

The utility decrement for babies and parents of babies admitted to critical care units was assumed to be the same as the utility decrement for women admitted to an intensive care unit, which was obtained from Seppänen[19]. For probabilistic analyses, uncertainty in both the general population utility (mean 0.946, sample size 549) and the baseline utility for admitted women (mean 0.907, sample size 214) was sampled using beta distributions (setting the alpha parameter = sample size * mean), and the disutility derived from this with an additional constraint so that it is never greater than zero. The following logical constraints were also applied to utility parameters:

- The utility for a caesarean-section was never greater than the utility for a vaginal delivery.
- The utility for an emergency caesarean -section was never greater than the utility for a vaginal delivery.
- The utility for mothers whose child had complications was never greater than the utility for mothers whose child had no or minor complications.
- The utility for mothers whose child died was never greater than the utility for mothers whose child had complications.

As with resource use, utility values varied by if a woman had PE and (with the exception of utilities for delivery) if the woman's PE status was correctly diagnosed.

2.4. COSTS AND UTILITIES: CHANGES TO THE MODEL STRUCTURE

In the updated DSU model the effectiveness of a test is linked to its sensitivity and specificity. In the original EAG model costs and utilities were linked to risk classification and if a PLGF-based test was used. Linking costs and utilities to test risk classification creates the potential for perverse incentives when comparing tests with different performance. To illustrate this, consider the neonatal costs for a women with PE receiving the Triage test:

- If classified as 'high risk' their assigned costs are £11,229
- If classified as 'low risk' their assigned costs are £2,272

Hence, a test that results in more incorrect classifications of low risk would result in reduced neonatal costs. Similarly, a woman with PE not receiving any test would be assigned a cost of £12,743 if classified as high risk and £3,769 if classified as low risk. Similar remarks hold for utility values. To avoid these perverse incentives, costs and utilities were instead assumed to vary by both a woman's PE status and (with the exception of delivery outcomes), if the PE status is correctly diagnosed.

These costs and utilities were derived from the original costs and utilities available in the EAG model, subject to the following restrictions:

- Women with PE will incur higher costs and lower utilities than women without.
- Where costs and utilities vary by diagnosis, an incorrect diagnosis will incur worse outcomes than a correct one.

The resulting costs and utilities, as well as further details on their derivation are provided in the previous sections.

There is also the potential for perverse incentives related to the clinical management decision of whether or not to hospitalise a woman based on the results of clinical assessment and a PLGF test. For women with PE, the decision to hospitalise results in increased costs compared with women with PE who are not hospitalised. Originally these increases were £629, £1290, and £1417 for women with severe, moderate, and mild hypertension (and a gestational age of less than 35 weeks). This increase in clinical management costs for a true positive is outweighed by cost savings for neonatal outcomes (£1648 in the short-term and £634 in the long-term). However,

there is a lot of uncertainty about the true neonatal cost savings (if any) for PLGF-based tests. When excluding neonatal outcomes, increased rates of true positives would result in increased costs and (as utility benefits are short-term and very small) hence would mean more effective PLGF-based tests are not cost-effective. It is unclear if the use of PLGF-based tests would lead to an increase in clinical management costs for women with PE. A cost-effectiveness analysis of the PARROT UK trial found that use of a PLGF-based test led to an overall cost-saving even when excluding neonatal costs.[20] However, this cost saving was partly due to a decrease in outpatient attendances amongst the testing-arm; in a separate publication it was noted that this decrease disappeared after adjustment for calendar time.[1] The following changes were made to the costs of clinical management:

- It was assumed that women with PE would require hospitalisation at some point to manage their condition. For those not identified, the hospitalisation cost was set to that for managing gestational severe hypertension in the original EAG model (£662; based on an NHS Payment by Results Tariff stay of up to three days).[15]
- In the base-case it was assumed that the costs of clinical management for PE would be the same irrespective of test outcome. This assumption was introduced to avoid the potential perverse disincentives related to testing and was removed in a scenario analysis.
- For the scenario analysis in which a true positive test result leads to greater costs than a false negative result, a change was made to the hospitalisation cost for true positives. In the original EAG model, it was assumed that women who were hospitalised to manage their PE would remain in hospital until delivery. Women with PE and a gestational age of less than 35 weeks have an average of 19 days to delivery, and evidence from PARROT UK[1] showed that the average number of inpatient nights (including for delivery) was 7.43 in the revealed group and 7.26 in the concealed group (weighted average of 7.36). Hence hospital costs for managing PE amongst these women was taken from the NHS Payment by Results Tariff 2020/21 (NZ18A), which is a fixed cost for stays of up to eight days (£1,465).[15]

When used to rule-out PE, PLGF-based tests may reduce the number of false-positives. Women without PE who were hospitalised to manage suspected PE were assumed to incur a fixed NHS Payment by Results Tariff 2020/21 (NZ18A), which covers stays of up to eight days (£1,465).[15] Compared with women without PE who were not hospitalised to manage suspected PE, this led to a cost increase of between £328 (women with severe hypertension and a gestational age less than 35 weeks, who incur an NHS Payment by Results Tariff stay of up to three days) and £1,472 (women with mild hypertension and a gestational age greater than 35 weeks).

In the original EAG model the only utility impact related to clinical management was a decrement of 0.028 for false-positive results, which was assumed to last until delivery. This assumption was retained for the updated DSU model.

2.5. OVERVIEW OF ANALYSES

This report includes the following analyses:

- Baseline population (to which relative estimates of test sensitivity and specificity are applied). Two options were considered: PARROT UK[1] (the base-case) and INSPIRE.[2]
- Clinical management decisions: four possible decisions relating to the proportion of women whose decision to admit would change following a test result. For the base-case analysis it was assumed that PLGF-based testing would only be used to rule-out PE.
- Distribution of hypertension categories: four different sources were considered (see Section 2.1.1), to cover a range of different values. For example, the proportion of patients with severe hypertension varied from 5.32% (PELICAN[3]) to 42.00% (original EAG DAR). The base-case used PARROT UK[1] (proportion with severe hypertension 20.56%)
- Inclusion of neonatal outcomes: as per the request for this project, the base-case included all neonatal outcomes. Two scenario analyses were considered: one in which long-term neonatal outcomes were excluded, and one in which all neonatal outcomes were excluded.

Both probabilistic and deterministic results are provided.

3. OVERVIEW OF NEW EVIDENCE AVAILABLE SINCE THE EAG DAR.

Only one study was identified: PARROT IRELAND.[4] This did not provide estimates of sensitivity and specificity, nor did it provide baseline values. It was possible to derive the distribution of hypertension categories from this publication, this was assessed in a sensitivity analysis.

3.1. SUMMARY OF THE PARROT IRELAND TRIAL

Since completion of the DAP53 EAG DAR, the PARROT-Ireland trial[4,21,22] has now been published. Further brief details of this study are provided in this section. The PARROT Ireland study was a multicentre, pragmatic, stepped-wedge cluster randomised controlled trial that assessed whether the addition of PLGF testing to current clinical practice improved maternal and neonatal outcomes. This study was conducted across seven large maternity hospitals in Ireland (from 29 June 2017 to 26 April 2019) and included adult women (aged 18 years or over) with singleton pregnancies who presented with signs and symptoms of suspected pre-eclampsia from 20 weeks (+0 days) to 36 weeks (+6 days) gestation (n= 2291). Each of the maternity hospitals acted as a cluster. All clusters commenced the trial as a control, and in turn, each cluster transitioned at random to use the intervention at pre-specified time points. By the end of the trial, all clusters progressed to the intervention arm. Participants whose maternity hospital was randomised to the control arm (n=1234) received usual hospital care based on national guidelines for hypertension in pregnancy (Health Service Executive and the Institute of Obstetrics and Gynaecology Irish guidelines for those in the Republic of Ireland[23] or the NICE guidelines[24] for those in Northern Ireland). In contrast, participants whose maternity hospital was randomised to the intervention arm (n=1057) had an immediate point of care test on maternal plasma to quantify PLGF in addition to routine hospital care and investigations, to help the clinical team in stratifying the level of further care needed during pregnancy. A suggested clinical management algorithm, based on the degree of hypertension present and the specific PLGF result, advocated a return to antenatal

surveillance for normal PLGF levels (100 pg/ml or more), step up care for those with low PLGF levels (between 12 and 100 ng/ml) and admission, assessment and observation for those with very low PLGF levels (less than 12 pg/ml).[4] Although fidelity to the algorithm was not assessed in the study, the final decision regarding further investigation, frequency of further review, and timing of delivery remained with the treating clinician. The main co-primary endpoints included composite measures of maternal morbidity and neonatal morbidity. All participants who completed the trial, aside from those enrolled in the transition periods (one week), were included in the analysis (using mixed-effects Poisson regression adjusted for time effects) by intention to treat (intervention arm, n=1017; control arm, n=1202). A summary of the study design and population characteristics is provided in Table 12.

Table 12: Study and population characteristics of the PARROT Ireland trial[4]

Study	Design	Location (centres)	Study period	Inclusion criteria	Exclusion criteria	Intervention	Comparator	Main outcomes types
PARROT Ireland	Multicentre, pragmatic, stepped wedge (step length about 3 months) cluster RCT (n=2291)	Ireland (7 maternity units [clusters])	June 2017 to April 2019	Adult women (aged 18 years or over) with singleton pregnancies who presented with signs and symptoms of suspected pre-eclampsia from 20 weeks (+0 days) to 36 weeks (+6 days) gestation	Confirmed pre-eclampsia, ≥37 weeks' gestation, abnormal bloods	Point of care test on maternal plasma to quantify PLGF in addition to usual hospital care and investigation (n=1057)	Usual hospital care and investigation (n=1234)	Comparative clinical outcomes: composite measures of maternal* and neonatal** morbidity

PLGF, placental growth factor; RCT, randomised control trial

*Maternal morbidity composites included: confirmed placental abruption, intensive care admission, central nervous system compromise (generalised tonic clonic seizure due to eclampsia, Glasgow Coma Scale <13, cerebral haemorrhage or infarct, cortical blindness, retinal detachment, transient ischaemic attack, reversible ischaemic neurological deficit), cardiorespiratory compromise (myocardial ischaemia or infarction, blood oxygen saturation <90%, >50% fraction of inspired oxygen for >1hour, intubation (other than for caesarean section), pulmonary oedema, need for positive inotrope support, haematological compromise (transfusion of any blood product, platelet count <100×109/L), liver compromise (hepatic dysfunction (ALT or AST >70IU/L), haematoma, rupture), kidney compromise (acute renal insufficiency [creatinine >150 µmol/L], hemodialysis), severe hypertension (systolic blood pressure ≥160mmHg on at least one occasion in either antenatal or postnatal period)

**Neonatal morbidity composites included: Perinatal death or death before hospital discharge, neonatal intensive care unit admission for ≥48hours, birthweight ≤5th customised centile (using Gestation Related Optimal Weight), Apgar score <7 at 5 minutes, umbilical artery acidosis at birth (cord pH <7.2, [variable excluded post hoc due to large amounts of missing data in neonates – see critical appraisal section for further details]), admission to neonatal unit, respiratory distress syndrome, intraventricular haemorrhage, retinopathy of prematurity, confirmed infection (confirmed on blood or cerebrospinal fluid cultures), necrotising enterocolitis

3.2. CRITICAL APPRAISAL OF THE PARROT IRELAND TRIAL

The risk of bias and methodological quality of the PARROT Ireland study was undertaken using criteria relevant to the type of study design and to the type of study findings reported. As the PARROT Ireland study only reported clinical effectiveness outcomes, the Cochrane risk of bias tool for randomised trials (version 1), as used by the EAG for consistency, was used to assess the potential risk of bias in the study. The criteria for assessing bias were the risk of selection bias (random sequence generation and allocation concealment), performance bias, detection bias, attrition bias and reporting bias. Additional forms of bias particular to cluster randomised trials (e.g., recruitment bias, comparability bias and analysis) were also considered.

The overall methodological quality of the PARROT Ireland study is summarised in Table 13. In general, the PARROT Ireland study was considered to be at low risk of bias. Further details are discussed below.

Table 13: Cochrane risk of bias summary - Review authors' judgements

Study	Random sequence generation	Allocation concealment	Blinding (participants; personnel)	Blinding	Random sequence generation	Allocation concealment
PARROT IRELAND	Low	Low	High*	Low	Low	Low

*Due to the nature of the intervention (a blood test), blinding of participants and investigators was not possible or achievable in this pragmatic stepped wedge cluster randomised trial, thus little weight was given to the absence of blinding for this domain in the overall assessment of the study

In the PARROT Ireland study, the trialists employed appropriate methods to generate a random allocation sequence. A restricted method of randomisation was used to provide a balance in total (expected) number of observations across intervention and control periods. The trial statisticians (who are unlikely to have motives or knowledge that predispose them to subvert the randomisation process) developed a randomisation sequence and determined the order in which the clusters received the intervention. All sites (clusters) and principal investigators were masked to the order until 12 weeks prior to the sites transition. Although the investigators were aware of the hospital's current randomisation schedule when approaching eligible women, the

participants themselves were blinded as to the hospital's randomisation until after recruitment. In addition, the study participants' baseline characteristics, and the proportion diagnosed with pre-eclampsia, were similar between the trial arms, suggesting a potential lack of selection bias (at least for measured variables).

Blinding of participants and investigators was not possible due to the nature of the intervention (a blood test). Whilst this was assessed as high risk of bias, little weight was given to the absence of blinding for this domain as this was not practical logistically or achievable in this pragmatic trial. Nevertheless, all clinical outcomes (all of which were secondary outcomes) were reviewed by a central adjudication panel consisting of a clinical doctor and a research midwife, who were masked to the site allocation and PLGF result. As such, the assessment of these clinical outcomes is unlikely to have introduced bias and is at low risk of detection bias. In addition, there was no evidence of selective outcome reporting and all outcomes prespecified in the protocol[21] appeared to have been reported in the results. However, as noted by the authors, the neonatal composite endpoint was amended post hoc to exclude the umbilical cord pH variable before the data were closed for analysis due to missing data in 60% of neonates. This failing was due to a study design limitation for conducting an interim analysis based on recruitment targets which that was delayed because of under-recruitment and a fixed trial end-date (a trial extension was not possible).

The level of participant attrition (withdrawal or lost to follow-up) in the PARROT Ireland study was low (<1% in each group). Although, sample size calculations (performed with 80% power assuming linear mixed models with categorical effects for time; random cluster and random cluster by period effect) were clearly reported and took account of the stepped wedge design, the study only recruited 57% of the intended sample size (n=4000 women) and was therefore underpowered for the co-primary outcome measures. All analyses were undertaken using an intention to treat approach (excluding those enrolled in the short transition periods) and adjusted for secular trends.

3.3. SUMMARY OF FINDINGS - PARROT IRELAND TRIAL

A summary of the key findings from the PARROT Ireland study are summarised in Table 14. The study found that the integration of point-of-care PLGF testing into routine clinical investigations in women with suspected pre-eclampsia had no significant impact on predicting either maternal (p=0.92) or neonatal morbidity (p=0.67) or perinatal death (p=0.47).

As previously noted, the PARROT Ireland trial did not provide evidence on sensitivity and specificity for standard assessment and use of the Triage test. Hence it could not be used to inform estimates of test performance. Evidence on the baseline population, in the form of hypertension severity, was available. As values were very similar between the two arms, a pooled average was used. This was converted to hypertension categories using the same approach as in the EAG DAR (see Section 2.1.1) by assuming a Normal distribution.

Table 14: Summary of key findings from the PARROT Ireland trial

Endpoints	**Intervention (n=1017)**	**Control (n=1202)**	**Risk ratio, adjusted Poisson* (95% CI)**	**P-value**
Pre-specified co-primary outcomes				
Maternal morbidity composite	330 (32.45%)	457 (38.02%)	1.01 (0.76 to 1.36)	p=0.92
Neonatal morbidity composite**	484*** (47.59%)	527 (43.84%)	1.03 (0.89 to 1.21)	p=0.67
Parameters used in economic model (mean, SD)	**Intervention (n=1009)**	**Control (n=1178)**	**Weighted average for model**	
Highest mean systolic blood pressure recorded in 48 hours before study entry (mm HG)*	133.29 (17.49)	136.29 (18.38)	134.91 (18.03)	

CI, confidence interval
* Poisson regression models adjusted for time and hospital
** Based on protocol amendment – morbidity composite excluded umbilical artery acidosis at birth variable
*** Data discrepancy, thus as reported in the abstract and text

3.4. COMPARISON WITH THE PARROT UK TRIAL

The findings from this study contradict the results from the PARROT UK trial[1] (n=1023), which used a similar trial design (11 maternity units, with step length of 6 weeks and duration of 17 months) and PLGF platform to the PARROT Ireland study but different primary outcomes (time from enrolment to diagnosis in PARROT UK and maternal and neonatal morbidity in PARROT Ireland). This study reported significant benefit with the addition of PLGF testing to routine clinical care in women with suspected preterm pre-eclampsia based on the median time to pre-eclampsia diagnosis (reduced from 4.1 to 1.9 days), and a significant reduction in severe maternal adverse outcomes from 5.4 to 3.8% (adjusted odds ratio, 0.32, 95% CI 0.11 to 0.96; p=0.043). There was no difference in gestational age at delivery (mean difference -0.77, 95% confidence interval -4.4 to 1.95, p-value 0.5731) or perinatal adverse outcomes (see Table 15).[1] To facilitate direct comparison between the two PARROT trials, the PARROT Ireland[4] investigators undertook post hoc analyses using the same composites to define adverse outcomes as the PARROT UK study (the maternal and neonatal adverse outcomes) and found no evidence of significant benefit to support the incorporation of PLGF testing into routine clinical investigations for women presenting with suspected preterm pre-eclampsia (maternal morbidity, p=0.58; neonatal morbidity, p=0.17). A summary of the comparative results is summarised in Table 15. As noted by the PARROT-Ireland study authors[4] and others[25], potential explanations for the differing results may be due to the PARROT Ireland study being under-powered to detect significant differences in the composite co-primary endpoints (maternal and neonatal morbidity) and subtle differences in the populations enrolled and examined. For example, a higher proportion of women with suspected fetal growth restriction (whilst considered a risk factor for preterm pre-eclampsia, it sometimes does not occur because of pre-eclampsia[26]) were recruited to the PARROT Ireland trial (approximately 55% in PARROT Ireland compared with 16% PARROT UK) and the incidence of pre-eclampsia among the UK trial participants was higher (approximately 35% in PARROT UK compared with 14% in PARROT Ireland). Hence the PARROT Ireland investigators noted that, whilst the trial results did not support the routine incorporation of PLGF-based testing, neither did they exclude the potential benefits of these tests.

Table 15: Comparison of maternal and neonatal adverse outcomes in the PARROT UK and PARROT Ireland trials (adapted from PARROT-Ireland)[4]

Endpoints	PARROT UK[13]			PARROT Ireland[4]		
	Intervention (n=573)	Control (n=446)	Adjusted Odds Ratio* (95% CI; p-value)	Intervention (n=1017)	Control (n=1202)	Adjusted Risk Ratio (95% CI; p-value)
Maternal adverse outcomes**	22 (4%)	24 (5%)	0·32 (0·11 to 0·96; p=0·04)	106 (10.42%)	131 (10.90%)	1.10 (0.79 to 1.52; p=0.58)
Perinatal adverse outcomes***	86 (15%)	63 (14%)	1·45 (0·73 to 2·90; p=NR)	87 (8.55%)	85 (7.07%)	1.66 (0.81 to 3.42; p=0.17)
Number diagnosed with pre-eclampsia**	205 (36%)	155 (35%)	NR	138 (13.57%)	177 (14.73%)	NR*****
Median time (days) to diagnose pre-eclampsia (IQR)	1.9 (0.5 to 9.2)	4.1 (0.8 to 14.7)	0·36 (0·15 to 0·87; p=0·03)	8 (1 to 23)	7 (1 to 25)	0.92 (0.56 to 1.49; p=0.73)

CI, confidence interval; IQR, interquartile range; NR, not reported

*adjusted Odds Ratios are reported as per the results of the PARROT UK trial

**Maternal deaths, Eclampsia, Stroke, Parenteral infusion of third-line antihypertensive required, Myocardial infarction, Blood oxygen saturation <90%, Intubation required (other than for caesarean section), Pulmonary oedema, Transfusion of blood products required, Platelet count <50 × 10^9 platelets per L, Hepatic dysfunction, Severe acute kidney injury, Dialysis required, Placental abruption

***Any grade of intraventricular haemorrhage, Seizure, Any grade of retinopathy of prematurity, Respiratory distress syndrome, Bronchopulmonary dysplasia, Necrotising enterocolitis (stage 2 or 3)

**** Diagnosis of pre-eclampsia: PARROT UK used the International Society for the Study of Hypertension in Pregnancy (ISSHP) 2014 guidelines[27] whereas PARROT Ireland used the National Institute for Health and Clinical Excellence 2010 guidelines on hypertension in pregnancy[24]

*****Mixed-effects linear regression model, with log-transformed time to diagnosis and adjusted for time and hospital

4. COST-EFFECTIVENESS RESULTS

4.1. PARROT UK BASELINE

4.1.1. Rule-out testing

Deterministic base-case results (which use PLGF-based tests to rule-out PE) are presented in Table 16. Incremental results (compared with the two definitions of standard assessment) are provided in Table 17, whilst the impact of excluding either long-term or all neonatal costs is demonstrated in Table 18. A full breakdown of base-case cost-effectiveness results by PE status and test outcome is provided in Appendix A.2.

Table 16: Deterministic base-case results, PLGF-based tests to rule-out PE

Rule-out testing	SA: DG23	SA: INSPIRE	Triage test	Elecsys	Elecsys add-on	DELFIA	BRAHMS
Total cost	£10,215	£10,223	£10,248	£10,262	£10,256	£10,225	£10,230
Test	£0	£0	£50	£79	£79	£37	£52
Clinical management	£620	£615	£604	£599	£599	£604	£600
Delivery	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781
Maternal short-term	£364	£365	£364	£363	£362	£363	£362
Neonatal short-term	£4,373	£4,377	£4,369	£4,361	£4,357	£4,362	£4,357
Neonatal long-term	£1,077	£1,084	£1,081	£1,079	£1,077	£1,078	£1,077
Total QALYs	17.6110	17.6093	17.6117	17.6139	17.6151	17.6137	17.6151
Clinical management	-1.41E-05	-9.18E-06	-9.13E-06	-8.41E-06	-8.60E-06	-9.16E-06	-9.05E-06
Delivery	0.035	0.035	0.035	0.035	0.035	0.035	0.035
Maternal short-term	0.384	0.384	0.384	0.384	0.384	0.384	0.384
Neonatal short-term	-0.001	-0.001	-0.001	-0.001	-0.001	-0.001	-0.001
Maternal long-term	17.363	17.363	17.363	17.364	17.364	17.364	17.364
Neonatal long-term	-0.171	-0.172	-0.170	-0.169	-0.168	-0.169	-0.168
True Positives	9.5%	8.0%	8.5%	8.8%	9.1%	9.0%	9.2%
True negatives	62.7%	65.9%	65.9%	66.4%	66.3%	65.9%	66.0%
False positives	9.2%	6.0%	6.0%	5.5%	5.6%	6.0%	5.9%
False negatives	18.6%	20.1%	19.6%	19.3%	19.0%	19.2%	18.9%

There was relatively little variation in total costs and QALYs between the different options. Costs were highest for the use of Elecsys (either stand-alone or as an add-on test) and lowest for the two standard assessments. This reflects the fact that these have the highest and lowest test costs, respectively. Costs of clinical management and neonatal outcomes were generally lowest for the Elecsys and BRAHMS tests.

These also generally provided the largest QALY gains, with all PLGF-based tests resulting in increased QALYs compared to the two standard assessments.

Standard assessment from DG23 had the highest rate of true positives, but also the highest rate of false positives (and hence the lowest rate of true negatives), reflecting a conservative approach to managing PE. The largest rate of true negatives was observed for the Elecsys test.

It should be noted that Table 16 shows the results of using assessment methods (both standard assessment and PLGF-based) to rule-out PE, compared with the use of blood pressure (hypertension severity) alone. Based on just blood pressure, rates of true positives and true negatives were 9.6% and 61.0% respectively, whilst rates of false positives and false negatives were 10.9% and 18.5%, respectively. Hence the use of additional assessment methods to rule-out PE leads to a decrease in the number of false positives, but at the expense of also reducing the number of true positives. Results for standard assessment from INSPIRE demonstrated a specificity of 80.1% for standard assessment, 77.8% for Elecsys add-on and 79.6% for Elecsys stand-alone.[2] The increased specificity for standard assessment (compared with PLGF-based tests) observed in INSPIRE is not reflected in fewer false positives for standard assessment because this trial comparison was based on use of Elecsys with a single threshold.

Table 17: Incremental base-case results, PLGF-based tests to rule-out PE

	Total costs		**Total QALYs**			
	DG23	**INSPIRE**	**DG23**	**INSPIRE**		
Standard assessment	£10,215	£10,223	17.6110	17.6093		
	Incremental costs		**Incremental QALYs**		**ICER**	
	DG23	**INSPIRE**	**DG23**	**INSPIRE**	**DG23**	**INSPIRE**
Triage test	£33.2	£25.5	0.0007	0.0024	£47,393	£10,777
Elecsys	£47.0	£39.3	0.0029	0.0046	£16,290	£8,638
Elecsys add-on	£41.2	£33.6	0.0041	0.0058	£10,099	£5,834
DELFIA	£10.5	£2.8	0.0027	0.0044	£3,874	£637
BRAHMS	£14.6	£6.9	0.0042	0.0058	£3,508	£1,183

All of the PLGF-based tests resulted in increased costs and QALYs when compared with either standard assessment. Incremental QALYs were all very small (always less

than 0.006), so even though the largest cost increase was £47, ICERs (per QALY) ranged from £637 to £47,393. Incremental costs were always lower than the cost of a test, which ranged from £37 for DELFIA to £79 for Elecsys.

Table 18: Impact on base-case results of excluding neonatal outcomes

Compared with DG23 SA					
Including neonatal outcomes	Triage test	Elecsys	Elecsys add-on	DELFIA	BRAHMS
Incremental cost	£33	£47	£41	£10	£15
Incremental QALYs	0.0007	0.0029	0.0041	0.0027	0.0042
ICER	£47,393	£16,290	£10,099	£3,874	£3,508
Excluding long-term neonatal outcomes					
Incremental cost	£29	£45	£41	£9	£15
Incremental QALYs	0.0002	0.0007	0.0010	0.0007	0.0010
ICER	£162,565	£64,239	£41,617	£13,531	£14,797
Excluding all neonatal outcomes					
Incremental cost	£33	£57	£57	£20	£31
Incremental QALYs	0.0002	0.0007	0.0010	0.0006	0.0010
ICER	£191,698	£83,026	£59,067	£31,164	£31,593
Compared with INSPIRE SA					
Including neonatal outcomes	Triage test	Elecsys	Elecsys add-on	DELFIA	BRAHMS
Incremental cost	£26	£39	£34	£3	£7
Incremental QALYs	0.0024	0.0046	0.0058	0.0044	0.0058
ICER	£10,777	£8,638	£5,834	£637	£1,183
Excluding long-term neonatal outcomes					
Incremental cost	£29	£45	£41	£9	£15
Incremental QALYs	0.0006	0.0011	0.0014	0.0010	0.0014
ICER	£50,952	£41,212	£29,739	£8,298	£10,518
Excluding all neonatal outcomes					
Incremental cost	£37	£61	£61	£24	£35
Incremental QALYs	0.0006	0.0011	0.0013	0.0010	0.0014
ICER	£66,568	£56,909	£45,167	£23,274	£25,553

As anticipated, excluding neonatal costs led to increases in the ICERs for all of the PLGF-based tests. The largest increases occurred when all neonatal outcomes were excluded, for this all PLGF-based tests had ICERs above £20,000.

Probabilistic results are provided in Table 19. Results are similar to the deterministic results. However, as the incremental QALYs (compared with standard assessment) are very small, there is relatively large variation in the ICERs, which are now all below

£12,500 per QALY. As with the deterministic results, the lowest ICERs are observed for DELFIA and the highest for the Triag teste. At a willingness to pay of £20,000 the largest net health effects were for Elecsys (add-on), although the value was very similar to that for both DELFIA and BRAHMS. The lowest net health effects were for both standard assessments.

Table 19: Probabilistic base-case results, PLGF-based tests to rule-out PE

			ICER vs standard assessment	
	Total cost	Total QALYs	DG23	INSPIRE
Standard assessment (DG23)	£10,238	17.4789		
Standard assessment (INSPIRE)	£10,247	17.4763		
Triage test	£10,267	17.4811	£12,478	£4,091
Elecsys	£10,286	17.4828	£12,254	£6,040
Elecsys as add-on	£10,281	17.4841	£8,150	£4,380
DELFIA	£10,252	17.4817	£4,852	£999
BRAHMS	£10,260	17.4829	£5,294	£1,957

4.1.2. Rule-out and rule-in tests

Three options for the use of tests to both rule-out and rule-in PE were explored. Two options were derived from the short survey of clinical experts (Section 2.1.4), and differ in the way that tests are used to rule-in PE ('standard' rule-in or 'cautious' rule-in). Evidence reported for the PreOS trial also provides insights into how testing is used to rule-out and rule-in PE. Full results for all three options are provided in the Appendix A.4. Results for the two survey-options were very similar, so only results for standard rule-in and PreOS are provided here. Table 20 shows deterministic results for rule-out and rule-in using the survey results, whilst results using PreOS evidence are provided in Table 21. Summary probabilistic cost-effectiveness results are provided in Table 22 and Table 23.

Table 20: Deterministic base-case results, PLGF-based tests to rule-out and rule-in PE (based on survey responses)

Rule-out and rule-in testing based on survey responses	SA: DG23	SA: INSPIRE	Triage test	Elecsys	Elecsys add-on	DELFIA	BRAHMS
Total cost	£10,724	£10,239	£10,203	£10,117	£10,111	£10,150	£10,133

Test	£0	£0	£50	£79	£79	£37	£52
Clinical management	£1,238	£844	£813	£761	£776	£816	£814
Delivery	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781
Maternal short-term	£361	£349	£345	£339	£337	£341	£339
Neonatal short-term	£4,357	£4,257	£4,219	£4,172	£4,159	£4,190	£4,170
Neonatal long-term	£987	£1,007	£995	£984	£977	£984	£976
Total QALYs	17.6217	17.6461	17.6569	17.6699	17.6737	17.6652	17.6710
Clinical management	-1.09E-03	-4.09E-04	-3.75E-04	-2.91E-04	-3.17E-04	-3.81E-04	-3.83E-04
Delivery	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352
Maternal short-term	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841
Neonatal short-term	-0.0006	-0.0005	-0.0005	-0.0004	-0.0004	-0.0004	-0.0004
Maternal long-term	17.3660	17.3715	17.3740	17.3771	17.3780	17.3760	17.3773
Neonatal long-term	-0.1618	-0.1437	-0.1356	-0.1257	-0.1228	-0.1292	-0.1248
True Positives	27.6%	21.7%	23.4%	24.8%	26.0%	25.3%	26.5%
True negatives	17.1%	49.0%	50.5%	54.4%	53.2%	50.2%	50.2%
False positives	54.8%	22.9%	21.4%	17.4%	18.7%	21.7%	21.7%
False negatives	0.6%	6.5%	4.7%	3.3%	2.1%	2.9%	1.6%

Table 21: Deterministic base-case results, PLGF-based tests to rule-out and rule-in PE (based on PreOS evidence)[14]

Rule-out and rule-in testing based on PreOS	SA: DG23	SA: INSPIRE	Triage test	Elecsys	Elecsys add-on	DELFIA	BRAHMS
Total cost	£10,305	£10,227	£10,228	£10,243	£10,240	£10,208	£10,223
Test	£0	£0	£50	£79	£79	£37	£52
Clinical management	£724	£656	£630	£624	£627	£630	£635
Delivery	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781
Maternal short-term	£364	£362	£360	£360	£359	£360	£359
Neonatal short-term	£4,374	£4,359	£4,344	£4,337	£4,334	£4,339	£4,336
Neonatal long-term	£1,062	£1,068	£1,063	£1,062	£1,060	£1,061	£1,060
Total QALYs	17.6118	17.6152	17.6195	17.6215	17.6225	17.6211	17.6220
Clinical management	-1.95E-04	-7.91E-05	-5.20E-05	-5.09E-05	-5.50E-05	-5.37E-05	-6.80E-05
Delivery	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352
Maternal short-term	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841
Neonatal short-term	-0.0006	-0.0006	-0.0006	-0.0006	-0.0006	-0.0006	-0.0006
Maternal long-term	17.3635	17.3643	17.3653	17.3657	17.3660	17.3656	17.3658
Neonatal long-term	-0.1701	-0.1676	-0.1644	-0.1629	-0.1621	-0.1631	-0.1624
True Positives	12.6%	11.0%	11.8%	11.9%	12.2%	12.1%	12.3%
True negatives	54.3%	60.9%	61.3%	62.1%	61.8%	61.3%	61.2%
False positives	17.6%	11.0%	10.5%	9.8%	10.1%	10.6%	10.7%
False negatives	15.6%	17.1%	16.4%	16.2%	15.9%	16.0%	15.8%

Outcomes are generally similar for all tests for both approaches, with the exception of standard assessment as used in DG23. For this, rates of false positives show a large

increase when using survey results to define clinical management decisions (from 18% to 55%), and a corresponding large increase in clinical management costs.

For both clinical management decisions based on survey results, use of any PLGF-based test always led to lower overall costs and higher QALYs than either standard assessment. This dominance of PLGF-tests was also seen in the probabilistic results, and when long-term neonatal outcomes were excluded. When excluding all neonatal outcomes, PLGF-based tests always dominated standard assessment as used in DG23. For standard assessment based on the INSPIRE trial, results varied depending on if 'standard rule-in' or 'cautious rule-in' was used, as summarised in Table 24.

For clinical management decisions based on the PreOS trial, PLGF-based trials always dominated standard assessment as used in DG23. This held for deterministic and probabilistic results, and when all neonatal outcomes were excluded. DELFIA and BRAHMS dominated standard assessment based on the INSPIRE trial. The Triage test had a deterministic ICER of £277 and was dominant in the probabilistic analysis. For Elecsys the ICER was £2,561 when used as stand-alone and £1,826 when used as an add-on. Similar ICERs were observed for the probabilistic results.

Across all three rule-in options, incremental net health effects were generally highest for Elecsys when used as an add-on to clinical management. In practice the other PLGF-based tests would also be used as add-ons, suggesting that the results presented here may under-estimate their cost-effectiveness.

Table 22: Incremental base-case results, PLGF-based tests to rule-out and rule-in PE (based on survey responses)

Rule-out and rule-in testing based on survey responses			ICER vs standard assessment	
	Total cost	Total QALYs	DG23	INSPIRE
Standard assessment (DG23)	£10,734	17.510		
Standard assessment (INSPIRE)	£10,251	17.544		
Triage test	£10,193	17.564	Dominates	Dominates
Elecsys	£10,128	17.577	Dominates	Dominates

Elecsys as add-on	£10,127	17.581	Dominates	Dominates
DELFIA	£10,176	17.567	Dominates	Dominates
BRAHMS	£10,162	17.572	Dominates	Dominates

Table 23: Incremental base-case results, PLGF-based tests to rule-out and rule-in PE (based on PreOS evidence)[14]

Rule-out and rule-in testing based on PreOS			ICER vs standard assessment	
	Total cost	Total QALYs	DG23	INSPIRE
Standard assessment (DG23)	£10,302	17.494		
Standard assessment (INSPIRE)	£10,224	17.499		
Triage test	£10,219	17.506	Dominates	Dominates
Elecsys	£10,239	17.508	Dominates	£1,715
Elecsys as add-on	£10,238	17.509	Dominates	£1,477
DELFIA	£10,207	17.507	Dominates	Dominates
BRAHMS	£10,223	17.507	Dominates	Dominates

Table 24: Incremental cost-effectiveness ratio vs standard assessment (INSPIRE) when excluding all neonatal outcome

	Survey: rule-out and rule-in	Survey: rule-out and cautious rule-in	PreOS: rule-out and rule-in
Triage test	£5,503	Dominates	£20,679
Elecsys	Dominates	£2,039	£30,064
Elecsys as add-on	Dominates	£3,246	£27,390
DELFIA	£314	Dominates	£6,390
BRAHMS	£2,037	£2,753	£17,796

4.1.3. Comparison of rule-out and rule-in tests

In general, the use of PLGF-based tests for both ruling-out and ruling-in PE provides more favourable estimates of cost-effectiveness than when just used to rule-out PE. A comparison of the incremental costs and QALYs is provided in Figure 3. For illustration this compares the Elecsys (add-on) test with standard assessment from DG23, and rule-in is based on the survey responses. This shows that rule-out and rule-in provides in general more incremental QALYs and fewer incremental costs when compared with rule-out testing alone. There is a lot of variation in the observed values.

For the two approaches, a summary of where cost differences are observed is provided in Figure 4. This illustrates that cost savings are largest for the clinical management of PE, followed by short-term neonatal costs. These savings are larger for the use of rule-out and rule-in testing. This is due to the very low specificity of standard assessment from DG23 (25%), which leads to a large increase in false positive results when used to rule-in PE; from 9.2% when used as rule-out to 54.8% when also used to rule-in. In comparison, for the Elecsys add-on test the increase is from 5.6% to 18.7%.

Figure 3: Incremental costs and QALYs for PLGF-based tests compared with standard assessment

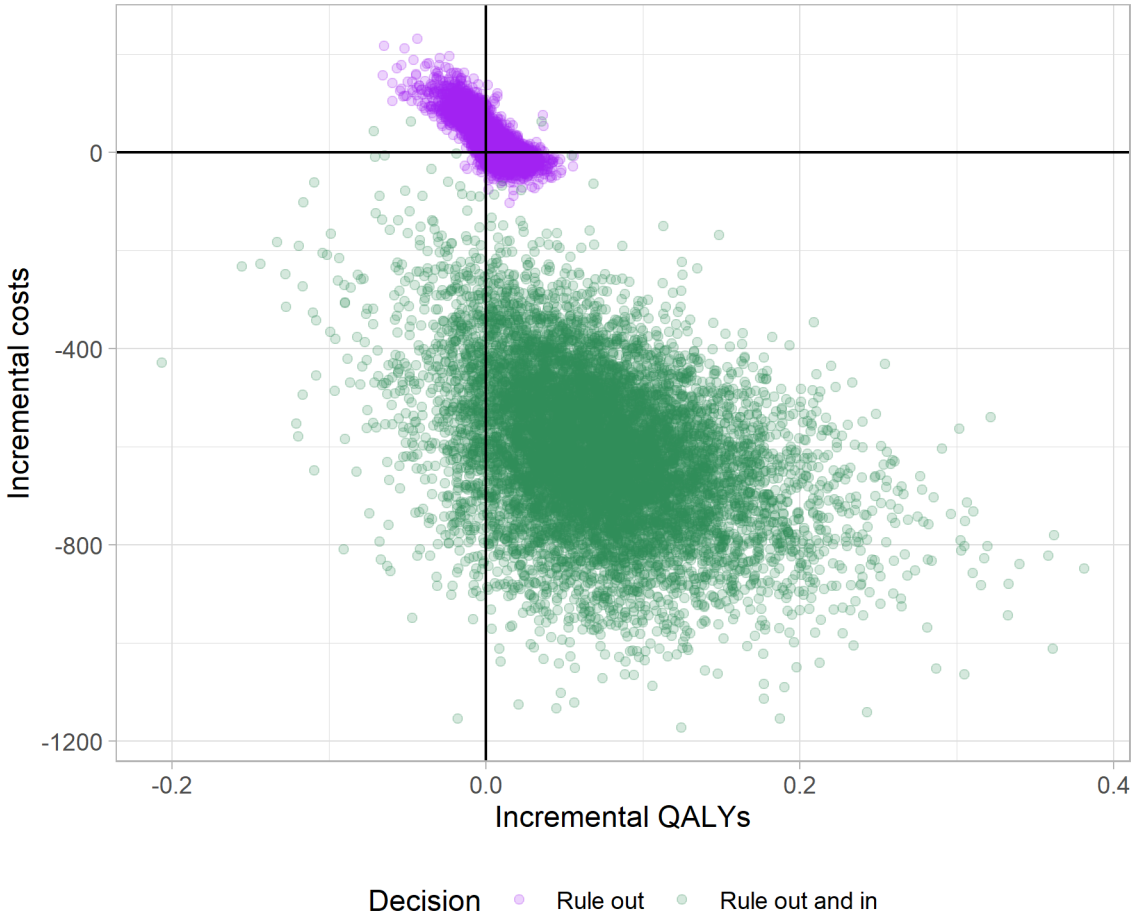
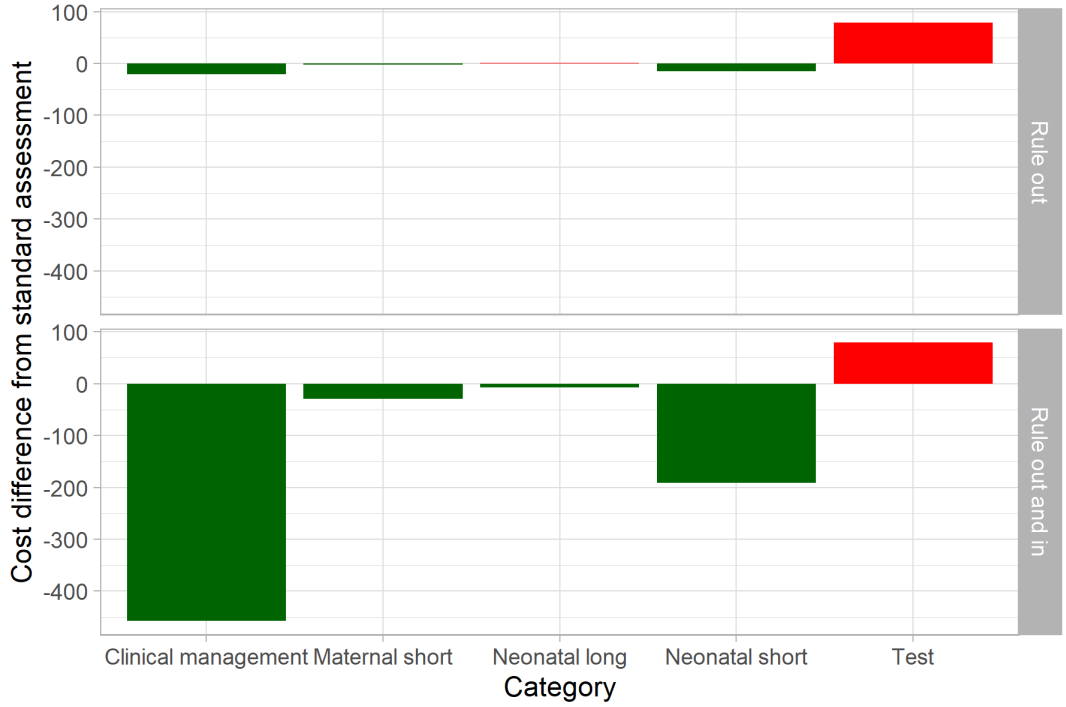


Figure 4: Breakdown of incremental costs for PLGF-based tests compared with standard assessment



4.1.4. Scenario analyses

For the included scenario analyses, deterministic ICERs are presented here, with full details provided in Appendices A.3 and A.4. Results are shown for both the strategy of using testing to only rule-out PE and using testing to both rule-out and rule-in PE. For the former approach three options were available; results were similar for each so are only shown for the standard rule-in option obtained from the clinical survey. Table 25 provides ICERs relative to standard assessment as used in DG23, whilst for Table 26 standard assessment is based on that in INSPIRE.

For both definitions of standard assessment, use of PLGF-based testing to rule-out and rule-in PE nearly always dominated standard assessment, for all five PLGF-based tests considered. The two exceptions were when using INSPIRE for both baseline test performance and standard assessment; for this ICERs for the Triage test and DELFIA were both approximately £15,000.

When using PLGF-based testing to rule-out PE, the two scenario analyses of 'true positive test results costing more than false negative results' and 'hypertension distribution from PELICAN' both provided very similar results to the base-case. ICERs were generally highest when using PARROT Ireland for the hypertension distribution and lowest (or PLGF-based testing was dominant) when using PELICAN for the hypertension distribution. When using INSPIRE as the base-line (and PLGF-based tests to rule-out PE), use of the Elecsys test (stand-alone or add-on) had ICERs ranging from £10,572 to £1,044,065 against standard assessment from INSPIRE. This may reflect that in INSPIRE the primary benefit of PLGF-based testing was to rule-in PE (more women with PE were correctly identified).

Table 25: Sensitivity analyses comparing PLGF-based tests with standard assessment from DG23

	Testing to rule-out PE	Testing to rule-out and rule-in PE
Base-case*		
Triage test	£47,393	Dominates
Elecsys	£16,290	Dominates
Elecsys as add-on	£10,099	Dominates
DELFIA	£3,874	Dominates
BRAHMS	£3,508	Dominates
INSPIRE for baseline test performance		
Triage test	£2,836	Dominates
Elecsys	£19,353	Dominates
Elecsys as add-on	£10,572	Dominates
DELFIA	Dominates	Dominates
BRAHMS	£3,027	Dominates
True positive test results cost more than false negative results		
Triage test	£43,279	Dominates
Elecsys	£15,603	Dominates
Elecsys as add-on	£9,829	Dominates
DELFIA	£3,283	Dominates

BRAHMS	£3,327	Dominates
Hypertension distribution from PARROT Ireland		
Triage test	£114,233	Dominates
Elecsys	£42,789	Dominates
Elecsys as add-on	£28,897	Dominates
DELFIA	£16,290	Dominates
BRAHMS	£15,015	Dominates
Hypertension distribution from PELICAN		
Triage test	£43,602	Dominates
Elecsys	£26,576	Dominates
Elecsys as add-on	£18,729	Dominates
DELFIA	Dominates	Dominates
BRAHMS	Dominates	Dominates
Hypertension distribution from EAG DAR (Triage, PE)		
Triage test	£7,090	Dominates
Elecsys	£895	Dominates
Elecsys as add-on	Dominates	Dominates
DELFIA	Dominates	Dominates
BRAHMS	Dominates	Dominates

* Baseline treatment effects and hypertension distribution from PARROT UK, true positive rest results cost same as false negatives.

Table 26: Sensitivity analyses comparing PLGF-based tests with standard assessment from INSPIRE

	Testing to rule-out PE	Testing to rule-out and rule-in PE
Base-case*		
Triage test	£10,777	Dominates
Elecsys	£8,638	Dominates
Elecsys as add-on	£5,834	Dominates

DELFIA	£637	Dominates
BRAHMS	£1,183	Dominates
INSPIRE for baseline test performance		
Triage test	£13,169	£15,673
Elecsys	£1,044,065	Dominates
Elecsys as add-on	£37,382	Dominates
DELFIA	£6,713	£14,379
BRAHMS	£14,726	Dominates
True positive test results cost more than false negative results		
Triage test	£11,395	Dominates
Elecsys	£9,156	Dominates
Elecsys as add-on	£6,398	Dominates
DELFIA	£1,266	Dominates
BRAHMS	£1,801	Dominates
Hypertension distribution from PARROT Ireland		
Triage test	£30,555	Dominates
Elecsys	£25,435	Dominates
Elecsys as add-on	£19,182	Dominates
DELFIA	£8,316	Dominates
BRAHMS	£9,396	Dominates
Hypertension distribution from PELICAN		
Triage test	£9,655	Dominates
Elecsys	£15,158	Dominates
Elecsys as add-on	£11,962	Dominates
DELFIA	Dominates	Dominates
BRAHMS	Dominates	Dominates
Hypertension distribution from EAG DAR (Triage, PE)		
Triage test	Dominates	Dominates

Elecsys	Dominates	Dominates
Elecsys as add-on	Dominates	Dominates
DELFIA	Dominates	Dominates
BRAHMS	Dominates	Dominates

* Baseline treatment effects and hypertension distribution from PARROT UK, true positive rest results cost same as false negatives.

5. DISCUSSION

The DSU provided a restructured and updated model in response to the DAC's concerns about the modelling approach undertaken by the EAG. This restructured model used a single baseline to which relative estimates of treatment effectiveness were applied. Probabilistic sensitivity analyses were complemented by a series of deterministic sensitivity analyses to explore uncertainty in how the results of PLGF-based tests influence decision making, the economic consequences of these decisions, and how results are affected by the choice of patient population. A short survey was also undertaken to obtain clinical input into how testing influences the clinical decision to admit a woman with suspected PE.

The use of relative treatment effects and clinical input into clinical management are particular strengths of this updated analysis. They ensure that a single population is used for all analyses, that standard assessment is consistently defined, and that realistic clinical management decisions are included.

There are however limitations with this work. In particular, there was substantial heterogeneity in the evidence base, particularly with regards to the population studied and test outcomes. This limits the usefulness of using relative treatment effects from different studies. Because of this a formal evidence synthesis was not conducted, nor was a fully incremental analysis reported. There was also heterogeneity in how PLGF-based tests are used in clinical practice, which makes it difficult to identify a single base-case for this.

There is also heterogeneity in how non-PLGF-based tests (standard assessments) are used to aid in the management of women with suspected PE. Two different approaches to standard assessment were considered for this report. In general, PLGF-based tests performed better when compared with standard assessment from DG23 than standard assessment from INSPIRE. The latter was based on a single large teaching hospital, and so may be representative of how suspected PE is managed in these types of setting, but not in others. Conversely, evidence on standard assessment from DG23 is from the USA and based on a study carried out between July 2009 and October 2010. Hence its relevance to current practice in England is unclear.

A further limitation is that the majority of evidence on treatment effects was for PLGF-based tests as stand-alone tests. In practice PLGF-based tests would be used as add-ons to standard assessment. Evidence for the performance of add-on tests was only available for the Elecsys test. Use of the Elecsys as an add-on generally provided more favourable cost-effectiveness results than use of stand-alone Elecsys. This suggests that cost-effectiveness results presented here for the other PLGF-based tests is likely to be under-estimated.

5.1. COMPARISONS WITH THE LITERATURE:

Since the EAG DAR repot, additional evidence on use of the Triage test has been published from the PARROT Ireland trial.[4] In contrast to the PARROT UK trial,[1] which found a statistically significant clinical benefit associated with PLGF-based testing, PARROT Ireland did not find any significant benefit. One suggested reason for this is that PARROT Ireland enrolled a population with less severe PE. Comparative estimates of test performance were not available from either PARROT trial, but evidence on baseline hypertension was. For the updated DSU model, when using hypertension evidence from PARROT Ireland, PLGF-based tests were found to had have favourable cost-effectiveness outcomes than when using hypertension evidence from PARROT UK.

There is a published cost-effectiveness analysis based on the PARROT-UK trial.[20] This did not include utility outcomes, but found that PLGF-based testing was cost-

saving. Results provided for the updated DSU model were sensitive to how test results were incorporated into clinical decision-making, and it is unclear what approach was taken for the PARROT UK trial. This limits comparisons with the PARROT UK cost-effectiveness analysis. In addition, some of the cost-savings observed in the PARROT UK cost-effectiveness analysis were due to a reduced number of outpatient appointments, which appears to be an artefact of the study design. There was no adjustment for this in the PARROT-UK cost-effectiveness analysis; such an adjustment would lead to worse cost-effectiveness outcomes for the Triage test, but the magnitude of this change is unclear. Use of testing to both rule-in and rule-out PE was generally found to be cost-saving in the analyses of this report, whilst testing to rule-out PE was not cost-saving. Hence either approach could be consistent with the results of the PARROT-UK cost-effectiveness analysis.

An existing UK-based cost-effectiveness analysis found that use of the Elecsys test was likely to be cost-saving.[28] However, this modelled cost-saving was based on an assumed reduced rate of hospitalisations due to the Elecsys test. This assumption was not based on any observed data, and more recent evidence from the INSPIRE trial suggests that use of the Elecsys test does not result in a reduction in hospitalisations. Hence the relevance of this existing analysis is unclear.

5.2. AREAS FOR FUTURE RESEARCH

Comparisons of PLGF-based tests, both to each other and to standard assessment, were hampered by the lack of studies that providing direct comparisons and reported relevant information on both accuracy and how PLGF-based tests influence clinical decision-making. Ideally this would be assessed (and reported) in a suitably powered study which evaluated PLGF-based tests as add-ons to standard assessment for a representative cohort of women with suspected PE.

It is also unclear if PLGF-based tests provide any long-term benefits. As this is potentially an important driver of cost-effectiveness results, extended follow-up on these outcomes would be beneficial.

5.3. CONCLUSION

The use of PLGF-based tests to either rule-out suspected PE or both rule-out and rule-in suspected PE was evaluated. The latter approach provided more favourable cost-effectiveness outcomes than the former. This is an intuitive finding, as using PLGF-based tests to both rule-out and rule-in PE uses more evidence from the test results.

Use of PLGF-based tests to rule-out and rule-in PE has the potential to provide improved outcomes at reduced cost when compared with standard assessment. However, results are limited by heterogeneity in the evidence, particularly with regards to outcomes assessed by PLGF-based test. In addition, any estimated QALY-benefits associated with PLGF-based tests were very small, and there was a lot of uncertainty about the impact of PLGF-based tests on improving neonatal outcomes, the accuracy of standard assessment, the population that would receive these tests, and how PLGF-based tests influence decision-making. These uncertainties all have the potential to impact on the incremental estimates of cost and QALYs for PLGF-based tests. Conversely, the majority of PLGF-based tests were evaluated as stand-alone tests. In practice, these would be used as add-ons to standard assessment, the results presented here suggest that use as an add-on leads to improved cost-effectiveness results compared with stand-alone use.

APPENDIX

A.1 ADDITIONAL DETAILS ON MODEL INPUTS

Note that in the following tables, for the beta distribution, data are presented as (numerator, denominator).

Table 27: Estimates of test sensitivity and specificity used in the model

Parameter	Mean	Distribution	Source
Baseline distribution of hypertension categories		Dirichlet (N = 1023)	Derived from PARROT UK[1]
Severe hypertension	20.56%		
Moderate hypertension	16.82%		
Mild hypertension	62.62%		
Distribution of pre-eclampsia by hypertension status		Dirichlet (N = 60)	Derived from PELICAN[5]
Severe hypertension	46.88%		
Moderate hypertension	34.76%		
Mild hypertension	20.18%		
Test sensitivity			
Triage <100	94.87%	Beta(37, 39)	PARROT UK[1]
Triage <12	74.36%	Beta(29, 39)	PARROT UK[1]
Triage <100	80.77%	Beta(21, 26)	COMPARE[6,29]
Triage <12	53.85%	Beta(14, 26)	COMPARE[6,29]
Elecsys >38	73.08%	Beta(19, 26)	COMPARE[6,29]
Elecsys >85	65.38%	Beta(17, 26)	COMPARE[6,29]
DELFIA >150	84.62%	Beta(22, 26)	COMPARE[6,29]
DELFIA >50	53.85%	Beta(14, 26)	COMPARE[6,29]
Elecsys >38	88.89%	Beta(8, 9)	Simon 2020[7]
BRAHMS >38	95.00%	Beta(9.5, 10)*	Simon 2020[7]
Elecsys >85	88.89%	Beta(8, 9)	Simon 2020[7]
BRAHMS >85	95.00%	Beta(9.5, 10)*	Simon 2020[7]
Elecsys >38 (no clinical judgement)	95.83%	Beta(23, 24)	INSPIRE[2]
Elecsys >38 with no clinical judgement)	98.00%	Beta(24.5, 25)	INSPIRE[2]
Clinical judgement	83.33%	Beta(15, 18)	INSPIRE[2]
Elecsys >38	90.48%	Beta(57, 63)	INSPIRE (rule-out)[12]
Elecsys >85	60.32%	Beta(38, 63)	INSPIRE (rule-in)[11]
Test specificity			
Triage <100	52.65%	Beta(119, 226)	PARROT UK[1]
Triage <12	84.07%	Beta(190, 226)	PARROT UK[1]
Triage <100	79.57%	Beta(222, 279)	COMPARE[6,29]
Triage <12	95.34%	Beta(266, 279)	COMPARE[6,29]

Elecsys >38	93.19%	Beta(260, 279)	COMPARE[6,29]
Elecsys >85	95.34%	Beta(266, 279)	COMPARE[6,29]
DELFIA >150	79.93%	Beta(223, 279)	COMPARE[6,29]
DELFIA >50	94.98%	Beta(222, 279)	COMPARE[6,29]
Elecsys >38	90.91%	Beta(30, 33)	Simon 2020[7]
BRAHMS >38	87.88%	Beta(29, 33)	Simon 2020[7]
Elecsys >85	96.97%	Beta(32, 33)	Simon 2020[7]
BRAHMS >85	93.94%	Beta(31, 33)	Simon 2020[7]
Elecsys >38 (no clinical judgement)	79.63%	Beta(129, 162)	INSPIRE[2]
Elecsys >38 with no clinical judgement)	77.78%	Beta(126, 162)	INSPIRE[2]
Clinical judgement	80.12%	Beta(133, 166)	INSPIRE[2]
Elecsys >38	81.76%	Beta(251, 307)	INSPIRE (rule-out)[12]
Elecsys >85	95.11%	Beta(292, 307)	INSPIRE (rule-in)[11]

* Denotes a continuity correction was applied.

Table 28: Evidence on resource use used in the model

Parameter	Mean	Distribution	Source
Time to delivery (days)			
Gestational age < 35 weeks, no pre-eclampsia	44.86	Normal(10% of mean)	Derived from PELICAN[5]
Gestational age < 35 weeks, pre-eclampsia	19.00	Normal(10% of mean)	Derived from PELICAN[5]
Gestational age ≥ 35 weeks, no pre-eclampsia	7.98	Normal(10% of mean)	Derived from PELICAN[5]
Gestational age ≥ 35 weeks, pre-eclampsia (not hospitalised)	4.91	Normal(10% of mean)	Derived from PELICAN[5]
Gestational age ≥ 35 weeks, pre-eclampsia or severe hypertension (hospitalised)	2	Not varied	Assumption
Proportion of women with a gestational age < 35 weeks	46%	Beta(287, 625)	PELICAN[5]
Onset of delivery		Dirichlet (N = 1018)	PARROT UK[1]
Spontaneous	15.42%		
Induced	46.46%		
Planned C section	38.11%		
Mode of delivery			PARROT UK[13]
High risk; unassisted	22.03%	Dirichlet (N = 236)	
High risk; assisted	3.81%		
High risk; emergency caesarean section	36.02%		
High risk; other	38.14%		

Intermediate risk; unassisted	40.00%	Dirichlet (N = 385)	
Intermediate risk; assisted	8.57%		
Intermediate risk; emergency caesarean section	24.42%		
Intermediate risk; other	27.01%		
Low risk; unassisted	47.53%	Dirichlet (N = 385)	
Low risk; assisted	10.13%		
Low risk; emergency caesarean section	16.10%		
Low risk; other	26.23%		
Use of magnesium sulphate			PARROT UK[13]
High risk	36.44%	Beta(86, 236)	
Intermediate risk	9.87%	Beta(38, 385)	
Low risk	2.86%	Beta(11, 385)	
Maternal outcomes: major complications			PARROT UK[13]
Test; high risk	6.15%	Beta(8, 130)	
Test; intermediate risk	3.77%	Beta(8, 212)	
Test; low risk	2.62%	Beta(6, 229)	
No test; high risk	5.66%	Beta(6, 106)	
No test; intermediate risk	6.94%	Beta(12, 173)	
No test; low risk	3.85%	Beta(6, 156)	
Child deaths (excluding stillbirths)			PARROT UK[13]
High risk	1.27%	Beta(3, 236)	
Intermediate risk	0.78%	Beta(3, 385)	
Low risk	0.26%	Beta(1, 385)	
Child deaths (including stillbirths)			PARROT UK[13]
High risk	4.66%	Beta(11, 236)	
Intermediate risk	1.56%	Beta(6, 385)	
Low risk	0.52%	Beta(2, 385)	
Neonatal admissions			PARROT UK[13]
High risk	65.68%	Beta(155, 236)	
Intermediate risk	32.99%	Beta(127, 385)	
Low risk	14.55%	Beta(56, 385)	
Neonatal healthcare resource use			PARROT UK[1]
Nights in intensive care or high-dependency units (with testing)	15.2	Gamma(std err = 0.12)	
Nights in intensive care or high-dependency units (without testing)	24.2	Gamma(std err = 0.31)	
Nights in a special baby care unit (with testing)	14.7	Gamma(std err = 1.03)	

Nights in a special baby care unit (without testing)	13.09	Gamma(std err = 1.02)	
Child deaths (excluding stillbirths)			PARROT UK[13]
High risk	28.81%	Beta(68, 236)	
Intermediate risk	11.95%	Beta(46, 385)	
Low risk	4.68%	Beta(18, 385)	
Child deaths (including stillbirths)			PARROT UK[13]
High risk	5.08%	Beta(12, 236)	
Intermediate risk	0.78%	Beta(3, 385)	
Low risk	0.52%	Beta(2, 385)	

Table 29: Utility and disutility values used in the model

Parameter	Mean	Distribution	Source
Disutility: false positive result	0.028	Log-normal (-3.58, 0.47)	Prosser 2008[30]
Birth to 3 weeks post-partum (vaginal delivery)	0.6766	Beta(48.04, 71)	Jansen 2007[31]
Birth to 3 weeks post-partum (cesarean section)	0.5895	Beta(21.22, 36)	Jansen 2007[31]
Birth to 3 weeks post-partum (emergency C section)	0.5167	Beta(17.57, 34)	Jansen 2007[31]
3 weeks to 12 weeks post-partum	0.8676	Beta(195.21, 225)	Bijlenga 2011[32]
12 weeks to 6 months post-partum	0.8683	Beta(166.71, 192)	Bijlenga 2011[32]
Decrement for women admitted to an intensive care unit	0.039	See text for details	Seppänen 2018[19]
Decrement for babies and parents of babies admitted to critical care units	0.039	See text for details	Seppänen 2018[19]
Mothers whose child had no / minor complications	17.42	Normal(10% of mean)	Varley-Campbell 2019[33]
Mothers whose child died	13.45	Normal(10% of mean)	Varley-Campbell 2019[33]
Mothers whose child had complications (respiratory distress syndrome and intraventricular haemorrhage)	17.05	Normal(10% of mean)	Varley-Campbell 2019[33]
Decrement for babies with complications (respiratory distress syndrome)	0.41	Normal(10% of mean)	Varley-Campbell 2019[33]
Decrement for babies with complications (intraventricular haemorrhage	0.91	Normal(10% of mean)	Varley-Campbell 2019[33]

Decrement for child's death	24.70	See text for details	Ara and Brazier[18]

A.2 ADDITIONAL BASE-CASE COST-EFFECTIVENESS RESULTS

Table 30: Base-case deterministic results, tests to rule-out PLGF

Rule-out PLGF testing	SA (INSPIRE)	Triage test	Elecsys	DELFIA	BRAHMS	Elecsys (add-on)	SA (DG23)
Total cost	£10,223	£10,248	£10,262	£10,225	£10,230	£10,256	£10,215
Test	£0	£50	£79	£37	£52	£79	£0
Clinical management	£615	£604	£599	£604	£600	£599	£620
PE: True positive	£78	£83	£86	£87	£90	£89	£92
PE: False negative	£184	£179	£176	£175	£172	£173	£169
No PE: True negative	£274	£263	£265	£263	£261	£263	£236
No PE: False positive	£79	£78	£72	£79	£78	£74	£121
Delivery	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781
PE: True positive	£336	£357	£369	£375	£387	£382	£397
PE: False negative	£839	£819	£806	£801	£789	£794	£779
No PE: True negative	£2,389	£2,390	£2,407	£2,389	£2,392	£2,402	£2,272
No PE: False positive	£217	£216	£199	£217	£214	£203	£334
Maternal short-term	£365	£364	£363	£363	£362	£362	£364
PE: True positive	£30	£32	£33	£34	£35	£34	£36
PE: False negative	£116	£113	£112	£111	£109	£110	£108
No PE: True negative	£196	£196	£197	£196	£196	£197	£186
No PE: False positive	£22	£22	£20	£22	£22	£21	£34
Neonatal short-term	£4,377	£4,369	£4,361	£4,362	£4,357	£4,357	£4,373
PE: True positive	£582	£617	£639	£648	£669	£660	£687
PE: False negative	£1,783	£1,739	£1,713	£1,701	£1,676	£1,686	£1,654
No PE: True negative	£1,811	£1,812	£1,825	£1,811	£1,813	£1,821	£1,723
No PE: False positive	£201	£200	£185	£201	£199	£189	£310
Neonatal long-term	£1,084	£1,081	£1,079	£1,078	£1,077	£1,077	£1,077
PE: True positive	£224	£237	£246	£249	£257	£254	£264
PE: False negative	£685	£669	£658	£654	£644	£648	£636
No PE: True negative	£158	£158	£159	£158	£158	£159	£150
No PE: False positive	£18	£17	£16	£18	£17	£16	£27
Total QALYs	17.6093	17.6117	17.6139	17.6137	17.6151	17.6151	17.6110
Clinical management	-9.18E-06	-9.13E-06	-8.41E-06	-9.16E-06	-9.05E-06	-8.60E-06	-1.41E-05
PE: True positive	0	0	0	0	0	0	0
PE: False negative	0	0	0	0	0	0	0
No PE: True negative	0	0	0	0	0	0	0
No PE: False positive	-9.18E-06	-9.13E-06	-8.41E-06	-9.16E-06	-9.05E-06	-8.60E-06	-1.41E-05
Delivery	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352
PE: True positive	0.003	0.003	0.003	0.003	0.003	0.003	0.003
PE: False negative	0.007	0.007	0.006	0.006	0.006	0.006	0.006

No PE: True negative	0.024	0.024	0.024	0.024	0.024	0.024	0.022
No PE: False positive	0.002	0.002	0.002	0.002	0.002	0.002	0.003
Maternal short-term	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841
PE: True positive	0.031	0.033	0.034	0.034	0.036	0.035	0.036
PE: False negative	0.077	0.075	0.074	0.074	0.072	0.073	0.071
No PE: True negative	0.253	0.253	0.255	0.253	0.253	0.255	0.241
No PE: False positive	0.023	0.023	0.021	0.023	0.023	0.022	0.035
Neonatal short-term	-0.0006	-0.0006	-0.0006	-0.0006	-0.0006	-0.0006	-0.0006
PE: True positive	0.000	0.000	0.000	0.000	0.000	0.000	0.000
PE: False negative	0.000	0.000	0.000	0.000	0.000	0.000	0.000
No PE: True negative	0.000	0.000	0.000	0.000	0.000	0.000	0.000
No PE: False positive	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Maternal long-term	17.3629	17.3634	17.3639	17.3639	17.3642	17.3642	17.3633
PE: True positive	1.397	1.482	1.534	1.557	1.605	1.585	1.649
PE: False negative	3.463	3.378	3.327	3.304	3.256	3.276	3.212
No PE: True negative	11.464	11.469	11.551	11.466	11.478	11.530	10.905
No PE: False positive	1.039	1.034	0.952	1.038	1.025	0.974	1.597
Neonatal long-term	-0.1722	-0.1704	-0.1687	-0.1688	-0.1677	-0.1678	-0.1709
PE: True positive	-0.015	-0.015	-0.016	-0.016	-0.017	-0.017	-0.017
PE: False negative	-0.109	-0.106	-0.105	-0.104	-0.102	-0.103	-0.101
No PE: True negative	-0.038	-0.038	-0.038	-0.038	-0.038	-0.038	-0.036
No PE: False positive	-0.011	-0.011	-0.010	-0.011	-0.011	-0.010	-0.017
True Positives	8.0%	8.5%	8.8%	9.0%	9.2%	9.1%	9.5%
True negatives	65.9%	65.9%	66.4%	65.9%	66.0%	66.3%	62.7%
False positives	6.0%	6.0%	5.5%	6.0%	5.9%	5.6%	9.2%
False negatives	20.1%	19.6%	19.3%	19.2%	18.9%	19.0%	18.6%

Table 31: Base-case deterministic results, tests to rule-out and rule-in PLGF

Rule-out PLGF testing	**SA (INSPIRE)**	**Triage test**	**Elecsys**	**DELFIA**	**BRAHMS**	**Elecsys (add-on)**	**SA (DG23)**
Total cost	£10,239	£10,203	£10,117	£10,150	£10,133	£10,111	£10,724
Test	£0	£50	£79	£37	£52	£79	£0
Clinical management	£844	£813	£761	£816	£814	£776	£1,238
PE: True positive	£202	£218	£231	£236	£247	£242	£257
PE: False negative	£60	£43	£31	£26	£15	£19	£5
No PE: True negative	£215	£208	£222	£207	£205	£217	£75
No PE: False positive	£367	£343	£277	£347	£348	£297	£901
Delivery	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781
PE: True positive	£905	£979	£1,037	£1,056	£1,108	£1,088	£1,152
PE: False negative	£270	£197	£139	£120	£68	£88	£23
No PE: True negative	£1,777	£1,830	£1,973	£1,820	£1,819	£1,929	£620
No PE: False positive	£829	£776	£632	£786	£786	£676	£1,986
Maternal short-term	£349	£345	£339	£341	£339	£337	£361
PE: True positive	£81	£88	£93	£95	£99	£98	£103
PE: False negative	£37	£27	£19	£17	£9	£12	£3
No PE: True negative	£146	£150	£162	£149	£149	£158	£51

No PE: False positive	£85	£80	£65	£81	£81	£69	£204
Neonatal short-term	£4,257	£4,219	£4,172	£4,190	£4,170	£4,159	£4,357
PE: True positive	£1,566	£1,694	£1,794	£1,827	£1,916	£1,882	£1,994
PE: False negative	£574	£418	£295	£254	£144	£187	£50
No PE: True negative	£1,347	£1,387	£1,496	£1,380	£1,379	£1,463	£470
No PE: False positive	£770	£721	£587	£729	£730	£628	£1,844
Neonatal long-term	£1,007	£995	£984	£984	£976	£977	£987
PE: True positive	£602	£651	£689	£702	£737	£723	£766
PE: False negative	£221	£161	£113	£98	£55	£72	£19
No PE: True negative	£117	£121	£130	£120	£120	£127	£41
No PE: False positive	£67	£63	£51	£64	£64	£55	£161
Total QALYs	17.6461	17.6569	17.6699	17.6652	17.6710	17.6737	17.6217
Clinical management	-4.09E-04	-3.75E-04	-2.91E-04	-3.81E-04	-3.83E-04	-3.17E-04	-1.09E-03
PE: True positive	0	0	0	0	0	0	0
PE: False negative	0	0	0	0	0	0	0
No PE: True negative	0	0	0	0	0	0	0
No PE: False positive	-4.09E-04	-3.75E-04	-2.91E-04	-3.81E-04	-3.83E-04	-3.17E-04	-1.09E-03
Delivery	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352
PE: True positive	0.007	0.008	0.008	0.009	0.009	0.009	0.009
PE: False negative	0.002	0.002	0.001	0.001	0.001	0.001	0.000
No PE: True negative	0.018	0.018	0.019	0.018	0.018	0.019	0.006
No PE: False positive	0.008	0.008	0.006	0.008	0.008	0.007	0.020
Maternal short-term	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841
PE: True positive	0.083	0.090	0.095	0.097	0.102	0.100	0.106
PE: False negative	0.025	0.018	0.013	0.011	0.006	0.008	0.002
No PE: True negative	0.188	0.194	0.209	0.193	0.193	0.204	0.066
No PE: False positive	0.088	0.082	0.067	0.083	0.083	0.072	0.210
Neonatal short-term	-0.0005	-0.0005	-0.0004	-0.0004	-0.0004	-0.0004	-0.0006
PE: True positive	-1.06E-04	-1.15E-04	-1.21E-04	-1.24E-04	-1.30E-04	-1.27E-04	-1.35E-04
PE: False negative	-1.35E-04	-9.81E-05	-6.93E-05	-5.96E-05	-3.39E-05	-4.39E-05	-1.16E-05
No PE: True negative	-8.79E-05	-9.05E-05	-9.76E-05	-9.01E-05	-9.00E-05	-9.55E-05	-3.07E-05
No PE: False positive	-1.85E-04	-1.73E-04	-1.41E-04	-1.76E-04	-1.76E-04	-1.51E-04	-4.44E-04
Maternal long-term	17.3715	17.3740	17.3771	17.3760	17.3773	17.3780	17.3660
PE: True positive	3.760	4.066	4.306	4.386	4.600	4.516	4.785
PE: False negative	1.115	0.811	0.573	0.493	0.280	0.363	0.096
No PE: True negative	8.528	8.780	9.471	8.735	8.731	9.260	2.974
No PE: False positive	3.969	3.717	3.028	3.762	3.766	3.238	9.511
Neonatal long-term	-0.1437	-0.1356	-0.1257	-0.1292	-0.1248	-0.1228	-0.1618
PE: True positive	-0.039	-0.042	-0.045	-0.046	-0.048	-0.047	-0.050
PE: False negative	-0.035	-0.026	-0.018	-0.016	-0.009	-0.011	-0.003
No PE: True negative	-0.028	-0.029	-0.031	-0.029	-0.029	-0.031	-0.010
No PE: False positive	-0.041	-0.039	-0.032	-0.039	-0.039	-0.034	-0.099
True Positives	21.7%	23.4%	24.8%	25.3%	26.5%	26.0%	27.6%
True negatives	49.0%	50.5%	54.4%	50.2%	50.2%	53.2%	17.1%
False positives	22.9%	21.4%	17.4%	21.7%	21.7%	18.7%	54.8%
False negatives	6.5%	4.7%	3.3%	2.9%	1.6%	2.1%	0.6%

Table 32: Base-case deterministic results, tests to rule-out and cautious rule-in PLGF

Rule-out PLGF testing	SA (INSPIRE)	Triage test	Elecsys	DELFIA	BRAHMS	Elecsys (add-on)	SA (DG23)
Total cost	£10,231	£10,179	£10,170	£10,138	£10,165	£10,162	£10,470
Test	£0	£50	£79	£37	£52	£79	£0
Clinical management	£730	£669	£665	£672	£695	£672	£929
PE: True positive	£140	£146	£157	£158	£168	£165	£175
PE: False negative	£122	£116	£105	£104	£94	£97	£87
No PE: True negative	£245	£246	£247	£245	£236	£244	£156
No PE: False positive	£223	£161	£155	£166	£197	£166	£511
Delivery	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781
PE: True positive	£621	£644	£696	£702	£743	£729	£775
PE: False negative	£555	£531	£480	£474	£433	£446	£401
No PE: True negative	£2,083	£2,214	£2,231	£2,205	£2,138	£2,208	£1,446
No PE: False positive	£523	£392	£375	£401	£467	£398	£1,160
Maternal short-term	£357	£353	£350	£351	£350	£349	£363
PE: True positive	£56	£58	£63	£63	£67	£66	£70
PE: False negative	£77	£74	£66	£66	£60	£62	£56
No PE: True negative	£171	£182	£183	£181	£175	£181	£119
No PE: False positive	£54	£40	£38	£41	£48	£41	£119
Neonatal short-term	£4,317	£4,286	£4,262	£4,265	£4,260	£4,253	£4,365
PE: True positive	£1,074	£1,114	£1,204	£1,214	£1,285	£1,262	£1,340
PE: False negative	£1,178	£1,129	£1,019	£1,007	£920	£948	£852
No PE: True negative	£1,579	£1,678	£1,691	£1,672	£1,621	£1,674	£1,096
No PE: False positive	£486	£364	£348	£372	£434	£370	£1,077
Neonatal long-term	£1,046	£1,040	£1,032	£1,032	£1,026	£1,027	£1,032
PE: True positive	£413	£428	£463	£467	£494	£485	£515
PE: False negative	£453	£434	£392	£387	£354	£364	£327
No PE: True negative	£137	£146	£147	£146	£141	£146	£95
No PE: False positive	£42	£32	£30	£32	£38	£32	£94
Total QALYs	17.6277	17.6363	17.6429	17.6424	17.6440	17.6457	17.6163
Clinical management	-2.09E-04	-1.24E-04	-1.23E-04	-1.29E-04	-1.74E-04	-1.36E-04	-5.54E-04
PE: True positive	0	0	0	0	0	0	0
PE: False negative	0	0	0	0	0	0	0
No PE: True negative	0	0	0	0	0	0	0
No PE: False positive	-2.09E-04	-1.24E-04	-1.23E-04	-1.29E-04	-1.74E-04	-1.36E-04	-5.54E-04
Delivery	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352
PE: True positive	0.005	0.005	0.006	0.006	0.006	0.006	0.006
PE: False negative	0.004	0.004	0.004	0.004	0.003	0.004	0.003
No PE: True negative	0.021	0.022	0.022	0.022	0.021	0.022	0.014
No PE: False positive	0.005	0.004	0.004	0.004	0.005	0.004	0.011
Maternal short-term	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841
PE: True positive	0.057	0.059	0.064	0.064	0.068	0.067	0.071
PE: False negative	0.051	0.049	0.044	0.044	0.040	0.041	0.037
No PE: True negative	0.221	0.235	0.236	0.234	0.227	0.234	0.153

No PE: False positive	0.055	0.042	0.040	0.042	0.050	0.042	0.123
Neonatal short-term	-0.0006	-0.0005	-0.0005	-0.0005	-0.0005	-0.0005	-0.0006
PE: True positive	-7.27E-05	-7.54E-05	-8.15E-05	-8.21E-05	-8.69E-05	-8.54E-05	-9.07E-05
PE: False negative	-2.77E-04	-2.65E-04	-2.39E-04	-2.37E-04	-2.16E-04	-2.23E-04	-2.00E-04
No PE: True negative	-1.03E-04	-1.10E-04	-1.10E-04	-1.09E-04	-1.06E-04	-1.09E-04	-7.15E-05
No PE: False positive	-1.17E-04	-8.76E-05	-8.38E-05	-8.95E-05	-1.04E-04	-8.89E-05	-2.59E-04
Maternal long-term	17.3672	17.3692	17.3708	17.3706	17.3710	17.3714	17.3646
PE: True positive	2.579	2.675	2.891	2.913	3.084	3.029	3.217
PE: False negative	2.289	2.193	1.979	1.956	1.786	1.841	1.654
No PE: True negative	9.996	10.625	10.706	10.582	10.262	10.596	6.939
No PE: False positive	2.504	1.877	1.795	1.919	2.238	1.905	5.554
Neonatal long-term	-0.1579	-0.1515	-0.1464	-0.1468	-0.1455	-0.1443	-0.1663
PE: True positive	-0.027	-0.028	-0.030	-0.030	-0.032	-0.032	-0.034
PE: False negative	-0.072	-0.069	-0.062	-0.062	-0.056	-0.058	-0.052
No PE: True negative	-0.033	-0.035	-0.035	-0.035	-0.034	-0.035	-0.023
No PE: False positive	-0.026	-0.020	-0.019	-0.020	-0.023	-0.020	-0.058
True Positives	14.9%	15.4%	16.7%	16.8%	17.8%	17.4%	18.5%
True negatives	57.5%	61.1%	61.5%	60.8%	59.0%	60.9%	39.9%
False positives	14.4%	10.8%	10.3%	11.1%	12.9%	11.0%	32.0%
False negatives	13.3%	12.7%	11.5%	11.3%	10.4%	10.7%	9.6%

Table 33: Base-case deterministic results, tests to rule-out and rule-in PLGF (as per PreOS)

Rule-out PLGF testing	SA (INSPIRE)	Triage test	Elecsys	DELFIA	BRAHMS	Elecsys (add-on)	SA (DG23)
Total cost	£10,227	£10,228	£10,243	£10,208	£10,223	£10,240	£10,305
Test	£0	£50	£79	£37	£52	£79	£0
Clinical management	£656	£630	£624	£630	£635	£627	£724
PE: True positive	£106	£113	£114	£116	£118	£117	£120
PE: False negative	£156	£149	£148	£146	£144	£145	£141
No PE: True negative	£239	£222	£227	£222	£223	£226	£201
No PE: False positive	£156	£145	£136	£146	£150	£140	£261
Delivery	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781
PE: True positive	£461	£491	£499	£507	£516	£511	£526
PE: False negative	£715	£684	£677	£669	£660	£665	£650
No PE: True negative	£2,207	£2,224	£2,250	£2,221	£2,218	£2,241	£1,969
No PE: False positive	£398	£382	£356	£384	£388	£365	£637
Maternal short-term	£362	£360	£360	£360	£359	£359	£364
PE: True positive	£41	£44	£45	£46	£46	£46	£47
PE: False negative	£99	£95	£94	£93	£91	£92	£90
No PE: True negative	£181	£182	£185	£182	£182	£184	£161
No PE: False positive	£41	£39	£36	£39	£40	£37	£65
Neonatal short-term	£4,359	£4,344	£4,337	£4,339	£4,336	£4,334	£4,374
PE: True positive	£797	£850	£863	£877	£893	£884	£909
PE: False negative	£1,519	£1,453	£1,438	£1,421	£1,401	£1,412	£1,381
No PE: True negative	£1,674	£1,686	£1,706	£1,684	£1,681	£1,699	£1,493

No PE: False positive	£370	£355	£330	£357	£360	£339	£591
Neonatal long-term	£1,068	£1,063	£1,062	£1,061	£1,060	£1,060	£1,062
PE: True positive	£306	£327	£332	£337	£343	£340	£349
PE: False negative	£584	£559	£553	£546	£539	£543	£531
No PE: True negative	£146	£147	£149	£147	£146	£148	£130
No PE: False positive	£32	£31	£29	£31	£31	£29	£51
Total QALYs	17.6152	17.6195	17.6215	17.6211	17.6220	17.6225	17.6118
Clinical management	-7.91E-05	-5.20E-05	-5.09E-05	-5.37E-05	-6.80E-05	-5.50E-05	-1.95E-04
PE: True positive	0	0	0	0	0	0	0
PE: False negative	0	0	0	0	0	0	0
No PE: True negative	0	0	0	0	0	0	0
No PE: False positive	-7.91E-05	-5.20E-05	-5.09E-05	-5.37E-05	-6.80E-05	-5.50E-05	-1.95E-04
Delivery	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352
PE: True positive	0.004	0.004	0.004	0.004	0.004	0.004	0.004
PE: False negative	0.006	0.006	0.005	0.005	0.005	0.005	0.005
No PE: True negative	0.022	0.022	0.022	0.022	0.022	0.022	0.019
No PE: False positive	0.004	0.004	0.004	0.004	0.004	0.004	0.006
Maternal short-term	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841
PE: True positive	0.042	0.045	0.046	0.047	0.047	0.047	0.048
PE: False negative	0.066	0.063	0.062	0.061	0.061	0.061	0.060
No PE: True negative	0.234	0.236	0.238	0.235	0.235	0.237	0.209
No PE: False positive	0.042	0.040	0.038	0.041	0.041	0.039	0.067
Neonatal short-term	-0.0006	-0.0006	-0.0006	-0.0006	-0.0006	-0.0006	-0.0006
PE: True positive	-5.39E-05	-5.75E-05	-5.83E-05	-5.93E-05	-6.04E-05	-5.98E-05	-6.15E-05
PE: False negative	-3.57E-04	-3.41E-04	-3.38E-04	-3.34E-04	-3.29E-04	-3.32E-04	-3.24E-04
No PE: True negative	-1.09E-04	-1.10E-04	-1.11E-04	-1.10E-04	-1.10E-04	-1.11E-04	-9.74E-05
No PE: False positive	-8.90E-05	-8.54E-05	-7.95E-05	-8.58E-05	-8.67E-05	-8.15E-05	-1.42E-04
Maternal long-term	17.3643	17.3653	17.3657	17.3656	17.3658	17.3660	17.3635
PE: True positive	1.913	2.041	2.070	2.105	2.143	2.122	2.182
PE: False negative	2.950	2.823	2.794	2.759	2.722	2.742	2.682
No PE: True negative	10.594	10.672	10.798	10.661	10.644	10.755	9.450
No PE: False positive	1.907	1.830	1.704	1.840	1.858	1.747	3.049
Neonatal long-term	-0.1676	-0.1644	-0.1629	-0.1631	-0.1624	-0.1621	-0.1701
PE: True positive	-0.020	-0.021	-0.022	-0.022	-0.022	-0.022	-0.023
PE: False negative	-0.093	-0.089	-0.088	-0.087	-0.086	-0.086	-0.084
No PE: True negative	-0.035	-0.035	-0.036	-0.035	-0.035	-0.035	-0.031
No PE: False positive	-0.020	-0.019	-0.018	-0.019	-0.019	-0.018	-0.032
True Positives	11.0%	11.8%	11.9%	12.1%	12.3%	12.2%	12.6%
True negatives	60.9%	61.3%	62.1%	61.3%	61.2%	61.8%	54.3%
False positives	11.0%	10.5%	9.8%	10.6%	10.7%	10.1%	17.6%
False negatives	17.1%	16.4%	16.2%	16.0%	15.8%	15.9%	15.6%

A.3 ADDITIONAL COST-EFFECTIVENESS RESULTS FOR RULE-IN TESTING

Table 34: Base-case probabilistic results

Rule-out PLGF testing	SA (INSPIRE)	Triage test	Elecsys	DELFIA	BRAHMS	Elecsys (add-on)	SA (DG23)
Total cost	£10,238	£10,247	£10,267	£10,286	£10,281	£10,252	£10,260
Test	£0	£0	£50	£79	£79	£37	£52
Clinical management	£621	£617	£605	£600	£601	£605	£602
PE: True positive	£91	£77	£83	£84	£86	£84	£85
PE: False negative	£173	£187	£180	£180	£177	£179	£178
No PE: True negative	£236	£274	£263	£264	£263	£262	£261
No PE: False positive	£121	£79	£79	£72	£74	£79	£77
Delivery	£3,787	£3,787	£3,787	£3,787	£3,787	£3,787	£3,787
PE: True positive	£390	£329	£358	£361	£371	£362	£367
PE: False negative	£794	£855	£826	£823	£812	£822	£817
No PE: True negative	£2,270	£2,386	£2,387	£2,404	£2,400	£2,386	£2,391
No PE: False positive	£334	£218	£216	£199	£204	£218	£213
Maternal short-term	£371	£372	£370	£369	£369	£370	£369
PE: True positive	£33	£28	£30	£31	£31	£31	£31
PE: False negative	£121	£130	£126	£126	£124	£125	£125
No PE: True negative	£181	£190	£190	£192	£191	£190	£191
No PE: False positive	£35	£23	£23	£21	£22	£23	£23
Neonatal short-term	£4,379	£4,383	£4,371	£4,367	£4,364	£4,370	£4,367
PE: True positive	£672	£566	£616	£622	£640	£624	£632
PE: False negative	£1,679	£1,808	£1,747	£1,740	£1,718	£1,738	£1,727
No PE: True negative	£1,719	£1,807	£1,808	£1,821	£1,817	£1,807	£1,810
No PE: False positive	£310	£202	£201	£185	£189	£202	£197
Neonatal long-term	£1,081	£1,088	£1,084	£1,083	£1,081	£1,083	£1,082
PE: True positive	£258	£218	£237	£239	£246	£240	£243
PE: False negative	£646	£695	£672	£669	£661	£668	£664
No PE: True negative	£150	£157	£157	£159	£158	£157	£158
No PE: False positive	£27	£18	£17	£16	£16	£18	£17
Total QALYs	17.4789	17.4763	17.4811	17.4828	17.4841	17.4817	17.4829
Clinical management	-1.59E-05	-1.03E-05	-1.03E-05	-9.47E-06	-9.69E-06	-1.03E-05	-1.01E-05
PE: True positive	0	0	0	0	0	0	0
PE: False negative	0	0	0	0	0	0	0
No PE: True negative	0	0	0	0	0	0	0
No PE: False positive	-1.59E-05	-1.03E-05	-1.03E-05	-9.47E-06	-9.69E-06	-1.03E-05	-1.01E-05
Delivery	0.0349	0.0349	0.0349	0.0349	0.0349	0.0349	0.0349
PE: True positive	0.003	0.003	0.003	0.003	0.003	0.003	0.003
PE: False negative	0.006	0.007	0.007	0.007	0.006	0.007	0.007
No PE: True negative	0.022	0.023	0.023	0.024	0.024	0.023	0.023
No PE: False positive	0.003	0.002	0.002	0.002	0.002	0.002	0.002
Maternal short-term	0.3840	0.3840	0.3840	0.3840	0.3840	0.3840	0.3840

PE: True positive	0.036	0.030	0.033	0.033	0.034	0.033	0.034
PE: False negative	0.073	0.078	0.076	0.075	0.074	0.075	0.075
No PE: True negative	0.240	0.253	0.253	0.254	0.254	0.253	0.253
No PE: False positive	0.035	0.023	0.023	0.021	0.022	0.023	0.023
Neonatal short-term	-0.0006	-0.0006	-0.0006	-0.0006	-0.0006	-0.0006	-0.0006
PE: True positive	-4.64E-05	-3.92E-05	-4.26E-05	-4.30E-05	-4.43E-05	-4.31E-05	-4.37E-05
PE: False negative	-4.02E-04	-4.33E-04	-4.18E-04	-4.17E-04	-4.11E-04	-4.16E-04	-4.13E-04
No PE: True negative	-1.15E-04	-1.20E-04	-1.20E-04	-1.21E-04	-1.21E-04	-1.20E-04	-1.21E-04
No PE: False positive	-7.62E-05	-4.96E-05	-4.94E-05	-4.55E-05	-4.66E-05	-4.97E-05	-4.85E-05
Maternal long-term	17.2945	17.2938	17.2952	17.2957	17.2961	17.2954	17.2958
PE: True positive	1.610	1.357	1.477	1.490	1.533	1.494	1.516
PE: False negative	3.239	3.489	3.371	3.358	3.315	3.353	3.332
No PE: True negative	10.856	11.412	11.418	11.499	11.476	11.411	11.434
No PE: False positive	1.590	1.036	1.030	0.949	0.972	1.037	1.014
Neonatal long-term	-0.2339	-0.2358	-0.2324	-0.2313	-0.2303	-0.2320	-0.2312
PE: True positive	-0.023	-0.019	-0.021	-0.021	-0.021	-0.021	-0.021
PE: False negative	-0.137	-0.148	-0.143	-0.142	-0.140	-0.142	-0.141
No PE: True negative	-0.052	-0.055	-0.055	-0.055	-0.055	-0.055	-0.055
No PE: False positive	-0.022	-0.015	-0.015	-0.013	-0.014	-0.015	-0.014
True Positives	9.3%	7.9%	8.5%	8.6%	8.9%	8.6%	8.8%
True negatives	62.5%	65.7%	65.8%	66.2%	66.1%	65.7%	65.9%
False positives	9.2%	6.0%	6.0%	5.5%	5.6%	6.0%	5.9%
False negatives	19.0%	20.4%	19.7%	19.6%	19.4%	19.6%	19.5%

Table 35: Use of INSPIRE for baseline test performance

Rule-out PLGF testing	**SA (INSPIRE)**	**Triage test**	**Elecsys**	**DELFIA**	**BRAHMS**	**Elecsys (add-on)**	**SA (DG23)**
Total cost	£10,203	£10,229	£10,270	£10,217	£10,235	£10,264	£10,225
Test	£0	£50	£79	£37	£52	£79	£0
Clinical management	£615	£602	£597	£602	£598	£598	£620
PE: True positive	£84	£90	£82	£90	£87	£85	£89
PE: False negative	£178	£172	£180	£172	£175	£177	£173
No PE: True negative	£281	£261	£263	£261	£260	£262	£234
No PE: False positive	£72	£78	£72	£79	£76	£74	£124
Delivery	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781
PE: True positive	£361	£385	£353	£386	£372	£366	£383
PE: False negative	£815	£790	£823	£790	£803	£809	£793
No PE: True negative	£2,408	£2,390	£2,407	£2,389	£2,396	£2,402	£2,265
No PE: False positive	£198	£216	£199	£216	£209	£203	£341
Maternal short-term	£363	£362	£363	£362	£363	£363	£365
PE: True positive	£32	£35	£32	£35	£33	£33	£34
PE: False negative	£113	£109	£114	£109	£111	£112	£110
No PE: True negative	£197	£196	£197	£196	£196	£197	£186
No PE: False positive	£20	£22	£20	£22	£21	£21	£35
Neonatal short-term	£4,364	£4,358	£4,368	£4,358	£4,362	£4,363	£4,380
PE: True positive	£624	£667	£610	£668	£644	£634	£662

PE: False negative	£1,731	£1,679	£1,748	£1,677	£1,706	£1,719	£1,684
No PE: True negative	£1,826	£1,812	£1,825	£1,811	£1,817	£1,821	£1,717
No PE: False positive	£184	£200	£185	£201	£195	£189	£317
Neonatal long-term	£1,080	£1,077	£1,081	£1,077	£1,079	£1,079	£1,079
PE: True positive	£240	£256	£235	£257	£248	£244	£255
PE: False negative	£665	£645	£672	£645	£656	£661	£647
No PE: True negative	£159	£158	£159	£158	£158	£159	£149
No PE: False positive	£16	£17	£16	£17	£17	£16	£28
Total QALYs	17.6129	17.6149	17.6120	17.6150	17.6137	17.6133	17.6090
Clinical management	-8.36E-06	-9.11E-06	-8.41E-06	-9.15E-06	-8.86E-06	-8.60E-06	-1.44E-05
PE: True positive	0	0	0	0	0	0	0
PE: False negative	0	0	0	0	0	0	0
No PE: True negative	0	0	0	0	0	0	0
No PE: False positive	-8.36E-06	-9.11E-06	-8.41E-06	-9.15E-06	-8.86E-06	-8.60E-06	-1.44E-05
Delivery	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352
PE: True positive	0.003	0.003	0.003	0.003	0.003	0.003	0.003
PE: False negative	0.007	0.006	0.007	0.006	0.006	0.007	0.006
No PE: True negative	0.024	0.024	0.024	0.024	0.024	0.024	0.022
No PE: False positive	0.002	0.002	0.002	0.002	0.002	0.002	0.003
Maternal short-term	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841
PE: True positive	0.033	0.035	0.032	0.035	0.034	0.034	0.035
PE: False negative	0.075	0.073	0.076	0.073	0.074	0.074	0.073
No PE: True negative	0.255	0.253	0.255	0.253	0.254	0.255	0.240
No PE: False positive	0.021	0.023	0.021	0.023	0.022	0.022	0.036
Neonatal short-term	-0.0006	-0.0006	-0.0006	-0.0006	-0.0006	-0.0006	-0.0006
PE: True positive	-4.22E-05	-4.51E-05	-4.13E-05	-4.52E-05	-4.36E-05	-4.29E-05	-4.48E-05
PE: False negative	-4.06E-04	-3.94E-04	-4.10E-04	-3.94E-04	-4.01E-04	-4.04E-04	-3.96E-04
No PE: True negative	-1.19E-04	-1.18E-04	-1.19E-04	-1.18E-04	-1.19E-04	-1.19E-04	-1.12E-04
No PE: False positive	-4.42E-05	-4.82E-05	-4.44E-05	-4.84E-05	-4.68E-05	-4.55E-05	-7.62E-05
Maternal long-term	17.3637	17.3642	17.3635	17.3642	17.3639	17.3638	17.3628
PE: True positive	1.499	1.600	1.465	1.603	1.546	1.522	1.590
PE: False negative	3.362	3.261	3.395	3.258	3.315	3.339	3.271
No PE: True negative	11.557	11.471	11.551	11.467	11.500	11.529	10.869
No PE: False positive	0.947	1.032	0.952	1.036	1.003	0.974	1.632
Neonatal long-term	-0.1694	-0.1679	-0.1701	-0.1679	-0.1688	-0.1691	-0.1724
PE: True positive	-0.016	-0.017	-0.015	-0.017	-0.016	-0.016	-0.017
PE: False negative	-0.106	-0.103	-0.107	-0.103	-0.104	-0.105	-0.103
No PE: True negative	-0.038	-0.038	-0.038	-0.038	-0.038	-0.038	-0.036
No PE: False positive	-0.010	-0.011	-0.010	-0.011	-0.010	-0.010	-0.017
True Positives	8.6%	9.2%	8.4%	9.2%	8.9%	8.8%	9.2%
True negatives	66.4%	65.9%	66.4%	65.9%	66.1%	66.3%	62.5%
False positives	5.5%	5.9%	5.5%	6.0%	5.8%	5.6%	9.4%
False negatives	19.5%	18.9%	19.7%	18.9%	19.2%	19.4%	19.0%

Table 36: True positive test results cost more than false negative results

Rule-out PLGF testing	SA (INSPIRE)	Triage test	Elecsys	DELFIA	BRAHMS	Elecsys (add-on)	SA (DG23)
Total cost	£10,247	£10,274	£10,288	£10,252	£10,257	£10,284	£10,243
Test	£0	£50	£79	£37	£52	£79	£0
Clinical management	£639	£629	£625	£630	£628	£627	£648
PE: True positive	£102	£109	£113	£114	£118	£116	£121
PE: False negative	£184	£179	£176	£175	£172	£173	£169
No PE: True negative	£274	£263	£265	£263	£261	£263	£236
No PE: False positive	£79	£78	£72	£79	£78	£74	£121
Delivery	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781
PE: True positive	£336	£357	£369	£375	£387	£382	£397
PE: False negative	£839	£819	£806	£801	£789	£794	£779
No PE: True negative	£2,389	£2,390	£2,407	£2,389	£2,392	£2,402	£2,272
No PE: False positive	£217	£216	£199	£217	£214	£203	£334
Maternal short-term	£365	£364	£363	£363	£362	£362	£364
PE: True positive	£30	£32	£33	£34	£35	£34	£36
PE: False negative	£116	£113	£112	£111	£109	£110	£108
No PE: True negative	£196	£196	£197	£196	£196	£197	£186
No PE: False positive	£22	£22	£20	£22	£22	£21	£34
Neonatal short-term	£4,377	£4,369	£4,361	£4,362	£4,357	£4,357	£4,373
PE: True positive	£582	£617	£639	£648	£669	£660	£687
PE: False negative	£1,783	£1,739	£1,713	£1,701	£1,676	£1,686	£1,654
No PE: True negative	£1,811	£1,812	£1,825	£1,811	£1,813	£1,821	£1,723
No PE: False positive	£201	£200	£185	£201	£199	£189	£310
Neonatal long-term	£1,084	£1,081	£1,079	£1,078	£1,077	£1,077	£1,077
PE: True positive	£224	£237	£246	£249	£257	£254	£264
PE: False negative	£685	£669	£658	£654	£644	£648	£636
No PE: True negative	£158	£158	£159	£158	£158	£159	£150
No PE: False positive	£18	£17	£16	£18	£17	£16	£27
Total QALYs	17.6093	17.6117	17.6139	17.6137	17.6151	17.6151	17.6110
Clinical management	-9.18E-06	-9.13E-06	-8.41E-06	-9.16E-06	-9.05E-06	-8.60E-06	-1.41E-05
PE: True positive	0	0	0	0	0	0	0
PE: False negative	0	0	0	0	0	0	0
No PE: True negative	0	0	0	0	0	0	0
No PE: False positive	-9.18E-06	-9.13E-06	-8.41E-06	-9.16E-06	-9.05E-06	-8.60E-06	-1.41E-05
Delivery	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352
PE: True positive	0.003	0.003	0.003	0.003	0.003	0.003	0.003
PE: False negative	0.007	0.007	0.006	0.006	0.006	0.006	0.006
No PE: True negative	0.024	0.024	0.024	0.024	0.024	0.024	0.022
No PE: False positive	0.002	0.002	0.002	0.002	0.002	0.002	0.003
Maternal short-term	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841
PE: True positive	0.031	0.033	0.034	0.034	0.036	0.035	0.036
PE: False negative	0.077	0.075	0.074	0.074	0.072	0.073	0.071
No PE: True negative	0.253	0.253	0.255	0.253	0.253	0.255	0.241
No PE: False positive	0.023	0.023	0.021	0.023	0.023	0.022	0.035

Neonatal short-term	-0.0006	-0.0006	-0.0006	-0.0006	-0.0006	-0.0006	-0.0006
PE: True positive	-3.94E-05	-4.18E-05	-4.32E-05	-4.39E-05	-4.52E-05	-4.47E-05	-4.65E-05
PE: False negative	-4.19E-04	-4.08E-04	-4.02E-04	-3.99E-04	-3.94E-04	-3.96E-04	-3.88E-04
No PE: True negative	-1.18E-04	-1.18E-04	-1.19E-04	-1.18E-04	-1.18E-04	-1.19E-04	-1.12E-04
No PE: False positive	-4.85E-05	-4.82E-05	-4.44E-05	-4.84E-05	-4.78E-05	-4.54E-05	-7.45E-05
Maternal long-term	17.3629	17.3634	17.3639	17.3639	17.3642	17.3642	17.3633
PE: True positive	1.397	1.482	1.534	1.557	1.605	1.585	1.649
PE: False negative	3.463	3.378	3.327	3.304	3.256	3.276	3.212
No PE: True negative	11.464	11.469	11.551	11.466	11.478	11.530	10.905
No PE: False positive	1.039	1.034	0.952	1.038	1.025	0.974	1.597
Neonatal long-term	-0.1722	-0.1704	-0.1687	-0.1688	-0.1677	-0.1678	-0.1709
PE: True positive	-0.015	-0.015	-0.016	-0.016	-0.017	-0.017	-0.017
PE: False negative	-0.109	-0.106	-0.105	-0.104	-0.102	-0.103	-0.101
No PE: True negative	-0.038	-0.038	-0.038	-0.038	-0.038	-0.038	-0.036
No PE: False positive	-0.011	-0.011	-0.010	-0.011	-0.011	-0.010	-0.017
True Positives	8.0%	8.5%	8.8%	9.0%	9.2%	9.1%	9.5%
True negatives	65.9%	65.9%	66.4%	65.9%	66.0%	66.3%	62.7%
False positives	6.0%	6.0%	5.5%	6.0%	5.9%	5.6%	9.2%
False negatives	20.1%	19.6%	19.3%	19.2%	18.9%	19.0%	18.6%

Table 37: Distribution of hypertension categories from PARROT Ireland

Rule-out PLGF testing	SA (INSPIRE)	Triage test	Elecsys	DELFIA	BRAHMS	Elecsys (add-on)	SA (DG23)
Total cost	£9,873	£9,907	£9,928	£9,890	£9,899	£9,925	£9,869
Test	£0	£50	£79	£37	£52	£79	£0
Clinical management	£532	£523	£519	£523	£520	£520	£534
PE: True positive	£38	£40	£41	£42	£43	£43	£44
PE: False negative	£188	£186	£185	£184	£183	£183	£182
No PE: True negative	£268	£259	£259	£259	£257	£258	£250
No PE: False positive	£38	£38	£35	£38	£37	£35	£58
Delivery	£3,762	£3,762	£3,762	£3,762	£3,762	£3,762	£3,762
PE: True positive	£161	£171	£177	£180	£185	£183	£190
PE: False negative	£871	£861	£855	£853	£847	£850	£842
No PE: True negative	£2,626	£2,626	£2,635	£2,626	£2,627	£2,632	£2,570
No PE: False positive	£104	£103	£95	£104	£103	£97	£160
Maternal short-term	£361	£361	£360	£360	£360	£360	£361
PE: True positive	£14	£15	£16	£16	£17	£16	£17
PE: False negative	£121	£119	£118	£118	£117	£118	£117
No PE: True negative	£215	£215	£216	£215	£215	£216	£211
No PE: False positive	£11	£11	£10	£11	£11	£10	£16
Neonatal short-term	£4,217	£4,213	£4,209	£4,210	£4,207	£4,207	£4,215
PE: True positive	£279	£296	£306	£311	£321	£317	£329
PE: False negative	£1,851	£1,830	£1,817	£1,812	£1,800	£1,805	£1,789
No PE: True negative	£1,991	£1,991	£1,997	£1,991	£1,992	£1,996	£1,948
No PE: False positive	£97	£96	£88	£96	£95	£90	£148
Neonatal long-term	£1,000	£999	£998	£998	£997	£997	£997

PE: True positive	£107	£114	£118	£119	£123	£122	£127
PE: False negative	£711	£703	£699	£696	£692	£694	£688
No PE: True negative	£173	£173	£174	£173	£173	£174	£170
No PE: False positive	£8	£8	£8	£8	£8	£8	£13
Total QALYs	17.6163	17.6175	17.6185	17.6184	17.6191	17.6191	17.6171
Clinical management	-4.40E-06	-4.38E-06	-4.03E-06	-4.39E-06	-4.34E-06	-4.12E-06	-6.76E-06
PE: True positive	0	0	0	0	0	0	0
PE: False negative	0	0	0	0	0	0	0
No PE: True negative	0	0	0	0	0	0	0
No PE: False positive	-4.40E-06	-4.38E-06	-4.03E-06	-4.39E-06	-4.34E-06	-4.12E-06	-6.76E-06
Delivery	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352
PE: True positive	0.001	0.001	0.001	0.001	0.001	0.001	0.002
PE: False negative	0.007	0.007	0.007	0.007	0.007	0.007	0.007
No PE: True negative	0.026	0.026	0.026	0.026	0.026	0.026	0.025
No PE: False positive	0.001	0.001	0.001	0.001	0.001	0.001	0.002
Maternal short-term	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841
PE: True positive	0.015	0.016	0.016	0.017	0.017	0.017	0.017
PE: False negative	0.080	0.079	0.079	0.078	0.078	0.078	0.077
No PE: True negative	0.278	0.278	0.279	0.278	0.278	0.279	0.272
No PE: False positive	0.011	0.011	0.010	0.011	0.011	0.010	0.017
Neonatal short-term	-0.0006	-0.0006	-0.0006	-0.0006	-0.0006	-0.0006	-0.0006
PE: True positive	-1.89E-05	-2.00E-05	-2.07E-05	-2.10E-05	-2.17E-05	-2.14E-05	-2.23E-05
PE: False negative	-4.35E-04	-4.30E-04	-4.27E-04	-4.25E-04	-4.23E-04	-4.24E-04	-4.20E-04
No PE: True negative	-1.30E-04	-1.30E-04	-1.30E-04	-1.30E-04	-1.30E-04	-1.30E-04	-1.27E-04
No PE: False positive	-2.32E-05	-2.31E-05	-2.13E-05	-2.32E-05	-2.29E-05	-2.18E-05	-3.57E-05
Maternal long-term	17.3645	17.3648	17.3650	17.3650	17.3652	17.3652	17.3647
PE: True positive	0.670	0.710	0.735	0.746	0.769	0.760	0.790
PE: False negative	3.595	3.555	3.530	3.519	3.496	3.505	3.475
No PE: True negative	12.602	12.605	12.644	12.603	12.609	12.633	12.334
No PE: False positive	0.498	0.495	0.456	0.497	0.491	0.467	0.765
Neonatal long-term	-0.1669	-0.1660	-0.1652	-0.1653	-0.1647	-0.1648	-0.1662
PE: True positive	-0.007	-0.007	-0.008	-0.008	-0.008	-0.008	-0.008
PE: False negative	-0.113	-0.112	-0.111	-0.111	-0.110	-0.110	-0.109
No PE: True negative	-0.042	-0.042	-0.042	-0.042	-0.042	-0.042	-0.041
No PE: False positive	-0.005	-0.005	-0.005	-0.005	-0.005	-0.005	-0.008
True Positives	3.9%	4.1%	4.2%	4.3%	4.4%	4.4%	4.6%
True negatives	72.4%	72.4%	72.7%	72.4%	72.5%	72.6%	70.9%
False positives	2.9%	2.9%	2.6%	2.9%	2.8%	2.7%	4.4%
False negatives	20.8%	20.6%	20.5%	20.4%	20.3%	20.3%	20.1%

Table 38: Distribution of hypertension categories from PELICAN

Rule-out PLGF testing	SA (INSPIRE)	Triage test	Elecsys	DELFIA	BRAHMS	Elecsys (add-on)	SA (DG23)
Total cost	£10,537	£10,543	£10,555	£10,528	£10,530	£10,555	£10,535
Test	£0	£50	£79	£37	£52	£79	£0
Clinical management	£612	£572	£557	£571	£561	£558	£613

PE: True positive	£20	£22	£22	£23	£23	£23	£24
PE: False negative	£266	£265	£264	£264	£263	£263	£262
No PE: True negative	£305	£265	£252	£265	£254	£253	£296
No PE: False positive	£20	£20	£19	£20	£20	£19	£31
Delivery	£3,792	£3,792	£3,792	£3,792	£3,792	£3,792	£3,792
PE: True positive	£87	£92	£96	£97	£100	£99	£103
PE: False negative	£1,172	£1,167	£1,163	£1,162	£1,159	£1,160	£1,156
No PE: True negative	£2,477	£2,477	£2,482	£2,477	£2,478	£2,481	£2,447
No PE: False positive	£56	£56	£51	£56	£55	£53	£86
Maternal short-term	£379	£379	£378	£379	£378	£378	£379
PE: True positive	£8	£8	£9	£9	£9	£9	£9
PE: False negative	£162	£162	£161	£161	£160	£161	£160
No PE: True negative	£203	£203	£204	£203	£203	£203	£201
No PE: False positive	£6	£6	£5	£6	£6	£5	£9
Neonatal short-term	£4,570	£4,568	£4,566	£4,567	£4,565	£4,565	£4,569
PE: True positive	£151	£160	£166	£168	£173	£171	£178
PE: False negative	£2,489	£2,478	£2,471	£2,468	£2,462	£2,464	£2,456
No PE: True negative	£1,878	£1,878	£1,882	£1,878	£1,879	£1,881	£1,855
No PE: False positive	£52	£52	£48	£52	£51	£49	£80
Neonatal long-term	£1,183	£1,182	£1,182	£1,181	£1,181	£1,181	£1,181
PE: True positive	£58	£61	£64	£65	£67	£66	£68
PE: False negative	£957	£953	£950	£949	£946	£947	£944
No PE: True negative	£164	£164	£164	£164	£164	£164	£162
No PE: False positive	£5	£5	£4	£5	£4	£4	£7
Total QALYs	17.5755	17.5761	17.5767	17.5766	17.5770	17.5770	17.5759
Clinical management	-2.38E-06	-2.36E-06	-2.18E-06	-2.37E-06	-2.34E-06	-2.23E-06	-3.65E-06
PE: True positive	0	0	0	0	0	0	0
PE: False negative	0	0	0	0	0	0	0
No PE: True negative	0	0	0	0	0	0	0
No PE: False positive	-2.38E-06	-2.36E-06	-2.18E-06	-2.37E-06	-2.34E-06	-2.23E-06	-3.65E-06
Delivery	0.0351	0.0351	0.0351	0.0351	0.0351	0.0351	0.0351
PE: True positive	0.001	0.001	0.001	0.001	0.001	0.001	0.001
PE: False negative	0.009	0.009	0.009	0.009	0.009	0.009	0.009
No PE: True negative	0.024	0.024	0.024	0.024	0.024	0.024	0.024
No PE: False positive	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Maternal short-term	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841
PE: True positive	0.008	0.008	0.009	0.009	0.009	0.009	0.009
PE: False negative	0.108	0.107	0.107	0.107	0.106	0.107	0.106
No PE: True negative	0.262	0.263	0.263	0.262	0.263	0.263	0.259
No PE: False positive	0.006	0.006	0.005	0.006	0.006	0.006	0.009
Neonatal short-term	-0.0007	-0.0007	-0.0007	-0.0007	-0.0007	-0.0007	-0.0007
PE: True positive	-1.02E-05	-1.08E-05	-1.12E-05	-1.14E-05	-1.17E-05	-1.16E-05	-1.20E-05
PE: False negative	-5.85E-04	-5.82E-04	-5.80E-04	-5.80E-04	-5.78E-04	-5.79E-04	-5.77E-04
No PE: True negative	-1.23E-04	-1.23E-04	-1.23E-04	-1.23E-04	-1.23E-04	-1.23E-04	-1.21E-04
No PE: False positive	-1.26E-05	-1.25E-05	-1.15E-05	-1.25E-05	-1.24E-05	-1.18E-05	-1.93E-05
Maternal long-term	17.3550	17.3551	17.3553	17.3552	17.3553	17.3553	17.3551

PE: True positive	0.362	0.384	0.397	0.403	0.416	0.411	0.427
PE: False negative	4.835	4.813	4.800	4.794	4.782	4.787	4.770
No PE: True negative	11.889	11.890	11.911	11.889	11.892	11.906	11.744
No PE: False positive	0.269	0.268	0.247	0.269	0.265	0.252	0.414
Neonatal long-term	-0.1979	-0.1975	-0.1970	-0.1971	-0.1968	-0.1968	-0.1976
PE: True positive	-0.004	-0.004	-0.004	-0.004	-0.004	-0.004	-0.004
PE: False negative	-0.152	-0.151	-0.151	-0.151	-0.150	-0.151	-0.150
No PE: True negative	-0.039	-0.039	-0.039	-0.039	-0.039	-0.039	-0.039
No PE: False positive	-0.003	-0.003	-0.003	-0.003	-0.003	-0.003	-0.004
True Positives	2.1%	2.2%	2.3%	2.3%	2.4%	2.4%	2.5%
True negatives	68.3%	68.3%	68.5%	68.3%	68.4%	68.4%	67.5%
False positives	1.6%	1.5%	1.4%	1.5%	1.5%	1.5%	2.4%
False negatives	28.0%	27.9%	27.8%	27.8%	27.7%	27.8%	27.7%

Table 39: Distribution of hypertension categories from EAG DAR (Triage, PE)

Rule-out PLGF testing	**SA (INSPIRE)**	**Triage test**	**Elecsys**	**DELFIA**	**BRAHMS**	**Elecsys (add-on)**	**SA (DG23)**
Total cost	£11,241	£11,235	£11,231	£11,202	£11,193	£11,219	£11,225
Test	£0	£50	£79	£37	£52	£79	£0
Clinical management	£828	£798	£786	£798	£790	£788	£837
PE: True positive	£160	£170	£176	£178	£184	£182	£189
PE: False negative	£204	£194	£188	£185	£180	£182	£175
No PE: True negative	£303	£274	£275	£273	£267	£273	£226
No PE: False positive	£161	£160	£148	£161	£159	£151	£248
Delivery	£3,834	£3,834	£3,834	£3,834	£3,834	£3,834	£3,834
PE: True positive	£687	£729	£755	£766	£790	£780	£811
PE: False negative	£887	£845	£820	£809	£785	£795	£763
No PE: True negative	£1,817	£1,819	£1,854	£1,817	£1,823	£1,845	£1,579
No PE: False positive	£443	£441	£406	£443	£437	£415	£681
Maternal short-term	£379	£377	£375	£375	£374	£374	£378
PE: True positive	£62	£65	£68	£69	£71	£70	£73
PE: False negative	£123	£117	£113	£112	£109	£110	£106
No PE: True negative	£149	£149	£152	£149	£149	£151	£129
No PE: False positive	£45	£45	£42	£45	£45	£43	£70
Neonatal short-term	£4,862	£4,846	£4,830	£4,831	£4,821	£4,821	£4,854
PE: True positive	£1,189	£1,261	£1,306	£1,325	£1,366	£1,349	£1,404
PE: False negative	£1,884	£1,796	£1,741	£1,718	£1,667	£1,688	£1,621
No PE: True negative	£1,377	£1,379	£1,405	£1,378	£1,382	£1,398	£1,197
No PE: False positive	£412	£410	£377	£411	£406	£386	£633
Neonatal long-term	£1,337	£1,331	£1,326	£1,325	£1,322	£1,323	£1,322
PE: True positive	£457	£485	£502	£509	£525	£519	£540
PE: False negative	£724	£690	£669	£660	£641	£649	£623
No PE: True negative	£120	£120	£122	£120	£120	£122	£104
No PE: False positive	£36	£36	£33	£36	£35	£34	£55
Total QALYs	17.5781	17.5830	17.5874	17.5870	17.5900	17.5899	17.5815
Clinical management	-1.87E-05	-1.87E-05	-1.72E-05	-1.87E-05	-1.85E-05	-1.76E-05	-2.88E-05

PE: True positive	0	0	0	0	0	0	0
PE: False negative	0	0	0	0	0	0	0
No PE: True negative	0	0	0	0	0	0	0
No PE: False positive	-1.87E-05	-1.87E-05	-1.72E-05	-1.87E-05	-1.85E-05	-1.76E-05	-2.88E-05
Delivery	0.0350	0.0350	0.0350	0.0350	0.0350	0.0350	0.0350
PE: True positive	0.006	0.006	0.006	0.006	0.006	0.006	0.007
PE: False negative	0.007	0.007	0.007	0.007	0.006	0.006	0.006
No PE: True negative	0.018	0.018	0.018	0.018	0.018	0.018	0.016
No PE: False positive	0.004	0.004	0.004	0.004	0.004	0.004	0.007
Maternal short-term	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841
PE: True positive	0.063	0.067	0.069	0.070	0.073	0.072	0.075
PE: False negative	0.081	0.078	0.075	0.074	0.072	0.073	0.070
No PE: True negative	0.192	0.193	0.196	0.193	0.193	0.195	0.167
No PE: False positive	0.047	0.047	0.043	0.047	0.046	0.044	0.072
Neonatal short-term	-0.0007	-0.0007	-0.0007	-0.0007	-0.0007	-0.0007	-0.0007
PE: True positive	-8.04E-05	-8.53E-05	-8.83E-05	-8.96E-05	-9.24E-05	-9.13E-05	-9.49E-05
PE: False negative	-4.43E-04	-4.22E-04	-4.09E-04	-4.03E-04	-3.91E-04	-3.96E-04	-3.81E-04
No PE: True negative	-8.99E-05	-9.00E-05	-9.17E-05	-8.99E-05	-9.02E-05	-9.13E-05	-7.81E-05
No PE: False positive	-9.90E-05	-9.85E-05	-9.08E-05	-9.89E-05	-9.77E-05	-9.28E-05	-1.52E-04
Maternal long-term	17.3556	17.3567	17.3578	17.3577	17.3584	17.3584	17.3564
PE: True positive	2.854	3.028	3.134	3.180	3.280	3.239	3.369
PE: False negative	3.660	3.488	3.382	3.336	3.237	3.278	3.149
No PE: True negative	8.718	8.729	8.896	8.721	8.747	8.852	7.576
No PE: False positive	2.123	2.112	1.945	2.120	2.094	1.989	3.263
Neonatal long-term	-0.1958	-0.1921	-0.1887	-0.1890	-0.1867	-0.1868	-0.1932
PE: True positive	-0.030	-0.032	-0.033	-0.033	-0.034	-0.034	-0.035
PE: False negative	-0.115	-0.110	-0.106	-0.105	-0.102	-0.103	-0.099
No PE: True negative	-0.029	-0.029	-0.029	-0.029	-0.029	-0.029	-0.025
No PE: False positive	-0.022	-0.022	-0.020	-0.022	-0.022	-0.021	-0.034
True Positives	16.4%	17.4%	18.1%	18.3%	18.9%	18.7%	19.4%
True negatives	50.1%	50.2%	51.1%	50.1%	50.3%	50.9%	43.5%
False positives	12.2%	12.2%	11.2%	12.2%	12.1%	11.5%	18.8%
False negatives	21.2%	20.2%	19.6%	19.3%	18.8%	19.0%	18.3%

A.4 ADDITIONAL COST-EFFECTIVENESS RESULTS FOR RULE-OUT TESTING

Table 40: Base-case probabilistic results

Rule-out PLGF testing	SA (INSPIRE)	Triage test	Elecsys	DELFIA	BRAHMS	Elecsys (add-on)	SA (DG23)
Total cost	£10,734	£10,251	£10,193	£10,128	£10,127	£10,176	£10,162
Test	£0	£0	£50	£79	£79	£37	£52
Clinical management	£1,235	£845	£813	£761	£777	£818	£807
PE: True positive	£250	£196	£218	£223	£233	£223	£228
PE: False negative	£12	£66	£43	£39	£29	£39	£34

No PE: True negative	£75	£214	£208	£222	£217	£206	£207
No PE: False positive	£898	£369	£342	£277	£299	£350	£337
Delivery	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781
PE: True positive	£1,122	£879	£981	£1,001	£1,046	£1,002	£1,022
PE: False negative	£56	£298	£197	£176	£132	£175	£155
No PE: True negative	£623	£1,770	£1,829	£1,971	£1,924	£1,813	£1,840
No PE: False positive	£1,981	£833	£775	£633	£680	£791	£764
Maternal short-term	£364	£351	£342	£337	£335	£341	£339
PE: True positive	£95	£75	£83	£85	£89	£85	£87
PE: False negative	£8	£46	£30	£27	£20	£27	£24
No PE: True negative	£50	£142	£146	£158	£154	£145	£147
No PE: False positive	£210	£89	£82	£67	£72	£84	£81
Neonatal short-term	£4,361	£4,261	£4,211	£4,178	£4,169	£4,205	£4,192
PE: True positive	£1,933	£1,515	£1,690	£1,726	£1,802	£1,727	£1,762
PE: False negative	£118	£632	£417	£373	£279	£371	£329
No PE: True negative	£472	£1,341	£1,385	£1,493	£1,457	£1,373	£1,394
No PE: False positive	£1,837	£773	£719	£587	£631	£734	£708
Neonatal long-term	£993	£1,013	£997	£992	£985	£994	£990
PE: True positive	£748	£586	£654	£668	£697	£668	£681
PE: False negative	£45	£244	£161	£144	£107	£143	£127
No PE: True negative	£41	£116	£120	£129	£126	£119	£121
No PE: False positive	£159	£67	£62	£51	£55	£64	£61
Total QALYs	17.5098	17.5441	17.5645	17.5772	17.5814	17.5669	17.5720
Clinical management	-1.21E-03	-4.59E-04	-4.17E-04	-3.25E-04	-3.56E-04	-4.28E-04	-4.11E-04
PE: True positive	0	0	0	0	0	0	0
PE: False negative	0	0	0	0	0	0	0
No PE: True negative	0	0	0	0	0	0	0
No PE: False positive	-1.21E-03	-4.59E-04	-4.17E-04	-3.25E-04	-3.56E-04	-4.28E-04	-4.11E-04
Delivery	0.0349	0.0349	0.0349	0.0349	0.0349	0.0349	0.0349
PE: True positive	0.009	0.007	0.008	0.008	0.008	0.008	0.008
PE: False negative	0.000	0.002	0.002	0.001	0.001	0.001	0.001
No PE: True negative	0.006	0.017	0.018	0.019	0.019	0.018	0.018
No PE: False positive	0.019	0.008	0.008	0.006	0.007	0.008	0.007
Maternal short-term	0.3842	0.3842	0.3842	0.3842	0.3842	0.3842	0.3842
PE: True positive	0.103	0.081	0.090	0.092	0.096	0.092	0.094
PE: False negative	0.005	0.027	0.018	0.016	0.012	0.016	0.014
No PE: True negative	0.066	0.188	0.194	0.209	0.204	0.192	0.195
No PE: False positive	0.210	0.088	0.082	0.067	0.072	0.084	0.081
Neonatal short-term	-0.0006	-0.0005	-0.0005	-0.0004	-0.0004	-0.0005	-0.0005
PE: True positive	-1.32E-04	-1.03E-04	-1.15E-04	-1.18E-04	-1.23E-04	-1.18E-04	-1.20E-04
PE: False negative	-2.73E-05	-1.49E-04	-9.80E-05	-8.73E-05	-6.49E-05	-8.67E-05	-7.72E-05
No PE: True negative	-3.09E-05	-8.77E-05	-9.06E-05	-9.76E-05	-9.53E-05	-8.97E-05	-9.12E-05
No PE: False positive	-4.43E-04	-1.87E-04	-1.73E-04	-1.42E-04	-1.52E-04	-1.77E-04	-1.71E-04
Maternal long-term	17.3139	17.3250	17.3311	17.3350	17.3361	17.3318	17.3334
PE: True positive	4.640	3.637	4.057	4.142	4.326	4.145	4.230
PE: False negative	0.228	1.219	0.804	0.719	0.538	0.717	0.633

No PE: True negative	2.988	8.488	8.770	9.452	9.225	8.691	8.824
No PE: False positive	9.458	3.981	3.701	3.021	3.247	3.779	3.647
Neonatal long-term	-0.2214	-0.1989	-0.1848	-0.1761	-0.1730	-0.1830	-0.1796
PE: True positive	-0.065	-0.051	-0.057	-0.058	-0.061	-0.058	-0.059
PE: False negative	-0.010	-0.052	-0.034	-0.030	-0.023	-0.030	-0.027
No PE: True negative	-0.014	-0.041	-0.042	-0.045	-0.044	-0.042	-0.042
No PE: False positive	-0.133	-0.056	-0.052	-0.042	-0.045	-0.053	-0.051
True Positives	26.8%	21.0%	23.5%	23.9%	25.0%	24.0%	24.4%
True negatives	17.2%	48.9%	50.5%	54.4%	53.1%	50.0%	50.8%
False positives	54.7%	23.0%	21.4%	17.5%	18.8%	21.8%	21.1%
False negatives	1.3%	7.1%	4.7%	4.2%	3.1%	4.2%	3.7%

Table 41: Use of INSPIRE for baseline test performance

Rule-out PLGF testing	SA (INSPIRE)	Triage test	Elecsys	DELFIA	BRAHMS	Elecsys (add-on)	SA (DG23)
Total cost	£10,075	£10,137	£10,170	£10,129	£10,152	£10,161	£10,799
Test	£0	£50	£79	£37	£52	£79	£0
Clinical management	£779	£816	£765	£820	£802	£781	£1,262
PE: True positive	£224	£245	£214	£246	£233	£227	£244
PE: False negative	£38	£17	£47	£16	£29	£35	£18
No PE: True negative	£238	£205	£219	£204	£207	£214	£66
No PE: False positive	£279	£349	£285	£354	£333	£306	£934
Delivery	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781
PE: True positive	£1,005	£1,100	£961	£1,103	£1,044	£1,018	£1,094
PE: False negative	£171	£75	£215	£73	£132	£157	£82
No PE: True negative	£1,969	£1,816	£1,957	£1,806	£1,851	£1,911	£547
No PE: False positive	£637	£789	£649	£800	£754	£695	£2,059
Maternal short-term	£341	£339	£343	£339	£341	£341	£366
PE: True positive	£90	£99	£86	£99	£94	£91	£98
PE: False negative	£24	£10	£30	£10	£18	£22	£11
No PE: True negative	£161	£149	£160	£148	£152	£157	£45
No PE: False positive	£65	£81	£67	£82	£77	£71	£211
Neonatal short-term	£4,185	£4,174	£4,205	£4,174	£4,190	£4,190	£4,393
PE: True positive	£1,738	£1,904	£1,662	£1,908	£1,805	£1,762	£1,893
PE: False negative	£363	£160	£456	£154	£281	£334	£173
No PE: True negative	£1,493	£1,377	£1,483	£1,369	£1,404	£1,449	£415
No PE: False positive	£591	£733	£603	£743	£700	£645	£1,912
Neonatal long-term	£989	£977	£996	£977	£985	£988	£997
PE: True positive	£668	£732	£639	£733	£694	£677	£728
PE: False negative	£139	£61	£175	£59	£108	£128	£67
No PE: True negative	£130	£120	£129	£119	£122	£126	£36
No PE: False positive	£51	£64	£52	£65	£61	£56	£166
Total QALYs	17.6661	17.6700	17.6606	17.6698	17.6652	17.6650	17.6118
Clinical management	-2.95E-04	-3.84E-04	-3.02E-04	-3.90E-04	-3.65E-04	-3.29E-04	-1.14E-03
PE: True positive	0	0	0	0	0	0	0
PE: False negative	0	0	0	0	0	0	0

No PE: True negative	0	0	0	0	0	0	0
No PE: False positive	-2.95E-04	-3.84E-04	-3.02E-04	-3.90E-04	-3.65E-04	-3.29E-04	-1.14E-03
Delivery	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352
PE: True positive	0.008	0.009	0.008	0.009	0.008	0.008	0.009
PE: False negative	0.001	0.001	0.002	0.001	0.001	0.001	0.001
No PE: True negative	0.019	0.018	0.019	0.018	0.018	0.019	0.005
No PE: False positive	0.006	0.008	0.006	0.008	0.007	0.007	0.020
Maternal short-term	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841
PE: True positive	0.092	0.101	0.088	0.101	0.096	0.094	0.101
PE: False negative	0.016	0.007	0.020	0.007	0.012	0.014	0.007
No PE: True negative	0.209	0.192	0.207	0.191	0.196	0.203	0.058
No PE: False positive	0.067	0.084	0.069	0.085	0.080	0.074	0.218
Neonatal short-term	-0.0004	-0.0004	-0.0005	-0.0004	-0.0004	-0.0004	-0.0007
PE: True positive	-1.18E-04	-1.29E-04	-1.12E-04	-1.29E-04	-1.22E-04	-1.19E-04	-1.28E-04
PE: False negative	-8.52E-05	-3.75E-05	-1.07E-04	-3.63E-05	-6.59E-05	-7.85E-05	-4.07E-05
No PE: True negative	-9.74E-05	-8.99E-05	-9.68E-05	-8.94E-05	-9.16E-05	-9.46E-05	-2.71E-05
No PE: False positive	-1.42E-04	-1.76E-04	-1.45E-04	-1.79E-04	-1.69E-04	-1.55E-04	-4.60E-04
Maternal long-term	17.3762	17.3771	17.3749	17.3771	17.3760	17.3759	17.3636
PE: True positive	4.173	4.570	3.990	4.580	4.334	4.229	4.543
PE: False negative	0.705	0.310	0.886	0.300	0.545	0.649	0.337
No PE: True negative	9.448	8.717	9.391	8.666	8.885	9.172	2.624
No PE: False positive	3.050	3.780	3.108	3.831	3.612	3.326	9.860
Neonatal long-term	-0.1286	-0.1255	-0.1328	-0.1257	-0.1292	-0.1294	-0.1693
PE: True positive	-0.043	-0.048	-0.042	-0.048	-0.045	-0.044	-0.047
PE: False negative	-0.022	-0.010	-0.028	-0.009	-0.017	-0.020	-0.011
No PE: True negative	-0.031	-0.029	-0.031	-0.029	-0.029	-0.030	-0.009
No PE: False positive	-0.032	-0.039	-0.032	-0.040	-0.038	-0.035	-0.103
True Positives	24.0%	26.3%	23.0%	26.4%	25.0%	24.4%	26.2%
True negatives	54.3%	50.1%	54.0%	49.8%	51.1%	52.7%	15.1%
False positives	17.6%	21.8%	17.9%	22.1%	20.8%	19.2%	56.8%
False negatives	4.1%	1.8%	5.1%	1.7%	3.2%	3.8%	2.0%

Table 42:True positive test results cost more than false negative results

Rule-out PLGF testing	**SA (INSPIRE)**	**Triage test**	**Elecsys**	**DELFIA**	**BRAHMS**	**Elecsys (add-on)**	**SA (DG23)**
Total cost	£10,312	£10,282	£10,200	£10,235	£10,222	£10,198	£10,817
Test	£0	£50	£79	£37	£52	£79	£0
Clinical management	£916	£891	£844	£901	£903	£863	£1,330
PE: True positive	£275	£297	£314	£320	£336	£330	£349
PE: False negative	£60	£43	£31	£26	£15	£19	£5
No PE: True negative	£215	£208	£222	£207	£205	£217	£75
No PE: False positive	£367	£343	£277	£347	£348	£297	£901
Delivery	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781
PE: True positive	£905	£979	£1,037	£1,056	£1,108	£1,088	£1,152
PE: False negative	£270	£197	£139	£120	£68	£88	£23
No PE: True negative	£1,777	£1,830	£1,973	£1,820	£1,819	£1,929	£620

No PE: False positive	£829	£776	£632	£786	£786	£676	£1,986
Maternal short-term	£349	£345	£339	£341	£339	£337	£361
PE: True positive	£81	£88	£93	£95	£99	£98	£103
PE: False negative	£37	£27	£19	£17	£9	£12	£3
No PE: True negative	£146	£150	£162	£149	£149	£158	£51
No PE: False positive	£85	£80	£65	£81	£81	£69	£204
Neonatal short-term	£4,257	£4,219	£4,172	£4,190	£4,170	£4,159	£4,357
PE: True positive	£1,566	£1,694	£1,794	£1,827	£1,916	£1,882	£1,994
PE: False negative	£574	£418	£295	£254	£144	£187	£50
No PE: True negative	£1,347	£1,387	£1,496	£1,380	£1,379	£1,463	£470
No PE: False positive	£770	£721	£587	£729	£730	£628	£1,844
Neonatal long-term	£1,007	£995	£984	£984	£976	£977	£987
PE: True positive	£602	£651	£689	£702	£737	£723	£766
PE: False negative	£221	£161	£113	£98	£55	£72	£19
No PE: True negative	£117	£121	£130	£120	£120	£127	£41
No PE: False positive	£67	£63	£51	£64	£64	£55	£161
Total QALYs	17.6461	17.6569	17.6699	17.6652	17.6710	17.6737	17.6217
Clinical management	-4.09E-04	-3.75E-04	-2.91E-04	-3.81E-04	-3.83E-04	-3.17E-04	-1.09E-03
PE: True positive	0	0	0	0	0	0	0
PE: False negative	0	0	0	0	0	0	0
No PE: True negative	0	0	0	0	0	0	0
No PE: False positive	-4.09E-04	-3.75E-04	-2.91E-04	-3.81E-04	-3.83E-04	-3.17E-04	-1.09E-03
Delivery	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352
PE: True positive	0.007	0.008	0.008	0.009	0.009	0.009	0.009
PE: False negative	0.002	0.002	0.001	0.001	0.001	0.001	0.000
No PE: True negative	0.018	0.018	0.019	0.018	0.018	0.019	0.006
No PE: False positive	0.008	0.008	0.006	0.008	0.008	0.007	0.020
Maternal short-term	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841
PE: True positive	0.083	0.090	0.095	0.097	0.102	0.100	0.106
PE: False negative	0.025	0.018	0.013	0.011	0.006	0.008	0.002
No PE: True negative	0.188	0.194	0.209	0.193	0.193	0.204	0.066
No PE: False positive	0.088	0.082	0.067	0.083	0.083	0.072	0.210
Neonatal short-term	-0.0005	-0.0005	-0.0004	-0.0004	-0.0004	-0.0004	-0.0006
PE: True positive	-1.06E-04	-1.15E-04	-1.21E-04	-1.24E-04	-1.30E-04	-1.27E-04	-1.35E-04
PE: False negative	-1.35E-04	-9.81E-05	-6.93E-05	-5.96E-05	-3.39E-05	-4.39E-05	-1.16E-05
No PE: True negative	-8.79E-05	-9.05E-05	-9.76E-05	-9.01E-05	-9.00E-05	-9.55E-05	-3.07E-05
No PE: False positive	-1.85E-04	-1.73E-04	-1.41E-04	-1.76E-04	-1.76E-04	-1.51E-04	-4.44E-04
Maternal long-term	17.3715	17.3740	17.3771	17.3760	17.3773	17.3780	17.3660
PE: True positive	3.760	4.066	4.306	4.386	4.600	4.516	4.785
PE: False negative	1.115	0.811	0.573	0.493	0.280	0.363	0.096
No PE: True negative	8.528	8.780	9.471	8.735	8.731	9.260	2.974
No PE: False positive	3.969	3.717	3.028	3.762	3.766	3.238	9.511
Neonatal long-term	-0.1437	-0.1356	-0.1257	-0.1292	-0.1248	-0.1228	-0.1618
PE: True positive	-0.039	-0.042	-0.045	-0.046	-0.048	-0.047	-0.050
PE: False negative	-0.035	-0.026	-0.018	-0.016	-0.009	-0.011	-0.003
No PE: True negative	-0.028	-0.029	-0.031	-0.029	-0.029	-0.031	-0.010

No PE: False positive	-0.041	-0.039	-0.032	-0.039	-0.039	-0.034	-0.099
True Positives	21.7%	23.4%	24.8%	25.3%	26.5%	26.0%	27.6%
True negatives	49.0%	50.5%	54.4%	50.2%	50.2%	53.2%	17.1%
False positives	22.9%	21.4%	17.4%	21.7%	21.7%	18.7%	54.8%
False negatives	6.5%	4.7%	3.3%	2.9%	1.6%	2.1%	0.6%

Table 43: Distribution of hypertension categories from PARROT Ireland

Rule-out PLGF testing	SA (INSPIRE)	Triage test	Elecsys	DELFIA	BRAHMS	Elecsys (add-on)	SA (DG23)
Total cost	£9,915	£9,881	£9,787	£9,831	£9,817	£9,786	£10,488
Test	£0	£50	£79	£37	£52	£79	£0
Clinical management	£797	£765	£707	£769	£768	£724	£1,249
PE: True positive	£171	£185	£197	£201	£212	£208	£221
PE: False negative	£55	£40	£28	£25	£14	£18	£5
No PE: True negative	£202	£198	£212	£197	£195	£207	£70
No PE: False positive	£369	£341	£269	£346	£347	£292	£953
Delivery	£3,762	£3,762	£3,762	£3,762	£3,762	£3,762	£3,762
PE: True positive	£779	£847	£902	£920	£969	£950	£1,011
PE: False negative	£253	£186	£130	£113	£64	£83	£22
No PE: True negative	£1,923	£1,982	£2,136	£1,972	£1,969	£2,089	£670
No PE: False positive	£807	£747	£594	£758	£761	£641	£2,059
Maternal short-term	£346	£341	£335	£338	£335	£334	£360
PE: True positive	£70	£76	£81	£83	£87	£85	£91
PE: False negative	£35	£26	£18	£16	£9	£11	£3
No PE: True negative	£158	£163	£175	£162	£161	£171	£55
No PE: False positive	£83	£77	£61	£78	£78	£66	£211
Neonatal short-term	£4,093	£4,057	£4,009	£4,030	£4,011	£3,998	£4,216
PE: True positive	£1,348	£1,465	£1,560	£1,591	£1,676	£1,643	£1,748
PE: False negative	£538	£394	£277	£240	£136	£176	£46
No PE: True negative	£1,458	£1,503	£1,620	£1,495	£1,493	£1,584	£508
No PE: False positive	£750	£694	£551	£704	£706	£595	£1,912
Neonatal long-term	£917	£906	£895	£895	£888	£889	£901
PE: True positive	£518	£563	£600	£612	£644	£632	£672
PE: False negative	£207	£152	£107	£92	£52	£68	£18
No PE: True negative	£127	£131	£141	£130	£130	£138	£44
No PE: False positive	£65	£60	£48	£61	£61	£52	£167
Total QALYs	17.6546	17.6650	17.6782	17.6727	17.6782	17.6814	17.6240
Clinical management	-4.63E-04	-4.25E-04	-3.29E-04	-4.31E-04	-4.34E-04	-3.59E-04	-1.25E-03
PE: True positive	0	0	0	0	0	0	0
PE: False negative	0	0	0	0	0	0	0
No PE: True negative	0	0	0	0	0	0	0
No PE: False positive	-4.63E-04	-4.25E-04	-3.29E-04	-4.31E-04	-4.34E-04	-3.59E-04	-1.25E-03
Delivery	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352
PE: True positive	0.006	0.007	0.007	0.007	0.008	0.008	0.008
PE: False negative	0.002	0.001	0.001	0.001	0.001	0.001	0.000
No PE: True negative	0.019	0.020	0.021	0.019	0.019	0.021	0.007

No PE: False positive	0.008	0.007	0.006	0.007	0.008	0.006	0.020
Maternal short-term	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841
PE: True positive	0.072	0.078	0.083	0.084	0.089	0.087	0.093
PE: False negative	0.023	0.017	0.012	0.010	0.006	0.008	0.002
No PE: True negative	0.204	0.210	0.226	0.209	0.209	0.221	0.071
No PE: False positive	0.086	0.079	0.063	0.080	0.081	0.068	0.218
Neonatal short-term	-0.0005	-0.0005	-0.0004	-0.0004	-0.0004	-0.0004	-0.0006
PE: True positive	-9.12E-05	-9.91E-05	-1.06E-04	-1.08E-04	-1.13E-04	-1.11E-04	-1.18E-04
PE: False negative	-1.26E-04	-9.26E-05	-6.51E-05	-5.63E-05	-3.19E-05	-4.13E-05	-1.09E-05
No PE: True negative	-9.51E-05	-9.81E-05	-1.06E-04	-9.76E-05	-9.74E-05	-1.03E-04	-3.32E-05
No PE: False positive	-1.80E-04	-1.67E-04	-1.33E-04	-1.69E-04	-1.70E-04	-1.43E-04	-4.60E-04
Maternal long-term	17.3735	17.3759	17.3790	17.3778	17.3790	17.3798	17.3665
PE: True positive	3.236	3.517	3.746	3.819	4.022	3.944	4.197
PE: False negative	1.045	0.766	0.538	0.466	0.264	0.342	0.090
No PE: True negative	9.227	9.514	10.252	9.465	9.451	10.024	3.218
No PE: False positive	3.865	3.579	2.843	3.629	3.642	3.070	9.862
Neonatal long-term	-0.1373	-0.1294	-0.1194	-0.1235	-0.1193	-0.1169	-0.1599
PE: True positive	-0.034	-0.037	-0.039	-0.040	-0.042	-0.041	-0.044
PE: False negative	-0.033	-0.024	-0.017	-0.015	-0.008	-0.011	-0.003
No PE: True negative	-0.030	-0.031	-0.034	-0.031	-0.031	-0.033	-0.011
No PE: False positive	-0.040	-0.037	-0.030	-0.038	-0.038	-0.032	-0.103
True Positives	18.6%	20.3%	21.6%	22.0%	23.2%	22.7%	24.2%
True negatives	53.0%	54.7%	58.9%	54.4%	54.3%	57.6%	18.5%
False positives	22.3%	20.6%	16.4%	20.9%	21.0%	17.7%	56.8%
False negatives	6.1%	4.4%	3.1%	2.7%	1.5%	2.0%	0.5%

Table 44: Distribution of hypertension categories from PELICAN

Rule-out PLGF testing	**SA (INSPIRE)**	**Triage test**	**Elecsys**	**DELFIA**	**BRAHMS**	**Elecsys (add-on)**	**SA (DG23)**
Total cost	£10,409	£10,336	£10,230	£10,274	£10,243	£10,220	£10,885
Test	£0	£50	£79	£37	£52	£79	£0
Clinical management	£851	£791	£726	£794	£784	£743	£1,259
PE: True positive	£213	£233	£249	£254	£268	£262	£280
PE: False negative	£73	£54	£38	£33	£18	£24	£6
No PE: True negative	£225	£191	£195	£190	£179	£191	£78
No PE: False positive	£340	£313	£245	£318	£319	£266	£895
Delivery	£3,792	£3,792	£3,792	£3,792	£3,792	£3,792	£3,792
PE: True positive	£937	£1,022	£1,093	£1,115	£1,178	£1,154	£1,231
PE: False negative	£322	£237	£166	£144	£81	£105	£28
No PE: True negative	£1,804	£1,861	£2,005	£1,852	£1,848	£1,960	£629
No PE: False positive	£729	£672	£528	£682	£685	£573	£1,904
Maternal short-term	£351	£346	£340	£342	£339	£338	£361
PE: True positive	£84	£92	£98	£100	£106	£104	£111
PE: False negative	£45	£33	£23	£20	£11	£15	£4
No PE: True negative	£148	£153	£164	£152	£152	£161	£52
No PE: False positive	£75	£69	£54	£70	£70	£59	£195

Neonatal short-term	£4,350	£4,307	£4,254	£4,272	£4,248	£4,238	£4,434
PE: True positive	£1,622	£1,768	£1,891	£1,929	£2,037	£1,996	£2,130
PE: False negative	£683	£503	£353	£306	£173	£224	£59
No PE: True negative	£1,368	£1,411	£1,520	£1,404	£1,401	£1,486	£477
No PE: False positive	£677	£624	£491	£633	£636	£532	£1,768
Neonatal long-term	£1,064	£1,050	£1,037	£1,036	£1,027	£1,029	£1,037
PE: True positive	£623	£680	£727	£741	£783	£767	£819
PE: False negative	£263	£193	£136	£118	£66	£86	£23
No PE: True negative	£119	£123	£132	£122	£122	£129	£42
No PE: False positive	£59	£54	£43	£55	£55	£46	£154
Total QALYs	17.6414	17.6536	17.6682	17.6637	17.6707	17.6731	17.6215
Clinical management	-4.42E-04	-4.05E-04	-3.14E-04	-4.11E-04	-4.13E-04	-3.42E-04	-1.19E-03
PE: True positive	0	0	0	0	0	0	0
PE: False negative	0	0	0	0	0	0	0
No PE: True negative	0	0	0	0	0	0	0
No PE: False positive	-4.42E-04	-4.05E-04	-3.14E-04	-4.11E-04	-4.13E-04	-3.42E-04	-1.19E-03
Delivery	0.0351	0.0351	0.0351	0.0351	0.0351	0.0351	0.0351
PE: True positive	0.008	0.008	0.009	0.009	0.009	0.009	0.010
PE: False negative	0.003	0.002	0.001	0.001	0.001	0.001	0.000
No PE: True negative	0.018	0.018	0.020	0.018	0.018	0.019	0.006
No PE: False positive	0.007	0.007	0.005	0.007	0.007	0.006	0.019
Maternal short-term	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841
PE: True positive	0.086	0.094	0.100	0.102	0.108	0.106	0.113
PE: False negative	0.030	0.022	0.015	0.013	0.007	0.010	0.003
No PE: True negative	0.191	0.197	0.212	0.196	0.196	0.208	0.067
No PE: False positive	0.077	0.071	0.056	0.072	0.073	0.061	0.202
Neonatal short-term	-0.0005	-0.0005	-0.0004	-0.0004	-0.0004	-0.0004	-0.0006
PE: True positive	-1.10E-04	-1.20E-04	-1.28E-04	-1.30E-04	-1.38E-04	-1.35E-04	-1.44E-04
PE: False negative	-1.60E-04	-1.18E-04	-8.29E-05	-7.19E-05	-4.06E-05	-5.26E-05	-1.39E-05
No PE: True negative	-8.93E-05	-9.21E-05	-9.92E-05	-9.16E-05	-9.15E-05	-9.70E-05	-3.11E-05
No PE: False positive	-1.63E-04	-1.50E-04	-1.18E-04	-1.52E-04	-1.53E-04	-1.28E-04	-4.25E-04
Maternal long-term	17.3705	17.3733	17.3767	17.3757	17.3773	17.3778	17.3659
PE: True positive	3.892	4.244	4.538	4.630	4.890	4.790	5.113
PE: False negative	1.327	0.978	0.685	0.594	0.336	0.435	0.115
No PE: True negative	8.659	8.932	9.623	8.886	8.870	9.409	3.019
No PE: False positive	3.492	3.219	2.530	3.265	3.281	2.744	9.119
Neonatal long-term	-0.1473	-0.1380	-0.1270	-0.1303	-0.1250	-0.1232	-0.1618
PE: True positive	-0.041	-0.044	-0.047	-0.048	-0.051	-0.050	-0.053
PE: False negative	-0.042	-0.031	-0.022	-0.019	-0.011	-0.014	-0.004
No PE: True negative	-0.029	-0.029	-0.032	-0.029	-0.029	-0.031	-0.010
No PE: False positive	-0.036	-0.034	-0.026	-0.034	-0.034	-0.029	-0.095
True Positives	22.4%	24.4%	26.1%	26.7%	28.2%	27.6%	29.5%
True negatives	49.8%	51.3%	55.3%	51.1%	51.0%	54.1%	17.4%
False positives	20.1%	18.5%	14.6%	18.8%	18.9%	15.8%	52.5%
False negatives	7.7%	5.7%	4.0%	3.4%	1.9%	2.5%	0.7%

Table 45: Distribution of hypertension categories from EAG DAR (Triage, PE)

Rule-out PLGF testing	SA (INSPIRE)	Triage test	Elecsys	DELFIA	BRAHMS	Elecsys (add-on)	SA (DG23)
Total cost	£11,135	£11,080	£11,003	£11,015	£10,985	£10,983	£11,391
Test	£0	£50	£79	£37	£52	£79	£0
Clinical management	£968	£927	£886	£928	£921	£896	£1,216
PE: True positive	£287	£308	£324	£330	£345	£339	£357
PE: False negative	£77	£55	£39	£34	£19	£25	£7
No PE: True negative	£252	£227	£239	£226	£219	£233	£88
No PE: False positive	£352	£335	£283	£339	£338	£299	£764
Delivery	£3,834	£3,834	£3,834	£3,834	£3,834	£3,834	£3,834
PE: True positive	£1,241	£1,334	£1,404	£1,428	£1,491	£1,466	£1,546
PE: False negative	£334	£240	£171	£146	£83	£108	£29
No PE: True negative	£1,415	£1,451	£1,569	£1,444	£1,447	£1,534	£493
No PE: False positive	£845	£809	£691	£816	£813	£726	£1,767
Maternal short-term	£360	£355	£349	£351	£348	£347	£364
PE: True positive	£111	£120	£126	£128	£134	£132	£139
PE: False negative	£46	£33	£24	£20	£12	£15	£4
No PE: True negative	£116	£119	£129	£118	£119	£126	£40
No PE: False positive	£87	£83	£71	£84	£83	£74	£181
Neonatal short-term	£4,713	£4,670	£4,622	£4,634	£4,609	£4,604	£4,750
PE: True positive	£2,146	£2,308	£2,428	£2,471	£2,579	£2,537	£2,674
PE: False negative	£709	£511	£363	£311	£177	£230	£61
No PE: True negative	£1,073	£1,100	£1,190	£1,095	£1,097	£1,163	£374
No PE: False positive	£785	£751	£642	£758	£755	£674	£1,640
Neonatal long-term	£1,259	£1,245	£1,232	£1,230	£1,221	£1,223	£1,227
PE: True positive	£825	£887	£933	£950	£992	£975	£1,028
PE: False negative	£273	£196	£139	£119	£68	£88	£24
No PE: True negative	£93	£96	£104	£95	£95	£101	£33
No PE: False positive	£68	£65	£56	£66	£66	£59	£143
Total QALYs	17.6227	17.6349	17.6481	17.6453	17.6525	17.6537	17.6156
Clinical management	-2.81E-04	-2.59E-04	-2.03E-04	-2.63E-04	-2.64E-04	-2.20E-04	-7.37E-04
PE: True positive	0	0	0	0	0	0	0
PE: False negative	0	0	0	0	0	0	0
No PE: True negative	0	0	0	0	0	0	0
No PE: False positive	-2.81E-04	-2.59E-04	-2.03E-04	-2.63E-04	-2.64E-04	-2.20E-04	-7.37E-04
Delivery	0.0350	0.0350	0.0350	0.0350	0.0350	0.0350	0.0350
PE: True positive	0.010	0.011	0.011	0.012	0.012	0.012	0.012
PE: False negative	0.003	0.002	0.001	0.001	0.001	0.001	0.000
No PE: True negative	0.014	0.014	0.015	0.014	0.014	0.015	0.005
No PE: False positive	0.008	0.008	0.007	0.008	0.008	0.007	0.017
Maternal short-term	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841
PE: True positive	0.114	0.123	0.129	0.131	0.137	0.135	0.142
PE: False negative	0.031	0.022	0.016	0.013	0.008	0.010	0.003
No PE: True negative	0.150	0.154	0.166	0.153	0.153	0.163	0.052
No PE: False positive	0.090	0.086	0.073	0.086	0.086	0.077	0.187

Neonatal short-term	-0.0006	-0.0005	-0.0005	-0.0005	-0.0005	-0.0005	-0.0006
PE: True positive	-1.45E-04	-1.56E-04	-1.64E-04	-1.67E-04	-1.74E-04	-1.72E-04	-1.81E-04
PE: False negative	-1.67E-04	-1.20E-04	-8.52E-05	-7.30E-05	-4.16E-05	-5.40E-05	-1.44E-05
No PE: True negative	-7.00E-05	-7.18E-05	-7.76E-05	-7.14E-05	-7.16E-05	-7.59E-05	-2.44E-05
No PE: False positive	-1.89E-04	-1.81E-04	-1.54E-04	-1.82E-04	-1.82E-04	-1.62E-04	-3.95E-04
Maternal long-term	17.3661	17.3689	17.3720	17.3713	17.3730	17.3733	17.3645
PE: True positive	5.152	5.540	5.829	5.931	6.192	6.089	6.418
PE: False negative	1.377	0.992	0.705	0.603	0.344	0.447	0.119
No PE: True negative	6.791	6.964	7.530	6.929	6.943	7.362	2.368
No PE: False positive	4.046	3.874	3.309	3.909	3.894	3.476	8.459
Neonatal long-term	-0.1616	-0.1523	-0.1422	-0.1444	-0.1388	-0.1380	-0.1665
PE: True positive	-0.054	-0.058	-0.061	-0.062	-0.065	-0.063	-0.067
PE: False negative	-0.043	-0.031	-0.022	-0.019	-0.011	-0.014	-0.004
No PE: True negative	-0.022	-0.023	-0.025	-0.023	-0.023	-0.024	-0.008
No PE: False positive	-0.042	-0.040	-0.034	-0.041	-0.041	-0.036	-0.088
True Positives	29.7%	31.9%	33.6%	34.2%	35.7%	35.1%	37.0%
True negatives	39.0%	40.0%	43.3%	39.8%	39.9%	42.3%	13.6%
False positives	23.3%	22.3%	19.1%	22.5%	22.4%	20.0%	48.7%
False negatives	8.0%	5.7%	4.1%	3.5%	2.0%	2.6%	0.7%

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Stakeholder	Comment no.	Page no.	Section no.	Comment	DSU Response
Quidel	1			No comments	No response required
Roche	2	-	-	We thank NICE and the DSU for preparing the review, updating the economic model and allowing us the opportunity to comment. We are very supportive of the changes made by the DSU to a linked evidence approach, allowing a fair comparison between strategies and avoiding any changes in cost-effectiveness being driven by trial differences.	No response required
Roche	3	-	-	The DSU report refers to the previous EAG modelling report. We would urge NICE to consider only publishing the DSU modelling report and not the previous EAG report in order to prevent any misinterpretation of the evidence and confusion arising from multiple conflicting economic analyses. Our fear is that publication of the previous EAG modelling report may lead to confusion among clinical teams and commissioners and is likely to have a negative effect on patient access to PlGF based testing.	No response required **NICE response** The EAG's original diagnostic assessment report (DAR) will be published with the draft guidance for transparency and because the systematic review has not been superseded by the DSU's report. A cover sheet has been added to the EAG's DAR to indicate the committee's concerns about the economic analyses in this work, as described in the draft guidance, and that this element of the EAG's report has been superseded by the DSU's report. Pages in

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Decision Report Unit Report - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	DSU Response
					the EAG's report that contain economic analysis have also been watermarked with 'Superseded by the DSU report' throughout.
Roche	4	6 and 63		The following statement is included in the executive summary and conclusions section: "Incremental costs and QALYs were always very small, with incremental costs always less than the cost of the test and incremental QALYs always less than 0.006". We object to the inclusion of this sentence as this is often the case with economic evaluations of diagnostic tests for two main reasons: i) When the prevalence of a condition is <50%, most patients do not have the condition and therefore receive little benefit from testing. ii) Improvements in pathway sensitivity and specificity are often incremental such that only a few additional people are correctly identified. We believe the focus of the discussion, in both the executive summary and the conclusions sections, should be on the added benefit to those patients who benefit from testing i.e. the incremental health benefit to those patients who move from a falsely negative diagnosis to a positive diagnosis and those who	We believe that this statement provides a useful summary of the results, no change required.

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Stakeholder	Comment no.	Page no.	Section no.	Comment	DSU Response
				move from a falsely positive diagnosis to a negative diagnosis.	
Roche	5			The INSPIRE trial is used as an alternative base case. As noted in our previous comments (comment 1c., dated 28/05/2021), the INSPIRE trial took place in a tertiary referral centre in a large teaching hospital with expertise in pre-eclampsia research. Among the INSPIRE clinical staff were professors of obstetrics and other staff highly skilled in the diagnosis/management of pre-eclampsia and in the trial only 26% of women with suspected pre-eclampsia were admitted within 24 hours in the clinical decision alone arm (without sFlt-1/PlGF testing). We would urge NICE to consider moving this base case analysis into a scenario analyses section, and downplaying its weight as a national base case. The reason for this is to improve the clarity of the conclusions for clinicians as comparative results from this analysis is unlikely to be applicable to most other UK hospitals, particularly smaller hospitals with less expertise/experience managing women with suspected pre-eclampsia and/or those in rural, less-accessible, settings.	The relevance of the INSPIRE trial is already discussed in section five. No change required

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Stakeholder	Comment no.	Page no.	Section no.	Comment	DSU Response
Roche	6			In contrast to the last EAG report, the DSU modelling additionally includes the Brahms and Delfia tests. We welcome their inclusion, as this could lead to greater patient access to PlGF-based tests, however we note there are important differences in the level of clinical evidence between these tests and the Elecsys and Quidel tests. There is no clinical utility data on either of these tests, and whilst it could be assumed that the clinical utility of such tests is likely to be similar to other PlGF-based tests, this depends on robust data on clinical accuracy i.e. sensitivity and specificity from prospective cohort studies. However, in some cases, the diagnostic accuracy of these tests were estimated in studies with very small sample sizes and with case-controlled design. Such studies are known to overestimate diagnostic accuracy (Rutjes 2006, NICE 2014). Therefore, we feel it would be pertinent for the DSU report to explore and characterise the uncertainty of the clinical accuracy of the PLGF-based tests, its effect on the model outcomes, and raise the potential significance of such uncertainty to avoid a wider issue of loss of confidence in all PlGF-based tests. Rutjes AW, Reitsma JB, Di Nisio M, Smidt N, van Rijn JC, Bossuyt PM. Evidence of bias and variation	A quality assessment of the studies providing evidence on the BRAHMS and DELFIA tests is provided in Tables 4 and 5. Uncertainty in sensitivity and specificity due to small sample sizes will be captures in the probabilistic sensitivity analysis. No change required.

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Stakeholder	Comment no.	Page no.	Section no.	Comment	DSU Response
				in diagnostic accuracy studies. CMAJ. 2006 Feb 14;174(4):469-76. doi: 10.1503/cmaj.050090. PMID: 16477057; PMCID: PMC1373751. National Institute for Health and Care Excellence Developing NICE guidelines: the manual 2014	
Roche	7	23		The DSU methodology for calculating relative accuracy between tests allows extrapolation of the accuracy of the individual tests to the different base cases. This is a unique approach where one might expect a meta-analysis, however given the similarities in the target populations within the different studies, it seems plausible that it provides reasonable estimates of accuracy. We do, however, question the validity of including a case-control study design in this methodology. Case control studies are prone to selection bias and the prevalence of the condition within the study population is often set by the study design and does not reflect that within the target population. These factors have an effect on the robustness of the estimates of diagnostic accuracy and it therefore seems inappropriate to include this type of study design in the relative accuracy calculations.	We acknowledge that a case-control study was used to obtain estimates of sensitivity and specificity for BRAHMS relative to Elecsys. This reflects the best available evidence, and the limitations of this study source is acknowledged as part of the quality assessment (see response to previous comment) Further, it is unclear if the limitations cited apply to relative effects. No change required.

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Stakeholder	Comment no.	Page no.	Section no.	Comment	DSU Response
Roche	8	17 - 25		We note that Tables 4-6 have been repeated 3 times.	Thank you for raising this. This is a formatting error, which does not affect the results of the report. Hence, no change required.
Roche	9	Table 16 and 20		Presenting 'Net Health Benefit' would be helpful for interpretation of these tables.	This information has now been included in the second addendum (dated 21st February 2022).
Roche	10	55		Please consider presenting a diagonal line representing the ICER (at £20k/QALY) on Figure 3.	As only a small handful of points fall within the north-east quadrant in Figure 3, we do not believe that this would add much benefit. No change required.
BMFMS	11	4		The DSU report provides a comprehensive summary of the revised cost effectiveness model. The assumptions appear to better reflect current clinical practice. Although there are clear limitations and some of the assumptions used in the models are imprecise, it is reassuring that the sensitivity analyses have not dramatically changed the findings. The findings are also plausible and consistent with clinical practice given that they show that the biggest savings are likely to be associated with the use of PlGF-based testing as an adjunct to clinical assessment. It is also reassuring that there is additional cost saving associated with both rule in and rule out use of the test; this also aligns with clinical experience.	No response required

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Stakeholder	Comment no.	Page no.	Section no.	Comment	DSU Response
				We are away that PlGF-based testing has been widely adopted across NHS hospitals. We welcome the findings of this report which supports the implementation of PlGF-based testin. The report provides additional evidence to support uptake across more sites facilitating equitable care for all pregnant women.	
BMFMS	12	15		Distribution of hypertension categories based on trial populations likely only to be partially reflective of true distributions – based on women participating in research which selects those women deemed not to have rapidly evolving disease/very severe hypertension. Changing the distributions did not materially change the findings but important to highlight that both clinical effectiveness and cost effectiveness are considerably reduced if the test is applied in a population of women where the prevalence of hypertension, and therefore pre-eclampsia, is not sufficiently high (ie PARROT Ireland).	No response required
BMFMS	13		2.1.4	Understandably a lot of focus in the model development on the decision to admit. This is only a very small part of the management pathway. As highlighted most often the result will direct an	No response required

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Stakeholder	Comment no.	Page no.	Section no.	Comment	DSU Response
				alternative monitoring pathway which may include admission or increased OP surveillance in some cases. As increased OP surveillance is less costly than IP admission, this will underestimate the cost benefits associated with rule in. In addition since the publication of PARROT and INSPIRE, many units are using home BP surveillance much more commonly for women at low/intermediate risk of pre-eclampsia – this again reduces the cost in women tested by reducing OP surveillance.	
BMFMS	14		2.1.4	The assumptions made about admission and length of admission for true positives and false negatives are much better aligned in the revised model compared with the previous EAG model.	No response required
PerkinElmer	1		3. Overview of new evidence available since the EAG DAR.	Since completion of the DAP53 EAG DAR, the study *Rule-in and rule-out of pre-eclampsia using DELFIA Xpress PlGF 1-2-3 and sFlt-1: PlGF ratio* by Bremner *et al.* (2021) has now been published. We request that Bremmer et al, 2021 is included in the assessment. This published study uses pre-specified thresholds derived from the COMPARE study for Placental growth factor (PlGF) and validates thresholds for soluble fms-like tyrosine-kinase 1 (s-Flt-1) (as s-Flt-1: PlGF ratio), to rule-in and rule-out disease in wome with suspected pre-eclampsia with	This information has been used to provide cost-effectiveness results for the DELFIA sFlt-1: PlGF ratio, which are described in the second addendum (dated 21st February 2022).

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Stakeholder	Comment no.	Page no.	Section no.	Comment	DSU Response
				suspected pre-eclampsia using DELFIA® Xpress PlGF1-2-3 and sFlt-1 assays. The clinical performance for the DELFIA Xpress PlGF 1-2-3 and DELFIA Xpress sFlt-1/PlGF reported in Bremner et al, 2021 is consistent with the clinical performance of the Elecsys test in the INSPIRE study. The same diagnostic criteria were used to evaluate clinical efficacy. The data required for DELFIA Xpress sFlt-1/PlGF to be included in the economic model is now peer reviewed (Bremner et al., 2021). We note that the analysis for DELFIA Xpress sFlt-1/PlGF is available in the DAP53 PlGF ScHARR model 20220128 [No ACIC]and respectfully request that NICE includes the DELFIA Xpress sFlt-1/PlGF in the economic model report.	
		19	*2.1.2. Prevalence of pre-eclampsia by hypertension status*	**For the COMPARE study the main concern was the lack of a pre-specified threshold for the BRAHMS test.** We believe that there is an error in the sentence. BRAHMS was not included in the COMPARE study. This should be DELFIA test.	Thank you for identifying this typo, which has been corrected in the erratum. The publication by Bremner and colleagues is noted (see also response to previous comment), but as this was published after the DSU report, no further change is required.

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Stakeholder	Comment no.	Page no.	Section no.	Comment	DSU Response
				To address the concern regarding the absence of a pre-specified threshold for the DELFIA Xpress PlGF test, we refer the diagnostic assessment group to the peer reviewed publication: *Rule-in and rule-out of pre-eclampsia using DELFIA Xpress PlGF 1-2-3 and sFlt-1: PlGF ratio by Bremner et al,2021.* As stated above this published study uses pre-specified thresholds derived from the COMPARE study for Placental growth factor (PlGF) and validates thresholds for soluble fms-like tyrosine-kinase 1 (s-Flt-1) (as s-Flt-1: PlGF ratio), to rule-in and rule-out disease in women with suspected pre-eclampsia, using DELFIA® Xpress PlGF1-2-3 and sFlt-1 assays.	
	3	82	Table 40	The price for the DELFIA test is incorrect (£79). Also, we believe there may be additional errors in that table. Please check.	Thank you for raising this. On inspection of the Appendices tables, the following typos were identified: • Titles for A3 and A4 were incorrectly swapped. Hence A3 should read "ADDITIONAL COST-EFFECTIVENESS RESULTS FOR RULE-OUT TESTING" and A4 is "ADDITIONAL COST-EFFECTIVENESS RESULTS FOR RULE-IN TESTING" • For Table 34 and Table 40 the contents are correct, but the headings are in the

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Stakeholder	Comment no.	Page no.	Section no.	Comment	DSU Response
					wrong order. The correct order is: SA (DG23), SA (INSPIRE), Triage test, Elecsys, Elecsys (add-on), DELFIA, BRAHMS. The correct Tables 34 and 40 are included in the erratum.
	4	21	Tables 4 & 5	The purpose of COMPARE was to look at the ability to predict delivery within 14 days secondary to suspected pre-eclampsia of three assays: the Triage PlGF test, the Elecsys sFlt-1/PlGF ratio and the DELFIA Xpress PlGF 1-2-3 test. Given the variable populations that have been used in the different clinical studies in the past, it is not surprising that the thresholds in the three products could be different. Therefore, the primary analysis was ROC area, which removes differences created by different thresholds. The ROC areas were identical between the three products when evaluated on the same patients. Any differences in specificity and sensitivity are therefore due to differences in the thresholds selected, but given the equivalent ROC areas, these assays are identical in predicting outcome in this population. Therefore, having a post-hoc defined threshold for the DELFIA is not a bias. We would recommend that in Table 4 regarding the Index test and the Reference Standard, the assessment of bias is re-considered.	We acknowledge that the primary analysis was a comparison of ROC areas, which were found to be identical. This does not change the fact that in this study the threshold used for DELFIA was defined post-hoc. The new publication came-out after the DSU report and is discussed in the second addendum (dated 21st February 2022). No further change required.

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				Furthermore, as the threshold that was selected as equivalent in COMPARE has been prospectively validated on a new population (Bremner et al. 2021), this confirms the equivalence between the assays.	
	5	34	2.2.1.2. Gestational age	**"For the latter there was no variation by risk, and data were from a confidential analysis."** We note that confidential data for Elecsys test was used in the economic model, we would respectfully ask you to consider including the data that is documented by Oxford University Hospital (John Radcliffe) (Verification report – PerkinElmer PlGF 1-2-3 & sFlt-1 timeresolveld fluoroimmunoassay on the DELFIA Xpress). This data forms a part of a larger planned publication which will include a clinical comparison versus the Roche's Elecsys assay. This has been delayed due to COVID absences and limitations in staffing. The target date for publication, agreed with the authors was January 31st 2022. This has been delayed due to challenges in accessing the clinical data from the archives due to COVID restrictions. We are waiting for confirmation of the new timeline.	The current analysis uses data from the PELICAN study. This allows a direct estimate of the proportion of women with a gestational age of less than 35 weeks. In scenario analyses conducted by the EAG, cost-effectiveness results were found to be robust to variation in the proportion of women with a gestational age of less than 35 weeks. We do not believe that further scenario analyses around this input are required. No change required.

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Comments on the DSU economic model

Stakeholder	Issue	Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Quidel	1	No comments		

VERIFICATION REPORT – PerkinElmer PlGF 1-2-3 & sFlt-1 time-resolved fluoro-immunoassay on the DELFIA XPress

1. Process

This document describes the verification process of PerkinElmer DELFIA Xpress PLGF 1-2-3 and sFlt-1 time-resolved fluoro-immunoassays, performed on the DELFIA Xpress random access analyzer. The kits are intended for the quantitative determination of Placental growth factor (PlGF) and soluble Fms-like tyrosine kinase-1 (sFlt-1) in maternal serum. When used in conjunction the ratio may be used as an aid in diagnosis of pre-eclampsia and for short term prediction of suspected pre-eclampsia.

2. Personnel

[redacted]

3. Timescale

The verification process was completed between July 2020 – Dec 2021.

4. Quality Goals

The assays were compared to the Roche Elecsys PlGF and sFlt-1 assays, already in use within the department and against manufacturers claims and external quality assurance performance.

An additional study assessing patient outcomes, is currently ongoing in order to verify patient cut offs.

The bias from the EQA target should be within ±20% as deemed acceptable performance by UK NEQAS, within ±10% is considered ideal.

Imprecision should be comparable to the manufacturer's achieved precision performance.

Performance for the assay will be compared with other sites also running the PerkinElmer DELFIA Xpress for sFlt-1 and PlGF.

We would suggest that when comparing the ratio from one site to another 95% of the ratios are within the same category (Appendix 1) but that on no occasion (0%) should a result be incorrectly allocated to the extremes of category (i.e., a low risk never becomes high risk and vice versa).

5. Methods and Results

5.1 Measurement Trueness

The manufacturer states "The calibration of both methods is anchored to an in-house primary calibrator series gravimetrically prepared from an in-house PlGF and sFlt-1 reference preparations. The secondary calibrator series is calibrated against the primary calibrator series. The calibrators in the kit are then calibrated against the above-mentioned secondary calibrators for value assignment"

The PlGF calibrator set is used to generate a full calibration curve using 5 calibrators (Cal B-F) and a blank (Cal A). This should be performed every 3 months or with a change in reagent lot, an adjustment to the calibration curve can be used when introducing a new lot of inducer, using only calibrators C and E.

There are currently no international calibration reference preparations available for PlGF or sFlt-1.

UK NEQAS Edinburgh and WEQAS external quality assurance specimens were analysed and compared with the ALTM target values (concentrations are displayed in pg/mL), These results are presented in table 2 and table 3.

Table 2 – UK NEQAS Edinburgh EQA

	Cobas Results			XPRESS Results			ALTM			Xpress group target
Dist.	**PIGF**	**SFLT**	**Ratio**	**PIGF**	**SFLT**	**Ratio**	**PIGF**	**SFLT**	**Ratio**	**PIGF**
70-Y030	62.9	1606	25.53	38.5	671.2	17.43	62	1473	22	42
70-Y029	25.34	312.8	12.34	19.2	108.1	5.63	27	300	11	21
70-Y028	32.29	420.7	13.03	26.3	147.8	5.62	35	389	11	25
85-073	60.51	1573	26.0	39.6	642.8	16.23	57	1387	23	41
85-074	111.60	1674	15.0	66.6	657.1	9.87	102	1484	13	75
85-075	55.34	1490	26.9	37.7	582.3	15.45	55	1340	23	38

Table 3 – WEQAS EQA

	Cobas Results			XPRESS Results			ALTM		
Dist.	**PIGF**	**SFLT**	**Ratio**	**PIGF**	**SFLT**	**Ratio**	**PIGF**	**sFlt**	**Ratio**
PE8	14.16	718	50.71	10.3	242	23.50	18.1	737.5	41.2
PE8	13.11	4543	346.53	10.2	1795.4	176.02	16.5	4605.3	284.2
PE8	12.96	4104	316.67	6.1	1277.7	209.46	15.6	4274.9	278.1

The results are not within the ±20% of target deemed ‘acceptable’ by UK NEQAS. However, with no available international reference preparations available differences between manufacturers and method groups are not entirely unexpected. There was good agreement with the DELFIA Xpress method group.

5.2 Measurement Accuracy

Comparison of 726 samples analysed using the Roche methodology (e411 analyser) currently in use in the laboratory displayed a significant difference between the Roche Elecsys (Roche) and DELFIA Xpress (DX) methods (table 5 & table 6).

Table 5- Descriptive Statistics

Analyte	N	Mean	Median	5th percentile	95th percentile	Min	Max
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Adjustment using the observed relationship between methods produces good concordance. Agreement tables with DELFIA Xpress cut-offs adjusted for level difference are displayed below.

Table 7 2- Aid in diagnosis, cross table (cut-off 38 ADJ)

	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

Table 8 3- Aid in diagnosis, rule-out agreement with 95 % confidence intervals (cut-off 38 ADJ)

	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Table 9 4- Aid in diagnosis, cross table (cut-off 85 ADJ)

	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

Table 105 - Aid in diagnosis, rule-in agreement with 95 % confidence intervals (cut-off 85 ADJ)

	Positive agreement	Negative agreement	Overall agreement
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

5.3 Measurement Precision

5.3.1 Intra-batch imprecision

The manufacturer quoted the following, based on analysing samples over 23 operating days, in 45 runs, with 4 replicates per sample, using 3 different kit lots. Our QC data will be based on 1 replicate per sample, to allow a like-

for-like comparison with the Roche, this should be considered when comparing to the precision achieved by the manufacturer, quoted below:

Table 11 - Manufacturer's claim PlGF precision

	Within run		Within lot		Between lot		Within laboratory (Total)	
Sample concentration (pg/mL)	**SD (pg/mL)**	**Total variation (CV %)**	**SD (pg/mL)**	**Total variation (CV %)**	**SD (pg/mL)**	**Total variation (CV %)**	**SD (pg/mL)**	**Total variation (CV %)**
19.2 (human serum)	0.8	4.1	1.2	6.3	0.3	1.5	1.3	6.5
25.7 (human serum)	1.2	4.7	1.7	6.5	0.6	2.2	1.8	6.8
35.6 (human serum)	1.2	3.5	2.0	5.6	0.9	2.5	2.2	6.2
38.0 (human serum)	1.3	3.3	2.0	5.1	1.0	2.7	2.2	5.8
89.7 (human serum)	2.4	2.7	4.3	4.8	3.1	3.5	5.3	5.9
110 (human serum)	3.0	2.7	4.5	4.1	3.7	3.3	5.8	5.3
151 (human serum)	4.3	2.8	7.2	4.8	6.5	4.3	9.7	6.4
356 (human serum)	9.9	2.8	13.7	3.8	12.5	3.5	18.5	5.2
2795 (spiked serum)	57.7	2.1	85.9	3.1	85.0	3.0	121	4.3
3818 (spiked serum)	69.3	1.8	110	2.9	116	3.0	160	4.2

Table 12 – Manufacturer's claim sFlt-1precision

	Within run		Within lot		Between lot		Within laboratory (Total)	
Sample concentration (pg/mL)	**SD (ng/L)**	**Total variation (CV %)**	**SD (ng/L)**	**Total variation (CV %)**	**SD (ng/L)**	**Total variation (CV %)**	**SD (ng/L)**	**Total variation (CV %)**
9.7 (human serum)	0.5	5.3	1.4	14.2	0.8	7.7	1.6	16.1
21.5 (human serum)	1.0	4.5	1.6	7.2	1.5	6.8	2.1	9.9
75.7 (human serum)	1.6	2.1	0.2	0.2	4.3	5.6	4.3	5.6
219 (human serum)	4.0	1.8	4.2	1.9	10.6	4.8	11.4	5.2
473 (human serum)	6.3	1.3	13.1	2.8	19.2	4.1	23.2	4.9
788 (quality control)	6.7	0.8	10.0	1.3	26.9	3.4	28.7	3.6
1090 (human serum)	13.3	1.2	21.1	1.9	36.0	3.3	41.7	3.8
1304 (spiked serum)	11.4	0.9	12.5	1.0	34.5	2.6	36.7	2.8
3589 (spiked serum)	37.1	1.0	60.1	1.7	81.7	2.3	101	2.8
5093 (quality control)	54.1	1.1	63.6	1.2	108	2.1	126	2.5
6022 (spiked serum)	57.2	0.9	154	2.5	134	2.2	204	3.4
9111 (spiked serum)	79.5	0.9	283	3.1	221	2.4	359	3.9

17683 (spiked serum)	151	0.9	766	4.3	520	2.9	926	5.2

The laboratory examined precision using a combination of patient samples and internal quality control material.

To assess within run precision, 18 patient samples, with a range of PlGF & sFlt-1 concentrations, were analysed 10 times, consecutively, within a run to determine intra-assay precision. Concentrations are displayed in pg/mL. The results obtained are presented in table 13 (PlGF) and table 14 (sFlt-1).

Table 13-

Table 14 sFlt-1

Intra-assay precision is acceptable in keeping with manufacturer claims.

5.3.2 Inter-batch imprecision

The two levels of QC material (PlGF252 low and high) were analysed using the same reagent and calibrator lot, analysed over 3 different PlGF calibrations & 4 different sFlt-1 calibrations. The results obtained are presented in tables 15 & 16 along with Roche precision for comparison.

Table 15

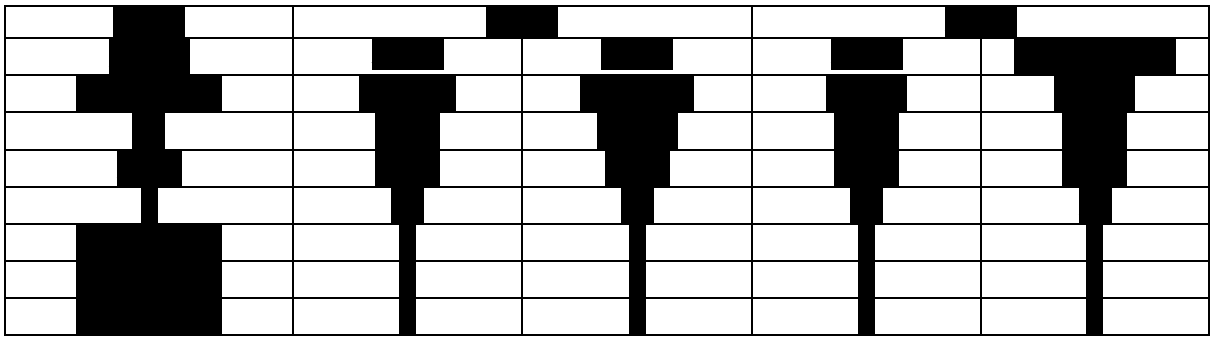
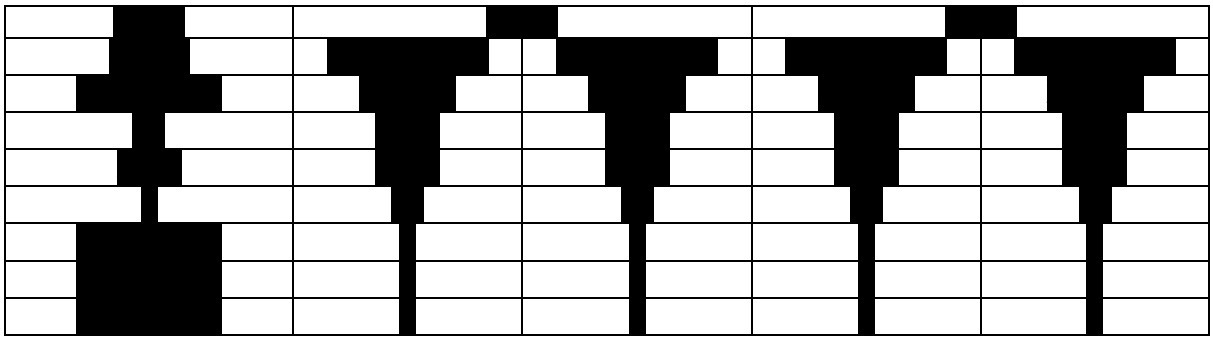


Table 16



5.3.3 Precision profiles

Precision profiles were generated using 726 patient samples analysed in duplicate during the study.

[redacted]

[redacted]

Figure 2 1: sFlt-1 within-run precision profile

Figure 32: sFlt-1/PlGF ratio within-run precision profile

5.3.3 Measurement intermediate precision (time, calibration, operator, equipment)

- Due to the automated nature of the assay the operator is unlikely to have an effect on the results.
- The DELFIA Xpress is an automated system, and there are no steps in the analytical process that are dependent on time of day. The temperature in the lab is tightly controlled by air-conditioning, therefore external temperature fluctuations during the day are minimized.
- No other pieces of external equipment are used that may affect results.
- Limited inter-calibration data was available at the time of verification but will continue to be monitored regularly as part of the quarterly review of IQC.

5.3.4 Between laboratory agreement

93 samples were analysed by another laboratory using the DELFIA Xpress and the comparison can be seen in table 17.

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.4 Measurement Uncertainty

Measurement uncertainty (MU) was calculated based on the inter-assay variability. See table 8 for measurement uncertainty.

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

The risk of uncertainty in the assay is summarised in table 8. There are currently no analytical performance specifications available for PlGF & sFlt-1 and it is not possible to define biological variation in pregnancy as levels change significantly during pregnancy. The clinical use of these assays is based on use of PlGF with sFlt-1 and expressed as a ratio.

We would define a local performance specification as one applied to the ratio as this is the clinical measure that will impact on patient outcome. The sFlt-1/PlGF ratio is used to define risk (INSPIRE study publication) in three categories: low (ratio <38); medium (ratio 38-85); and high risk (ratio >85). We would suggest that when comparing the ratio from one site to another 95% of the ratios are within the same category (low, intermediate or high) but that on no occasion (0%) should a result be incorrectly allocated to the extremes of category (i.e. a low risk never becomes high risk and vice versa).

Summary

- Quality goals have been achieved.
- Precision is acceptable in keeping with manufacturer claims.
- Adjustment using the observed relationship between methods produces good concordance with the Roche methods.

6. References

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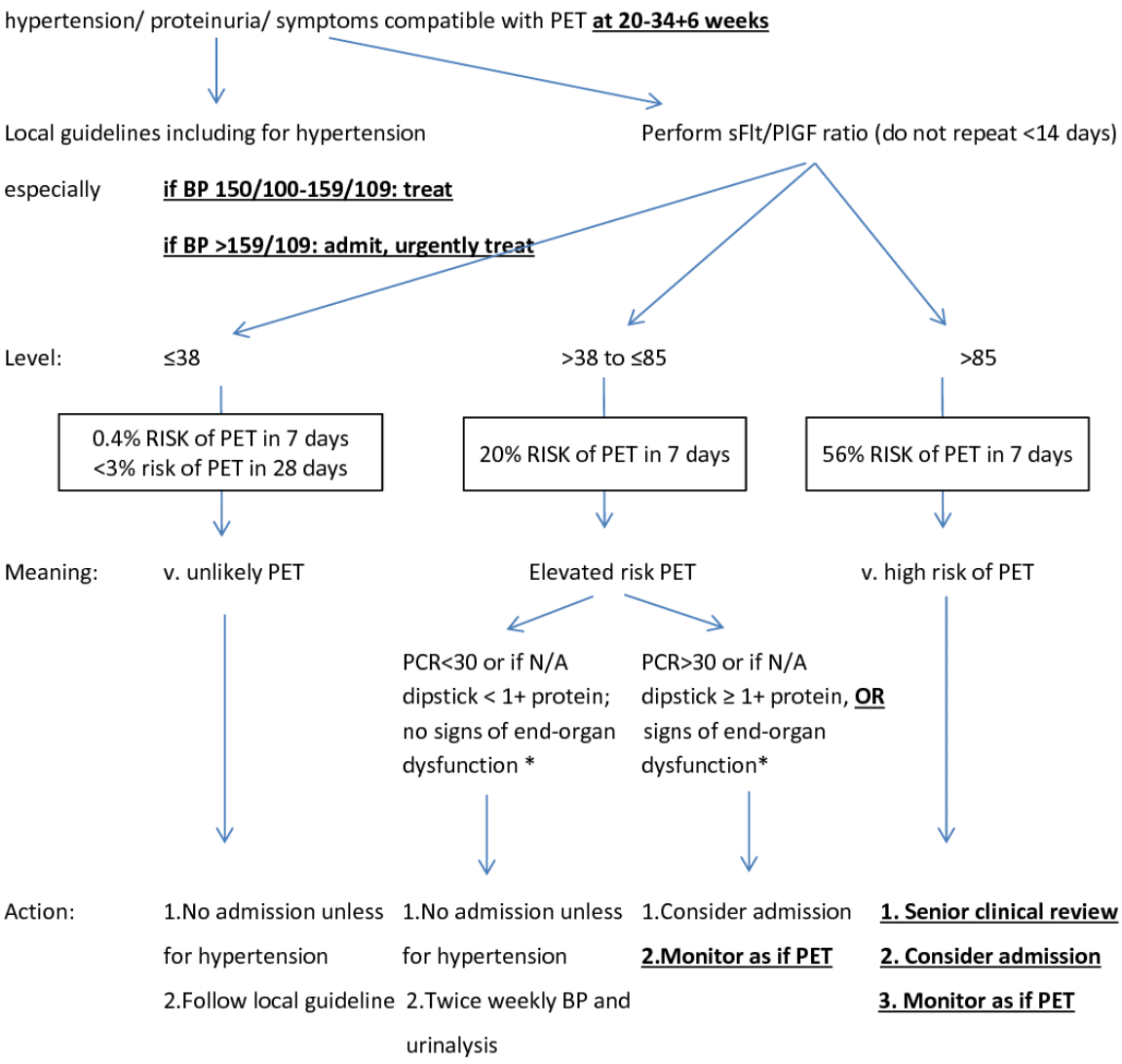
Jones C. Oliveira C. Smith I. Vatish M. Thomas C. Analytical Evaluation of PlGF and sFlt-1 for Assessment of Pre-Eclampsia. Poster presentation. IBMS congress 2017. Birmingham.

Armstrong-Buisseret L, Godolphin PJ, Bradshaw L, Mitchell E, Ratcliffe S, Storey C, Heazell AEP. Standard care informed by the result of a placental growth factor blood test versus standard care alone in women with reduced fetal movement at or after 36+0 weeks' gestation: a pilot randomised controlled trial. Pilot Feasibility Study. 2020 Feb 13;6:23. doi: 10.1186/s40814-020-0561-z.

Armstrong-Buisseret L, Haslam S, James T, Bradshaw L, Heazell A. Verification of Placental Growth Factor and Soluble-fms-like Tyrosine Kinase 1 Assay Performance in Late Pregnancy and their Diagnostic Test Accuracy in Women with Reduced Fetal Movement. Ann Clin Biochem. 2020 Feb 21:4563220911993. doi: 10.1177/0004563220911993. [Epub ahead of print]

Appendix 1

Out-Patient Suspicion of Pre Eclampsia (PET):



Note:

This is guideline should be regarded as additional to local hypertension/ preeclampsia guidelines and should not replace it.

sFlt/PlGF ratio DOES NOT predict hypertension which may be life threatening in absence of pre eclampsia: local/ national hypertension guidelines should be followed.

Ultrasound and steroids should be considered as per local guideline

*as per ISSHP criteria (creatinine >90 umol/L; elevated transaminases (2x normal) +/- severe RUQ/ epigastric pain; eclampsia, altered mental status, blindness, stroke, or more commonly hyperreflexia when accompanied by clonus, severe headaches when accompanied by hyperreflexia, persistent visual scotomata; thrombocytopenia, DIC, haemolysis; foetal growth restriction)

Guideline developed by Drs Manu Vatish, Sofia Cerdeira and Lawrence Impey

Refs: https://www.nice.org.uk/guidance/dg23/chapter/1-recommendations

PLGF-BASED TESTING TO HELP DIAGNOSE SUSPECTED PRE-ECLAMPSIA (UPDATE OF DG23): ADDENDUM 1

REPORT BY THE DECISION SUPPORT UNIT

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ABOUT THE DECISION SUPPORT UNIT

The Decision Support Unit (DSU) External Assessment Centre is based at the University of Sheffield with members at York, Bristol, Leicester and the London School of Hygiene and Tropical Medicine. The DSU is commissioned by The National Institute for Health and Care Excellence (NICE) to provide a research and training resource to support the Institute's Centre for Health Technology Evaluation Programmes. Please see our website for further information www.nicedsu.org.uk.

The production of this document was funded by the National Institute for Health and Care Excellence (NICE) through its Decision Support Unit. The views, and any errors or omissions, expressed in this document are of the authors only. NICE may take account of part or all of this document if it considers it appropriate, but it is not bound to do so.

This report should be referenced as follows:

Kearns B., Wailoo A., Abdullah P., PLGF-Based Testing to Help Diagnose Suspected Pre-Eclampsia (Update of DG23): Addendum 1. NICE DSU Report 2022.

CONTENTS

TABLES AND FIGURES

1. ADDITIONAL RESULTS

1.1. RULE-OUT PLGF TESTING APPLIED TO THE OUTCOMES OF STANDARD ASSESSMENT

1.1.1. Methods

An additional analysis was undertaken to explore the use of PLGF-based tests as a rule-out. This analysis applies PLGF-based tests to the results of standard assessment (which itself was based on rule-out and rule-in of PE). This worked in the following manner:

- Women entered the model with an initial suspicion of PE, stratified by hypertension severity.
- Based on the prevalence of PE by hypertension severity, and the accuracy of standard assessment (sensitivity and specificity), estimates were obtained for the number of women who would be admitted based on clinical assessment.
- This information on both the proportion of women who would be admitted under standard assessment, and the proportion of PE amongst these women, was combined with the accuracy of PLGF-based tests (sensitivity and specificity) to rule-out PE amongst some of the women. This had the effect of reducing the number of admitted women.

Figure 1 demonstrates how this was captured within an economic model. Evidence on how the initial distribution of hypertension severity, the outcomes of standard assessment, and the outcomes of a PLGF-based test were combined are provided in Table 1 (based on ‘rule-out and rule-in’ and ‘rule-out’ from the survey of clinical experts and reported in Table 9 of the original DSU report).

The main assumption of this additional analysis is that the test performance of PLGF-based tests is unaffected by the outcomes of standard assessment. That is, the sensitivity and specificity of PLGF-based tests are the same for the following groups:

- Women with a suspicion of PE.
- Women with a suspicion of PE who would be admitted for hospital based on the outcomes of standard assessment.

Figure 1: Decision tree applying PLGF-based tests to rule out PE following standard assessment

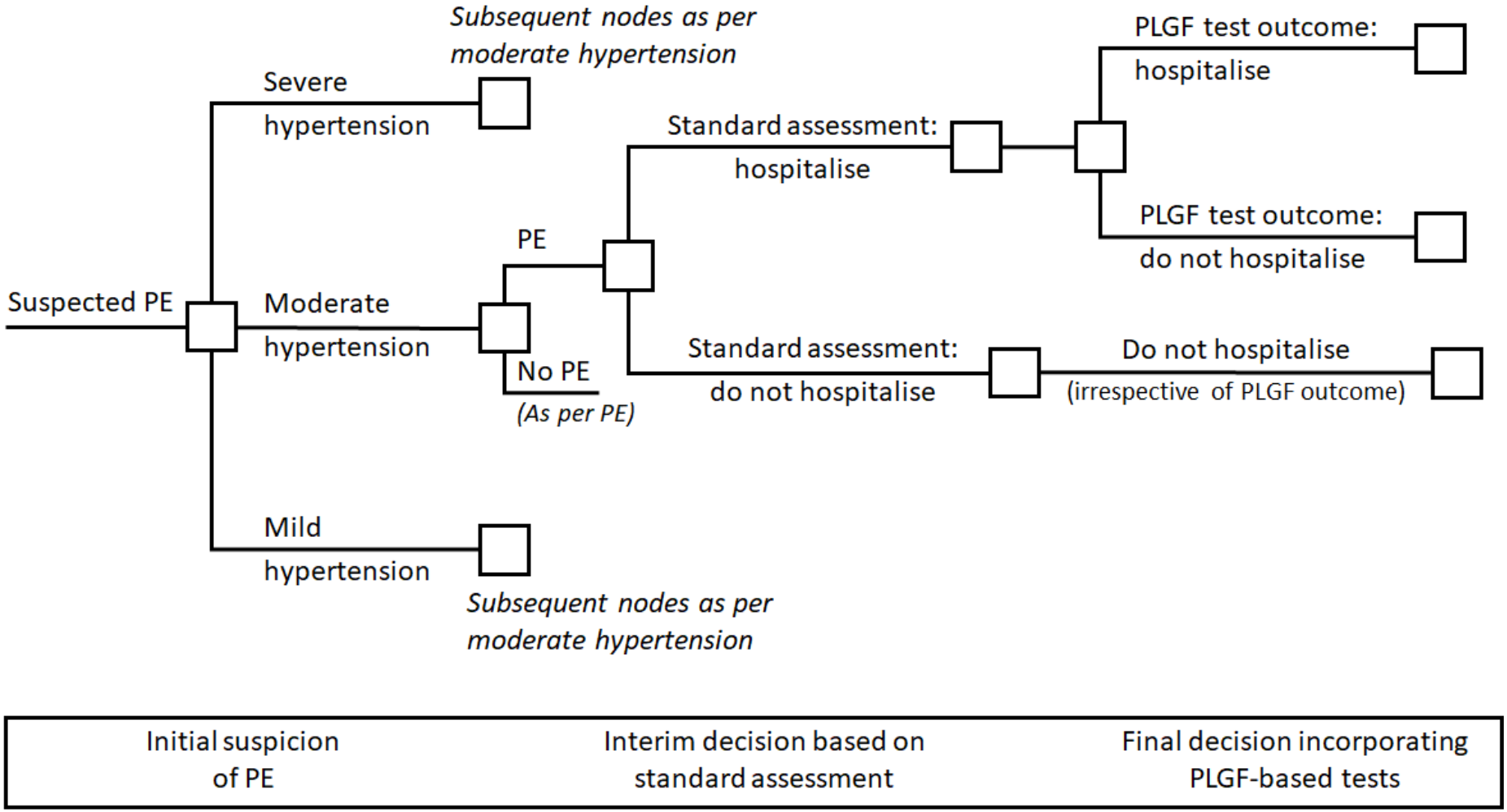

Table 1: Relationships between initial suspicion of PE, outcomes of standard assessment, and outcomes of PLGF-based test

Hypertension severity	Outcome of standard assessment	Percent admitted based on standard assessment	Outcome of PLGF-based test	Percent admitted based on PLGF-based test
Mild	Low risk	0%	Low risk	0%
Moderate	Low risk	0%	Low risk	0%
Severe	Low risk	38%	Low risk	14%
Mild	High risk	100%	Low risk	38%
Moderate	High risk	100%	Low risk	38%
Severe	High risk	100%	Low risk	38%
Mild	Low risk	0%	Intermediate risk	0%
Moderate	Low risk	0%	Intermediate risk	0%
Severe	Low risk	38%	Intermediate risk	23%
Mild	High risk	100%	Intermediate risk	60%
Moderate	High risk	100%	Intermediate risk	60%
Severe	High risk	100%	Intermediate risk	60%
Mild	Low risk	0%	High risk	0%
Moderate	Low risk	0%	High risk	0%
Severe	Low risk	38%	High risk	38%
Mild	High risk	100%	High risk	100%
Moderate	High risk	100%	High risk	100%
Severe	High risk	100%	High risk	100%

This analysis uses the base-case settings for all other inputs (hypertension distribution and baseline test performance both from PARROT UK, true positives do not cost more than false negatives). Results are provided in the following tables. Note that as PLGF-based tests were applied to the outcomes of standard assessment, two sets of results are included; one where standard assessment is based on DG23, and one where it is based on INSPIRE.

1.1.2. Results

An overview of costs and QALYs are provided for the two types of standard assessment: based on DG23 in Table 2 and based on INSPIRE in Table 3. Full results are provided in the Appendix (Table 8 and Table 9, respectively).

Table 2: Deterministic results, PLGF-based tests to rule-out PE compared with standard assessment from DG23

Rule-out testing	SA: DG23	Triage test	Elecsys	Elecsys add-on	DELFIA	BRAHMS
Total cost	£10,724	£10,444	£10,432	£10,416	£10,402	£10,394
Test	£0	£50	£79	£79	£37	£52
Clinical management	£1,238	£1,016	£1,012	£1,013	£1,016	£1,015
Delivery	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781
Maternal short-term	£361	£349	£346	£344	£347	£345
Neonatal short-term	£4,357	£4,255	£4,226	£4,216	£4,236	£4,220
Neonatal long-term	£987	£993	£987	£982	£986	£980
Total QALYs	17.6217	17.6482	17.6561	17.6591	17.6539	17.6583
Clinical management	-0.00109	-0.00005	-0.00004	-0.00004	-0.00005	-0.00005
Delivery	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352
Maternal short-term	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841
Neonatal short-term	-0.0006	-0.0005	-0.0005	-0.0005	-0.0005	-0.0005
Maternal long-term	17.3660	17.3719	17.3738	17.3745	17.3733	17.3743
Neonatal long-term	-0.1618	-0.1424	-0.1364	-0.1341	-0.1381	-0.1347
True Positives	27.6%	24.4%	25.3%	26.1%	25.6%	26.5%
True negatives	17.1%	42.0%	44.4%	43.7%	41.9%	42.3%
False positives	54.8%	29.9%	27.5%	28.1%	30.0%	29.6%
False negatives	0.6%	3.7%	2.8%	2.0%	2.5%	1.7%

Table 3: Deterministic results, PLGF-based tests to rule-out PE compared with standard assessment from INSPIRE

Rule-out testing	SA: INSPIRE	Triage test	Elecsys	Elecsys add-on	DELFIA	BRAHMS
Total cost	£10,239	£10,139	£10,144	£10,129	£10,104	£10,101
Test	£0	£50	£79	£79	£37	£52
Clinical management	£844	£711	£710	£710	£711	£711
Delivery	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781
Maternal short-term	£349	£347	£345	£343	£345	£343
Neonatal short-term	£4,257	£4,234	£4,217	£4,207	£4,218	£4,207
Neonatal long-term	£1,007	£1,017	£1,012	£1,008	£1,011	£1,007
Total QALYs	17.6461	17.6516	17.6564	17.6592	17.6561	17.6594
Clinical management	-0.00041	-0.00002	-0.00002	-0.00002	-0.00002	-0.00002
Delivery	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352
Maternal short-term	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841

Neonatal short-term	-0.0005	-0.0005	-0.0005	-0.0005	-0.0005	-0.0005
Maternal long-term	17.3715	17.3728	17.3739	17.3745	17.3738	17.3746
Neonatal long-term	-0.1437	-0.1398	-0.1362	-0.1341	-0.1364	-0.1339
True Positives	21.7%	19.2%	19.9%	20.5%	20.2%	20.8%
True negatives	49.0%	59.4%	60.4%	60.1%	59.4%	59.5%
False positives	22.9%	12.5%	11.5%	11.7%	12.5%	12.4%
False negatives	6.5%	8.9%	8.3%	7.6%	8.0%	7.3%

The reduction in hospitalisations when applying PLGF-based tests to the results of standard assessment led to a reduction in both true positives (women with PE who were hospitalised) and false positives (women without PE who were hospitalised). True positive rates generally fell by 1% to 3% (for both types of standard assessment). For false positives, rates fell by 25% to 27% (standard assessment based on DG23) and by 10% to 11% (standard assessment based on DG23).

As expected, for both types of standard assessment, use of PLGF-based tests for subsequent rule-out of PE led to a decrease in overall costs. This decrease was largest for clinical management, followed by short-term neonatal costs. Cost-savings for PLGF-based tests were larger when standard assessment was based on DG23.

Use of PLGF-based tests for subsequent rule-out of PE led to an increase in overall QALYs. These increased QALYs were primarily driven by long-term neonatal and maternal QALY gains, which represented 95% to 97% of the incremental QALYs. As with costs, benefits were greatest when standard assessment was based on DG23.

Table 4: Incremental deterministic results, PLGF-based tests to rule-out PE

	Total costs		**Total QALYs**			
	DG23	**INSPIRE**	**DG23**	**INSPIRE**		
Standard assessment	£10,724	£10,239	17.6217	17.6461		
	Incremental costs		**Incremental QALYs**		**Incremental net health effects (willingness to pay = £20,000)**	
	DG23	**INSPIRE**	**DG23**	**INSPIRE**	**DG23**	**INSPIRE**
Triage test	-£280.0	-£99.8	0.0265	0.0055	£810	£210
Elecsys	-£292.5	-£95.5	0.0344	0.0103	£981	£302
Elecsys add-on	-£308.0	-£109.7	0.0374	0.0130	£1,056	£370
DELFIA	-£321.8	-£135.5	0.0322	0.0100	£965	£336
BRAHMS	-£330.1	-£137.7	0.0366	0.0133	£1,062	£403

An overview of incremental costs and QALYs, along with incremental net health effects at a willingness to pay of £20,000 is provided in Table 4. Results excluding neonatal outcomes are shown in Table 5. All of the PLGF-based tests dominated both types of standard assessment. These findings held even when all neonatal outcomes were removed. At a willingness to pay of £20,000, incremental net health effects compared with standard assessment from DG23 ranged from £810 (Triage test) to £1,061 (BRAHMS). When compared with standard assessment from INSPIRE, incremental net health effects ranged from £210 (Triage test) to £403 (BRAHMS).

Table 5: Impact on base-case results of excluding neonatal outcomes

Compared with DG23 SA					
Including neonatal outcomes	Triage test	Elecsys	Elecsys add-on	DELFIA	BRAHMS
Incremental cost	-£280	-£293	-£308	-£322	-£330
Incremental QALYs	0.02652	0.03441	0.03741	0.03217	0.03658
ICER	Dominates	Dominates	Dominates	Dominates	Dominates
Excluding long-term neonatal outcomes					
Incremental cost	-£287	-£292	-£303	-£321	-£324
Incremental QALYs	0.0071	0.0090	0.0097	0.0085	0.0095
ICER	Dominates	Dominates	Dominates	Dominates	Dominates
Excluding all neonatal outcomes					
Incremental cost	-£184	-£162	-£162	-£199	-£186
Incremental QALYs	0.0070	0.0089	0.0096	0.0084	0.0094
ICER	Dominates	Dominates	Dominates	Dominates	Dominates
Compared with INSPIRE SA					
Including neonatal outcomes	Triage test	Elecsys	Elecsys add-on	DELFIA	BRAHMS
Incremental cost	-£100	-£96	-£110	-£136	-£138
Incremental QALYs	0.0055	0.0103	0.0130	0.0100	0.0133
ICER	Dominates	Dominates	Dominates	Dominates	Dominates
Excluding long-term neonatal outcomes					
Incremental cost	-£110	-£101	-£111	-£139	-£138
Incremental QALYs	0.0016	0.0028	0.0034	0.0027	0.0035
ICER	Dominates	Dominates	Dominates	Dominates	Dominates
Excluding all neonatal outcomes					
Incremental cost	-£86	-£60	-£61	-£100	-£87
Incremental QALYs	0.0016	0.0027	0.0034	0.0027	0.0034
ICER	Dominates	Dominates	Dominates	Dominates	Dominates

Results from probabilistic sensitivity analyses are provided in Table 6 (standard assessment from DG23) and Table 7 (standard assessment from INSPIRE) and are very similar to the deterministic analyses. PLGF-based tests again dominate both types of standard assessment and generate similar incremental net health effects. One difference is that, based on probabilistic analyses, use of Elecsys as an add-on generates the greatest incremental net health effects for both types of standard assessment. Differences between PLGF-based tests were however small.

Table 6: Probabilistic results, PLGF-based tests to rule-out PE compared with standard assessment from DG23

	Total cost	Total QALYs	INHE*
Standard assessment (DG23)	£10,757	17.520	
Triage test	£10,473	17.557	£1,025
Elecsys	£10,474	17.564	£1,171
Elecsys as add-on	£10,463	17.567	£1,244
DELFIA	£10,452	17.559	£1,089
BRAHMS	£10,453	17.563	£1,161

* Incremental net health effects at a willingness to pay of £20,000.

Table 7: Probabilistic results, PLGF-based tests to rule-out PE compared with standard assessment from INSPIRE

	Total cost	Total QALYs	INHE*
Standard assessment (INSPIRE)	£10,258	17.550	
Triage test	£10,157	17.557	£261
Elecsys	£10,170	17.562	£330
Elecsys as add-on	£10,157	17.565	£416
DELFIA	£10,138	17.559	£314
BRAHMS	£10,143	17.562	£360

* Incremental net health effects at a willingness to pay of £20,000.

APPENDIX

A.1 ADDITIONAL COST-EFFECTIVENESS RESULTS

Table 8: Deterministic results, tests to rule-out PLGF compared with standard assessment from DG23

Rule-out PLGF testing	SA: DG23	Triage test	Elecsys	Elecsys add-on	DELFIA	BRAHMS
Total cost	£10,724	£10,444	£10,432	£10,416	£10,402	£10,394
Test	£0	£50	£79	£79	£37	£52
Clinical management	£1,238	£1,016	£1,012	£1,013	£1,016	£1,015
PE: True positive	£257	£238	£246	£254	£250	£258
PE: False negative	£5	£36	£27	£19	£24	£16
No PE: True negative	£75	£349	£377	£369	£347	£352
No PE: False positive	£901	£394	£363	£371	£395	£390
Delivery	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781
PE: True positive	£1,152	£1,021	£1,057	£1,092	£1,072	£1,106
PE: False negative	£23	£155	£119	£84	£103	£70
No PE: True negative	£620	£1,523	£1,608	£1,586	£1,519	£1,532
No PE: False positive	£1,986	£1,083	£997	£1,020	£1,087	£1,074
Maternal short-term	£361	£349	£346	£344	£347	£345
PE: True positive	£103	£92	£95	£98	£96	£99
PE: False negative	£3	£21	£16	£12	£14	£10
No PE: True negative	£51	£125	£132	£130	£125	£126
No PE: False positive	£204	£111	£102	£105	£111	£110
Neonatal short-term	£4,357	£4,255	£4,226	£4,216	£4,236	£4,220
PE: True positive	£1,994	£1,766	£1,828	£1,889	£1,855	£1,913
PE: False negative	£50	£329	£253	£178	£220	£148
No PE: True negative	£470	£1,155	£1,219	£1,202	£1,152	£1,161
No PE: False positive	£1,844	£1,006	£926	£947	£1,009	£997
Neonatal long-term	£987	£993	£987	£982	£986	£980
PE: True positive	£766	£679	£703	£726	£713	£735
PE: False negative	£19	£126	£97	£68	£84	£57
No PE: True negative	£41	£101	£106	£105	£100	£101
No PE: False positive	£161	£88	£81	£82	£88	£87
Total QALYs	17.6217	17.6482	17.6561	17.6591	17.6539	17.6583
Clinical management	-1.09E-03	-4.58E-05	-4.22E-05	-4.31E-05	-4.60E-05	-4.54E-05
PE: True positive	0	0	0	0	0	0
PE: False negative	0	0	0	0	0	0
No PE: True negative	0	0	0	0	0	0
No PE: False positive	-1.09E-03	-4.58E-05	-4.22E-05	-4.31E-05	-4.60E-05	-4.54E-05
Delivery	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352
PE: True positive	0.009	0.008	0.009	0.009	0.009	0.009
PE: False negative	0.000	0.001	0.001	0.001	0.001	0.001
No PE: True negative	0.006	0.015	0.016	0.016	0.015	0.015

No PE: False positive	0.020	0.011	0.010	0.010	0.011	0.011
Maternal short-term	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841
PE: True positive	0.106	0.094	0.097	0.100	0.098	0.102
PE: False negative	0.002	0.014	0.011	0.008	0.010	0.006
No PE: True negative	0.066	0.161	0.170	0.168	0.161	0.162
No PE: False positive	0.210	0.115	0.106	0.108	0.115	0.114
Neonatal short-term	-0.0006	-0.0005	-0.0005	-0.0005	-0.0005	-0.0005
PE: True positive	-1.35E-04	-1.19E-04	-1.24E-04	-1.28E-04	-1.25E-04	-1.29E-04
PE: False negative	-1.16E-05	-7.72E-05	-5.93E-05	-4.18E-05	-5.16E-05	-3.48E-05
No PE: True negative	-3.07E-05	-7.54E-05	-7.96E-05	-7.85E-05	-7.52E-05	-7.58E-05
No PE: False positive	-4.44E-04	-2.42E-04	-2.23E-04	-2.28E-04	-2.43E-04	-2.40E-04
Maternal long-term	17.3660	17.3719	17.3738	17.3745	17.3733	17.3743
PE: True positive	4.785	4.239	4.388	4.534	4.452	4.592
PE: False negative	0.096	0.639	0.491	0.345	0.427	0.288
No PE: True negative	2.974	7.308	7.718	7.611	7.289	7.352
No PE: False positive	9.511	5.186	4.777	4.884	5.205	5.142
Neonatal long-term	-0.1618	-0.1424	-0.1364	-0.1341	-0.1381	-0.1347
PE: True positive	-0.050	-0.044	-0.046	-0.047	-0.046	-0.048
PE: False negative	-0.003	-0.020	-0.015	-0.011	-0.013	-0.009
No PE: True negative	-0.010	-0.024	-0.025	-0.025	-0.024	-0.024
No PE: False positive	-0.099	-0.054	-0.050	-0.051	-0.054	-0.054
True Positives	27.6%	24.4%	25.3%	26.1%	25.6%	26.5%
True negatives	17.1%	42.0%	44.4%	43.7%	41.9%	42.3%
False positives	54.8%	29.9%	27.5%	28.1%	30.0%	29.6%
False negatives	0.6%	3.7%	2.8%	2.0%	2.5%	1.7%

Table 9: Deterministic results, tests to rule-out PLGF compared with standard assessment from INSPIRE

Rule-out PLGF testing	**SA: INSPIRE**	**Triage test**	**Elecsys**	**Elecsys add-on**	**DELFIA**	**BRAHMS**
Total cost	£10,239	£10,139	£10,144	£10,129	£10,104	£10,101
Test	£0	£50	£79	£79	£37	£52
Clinical management	£844	£711	£710	£710	£711	£711
PE: True positive	£202	£187	£193	£200	£196	£202
PE: False negative	£60	£81	£74	£68	£72	£65
No PE: True negative	£215	£279	£290	£287	£278	£280
No PE: False positive	£367	£164	£151	£155	£165	£163
Delivery	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781
PE: True positive	£905	£802	£830	£858	£842	£869
PE: False negative	£270	£374	£345	£318	£333	£307
No PE: True negative	£1,777	£2,154	£2,189	£2,180	£2,152	£2,158
No PE: False positive	£829	£452	£416	£426	£454	£448
Maternal short-term	£349	£347	£345	£343	£345	£343
PE: True positive	£81	£72	£75	£77	£76	£78
PE: False negative	£37	£52	£48	£44	£46	£42
No PE: True negative	£146	£177	£180	£179	£176	£177

No PE: False positive	£85	£46	£43	£44	£47	£46
Neonatal short-term	£4,257	£4,234	£4,217	£4,207	£4,218	£4,207
PE: True positive	£1,566	£1,388	£1,436	£1,484	£1,458	£1,503
PE: False negative	£574	£793	£734	£675	£708	£652
No PE: True negative	£1,347	£1,633	£1,660	£1,653	£1,632	£1,636
No PE: False positive	£770	£420	£387	£395	£421	£416
Neonatal long-term	£1,007	£1,017	£1,012	£1,008	£1,011	£1,007
PE: True positive	£602	£533	£552	£571	£560	£578
PE: False negative	£221	£305	£282	£259	£272	£250
No PE: True negative	£117	£142	£145	£144	£142	£142
No PE: False positive	£67	£37	£34	£34	£37	£36
Total QALYs	17.6461	17.6516	17.6564	17.6592	17.6561	17.6594
Clinical management	-4.09E-04	-1.91E-05	-1.76E-05	-1.80E-05	-1.92E-05	-1.89E-05
PE: True positive	0	0	0	0	0	0
PE: False negative	0	0	0	0	0	0
No PE: True negative	0	0	0	0	0	0
No PE: False positive	-4.09E-04	-1.91E-05	-1.76E-05	-1.80E-05	-1.92E-05	-1.89E-05
Delivery	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352
PE: True positive	0.007	0.006	0.007	0.007	0.007	0.007
PE: False negative	0.002	0.003	0.003	0.003	0.003	0.002
No PE: True negative	0.018	0.021	0.022	0.021	0.021	0.021
No PE: False positive	0.008	0.004	0.004	0.004	0.004	0.004
Maternal short-term	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841
PE: True positive	0.083	0.074	0.076	0.079	0.077	0.080
PE: False negative	0.025	0.034	0.032	0.029	0.031	0.028
No PE: True negative	0.188	0.228	0.232	0.231	0.228	0.229
No PE: False positive	0.088	0.048	0.044	0.045	0.048	0.047
Neonatal short-term	-0.0005	-0.0005	-0.0005	-0.0005	-0.0005	-0.0005
PE: True positive	-1.06E-04	-9.39E-05	-9.72E-05	-1.00E-04	-9.86E-05	-1.02E-04
PE: False negative	-1.35E-04	-1.86E-04	-1.72E-04	-1.58E-04	-1.66E-04	-1.53E-04
No PE: True negative	-8.79E-05	-1.07E-04	-1.08E-04	-1.08E-04	-1.06E-04	-1.07E-04
No PE: False positive	-1.85E-04	-1.01E-04	-9.30E-05	-9.51E-05	-1.01E-04	-1.00E-04
Maternal long-term	17.3715	17.3728	17.3739	17.3745	17.3738	17.3746
PE: True positive	3.760	3.331	3.448	3.563	3.499	3.608
PE: False negative	1.115	1.541	1.425	1.311	1.375	1.265
No PE: True negative	8.528	10.337	10.508	10.463	10.329	10.355
No PE: False positive	3.969	2.164	1.993	2.038	2.172	2.145
Neonatal long-term	-0.1437	-0.1398	-0.1362	-0.1341	-0.1364	-0.1339
PE: True positive	-0.039	-0.035	-0.036	-0.037	-0.036	-0.038
PE: False negative	-0.035	-0.048	-0.045	-0.041	-0.043	-0.040
No PE: True negative	-0.028	-0.034	-0.035	-0.035	-0.034	-0.034
No PE: False positive	-0.041	-0.023	-0.021	-0.021	-0.023	-0.022
True Positives	21.7%	19.2%	19.9%	20.5%	20.2%	20.8%
True negatives	49.0%	59.4%	60.4%	60.1%	59.4%	59.5%
False positives	22.9%	12.5%	11.5%	11.7%	12.5%	12.4%
False negatives	6.5%	8.9%	8.3%	7.6%	8.0%	7.3%

PLGF-BASED TESTING TO HELP DIAGNOSE SUSPECTED PRE-ECLAMPSIA (UPDATE OF DG23): ADDENDUM 2

REPORT BY THE DECISION SUPPORT UNIT

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The production of this document was funded by the National Institute for Health and Care Excellence (NICE) through its Decision Support Unit. The views, and any errors or omissions, expressed in this document are of the authors only. NICE may take account of part or all of this document if it considers it appropriate, but it is not bound to do so.

This report should be referenced as follows:

Kearns B., Wailoo A., Abdullah P., PLGF-Based Testing to Help Diagnose Suspected Pre-Eclampsia (Update of DG23): Addendum 2. NICE DSU Report 2022.

CONTENTS

TABLES

1. ADDITIONAL ANALYSIS OF THE DELFIA RATIO TEST

1.1. INTRODUCTION AND METHODS

Since the submission of the DSU report, a new publication has become available that compares the diagnostic accuracy (sensitivity and specificity) of the DELFIA Xpress PlGF 1-2-3 test with the DELFIA sFlt1/PlGF ratio test[1]. The former test was included in the DSU report (referred to as the 'DELFIA' test), but the latter (hereafter referred to as the 'DELFIA ratio' test) was not included due to a lack of evidence. As new evidence is now available, additional analyses were performed to provide estimates of the cost-effectiveness of PLGF-based testing with the DELFIA ratio test.

Evidence on the diagnostic accuracy of the DELFIA ratio test is obtained from the publication by Bremner and colleagues[1], which is quality assessed in Table 1 and Table 2. This publication reported the results of a prospective longitudinal study conducted at two London obstetric tertiary referral centres. Enrolled women were aged 18 and over, with a gestational age of 20 to 40 (+6) weeks. An overview of sensitivity and specificity values from this study is provided in Table 3. For comparison, this table also provides values for the DELFIA test used in the DSU report, which was taken from the COMPARE study (as reported by Giblin and colleagues)[2].

Table 1: Quality assessment of Bremner study: risk of bias

Patient selection	
1. Was a consecutive or random sample of patients enrolled?	Yes
2. Was a case-control design avoided?	Yes
3. Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low
Index test	
1. Were the index test results interpreted without knowledge of the results of the reference standard?	N/A
2. If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low
Reference standard	
1. Is the reference standard likely to correctly classify the target condition?	Yes
2. Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Flow and Timing	

1. Was there an appropriate interval between index test(s) and reference standard?	Yes
2. Did all patients receive a reference standard?	Yes
3. Did patients receive the same reference standard?	Yes
4. Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low

Table 2: Quality assessment of Bremner study: applicability

Patient selection	
Is there concern that the included patients and settings do not match the review question?	Low
Index test	
Is there concern that the index test, its conduct, or interpretation differ from the review question? i.e. used/followed decision tool	Low
Reference standard	
Is there concern that the target condition as defined by the reference standard does not match the review question?	Low

Table 3: Absolute sensitivity and specificity values for the DELFIA and DELFIA ratio tests

Bremner and colleagues (PE within 7 days, GA 20 to 33[+6] weeks)[1]	**Sensitivity**	**Specificity**
DELFIA ≥150 (Rule-out)	0.722	0.780
DELFIA <50 (Rule-in)	0.389	0.907
DELFIA ratio <50 (Rule-out)	0.500	0.890
DELFIA ratio ≥70 (Rule-in)	0.389	0.898
Bremner and colleagues (PE within 28 days, GA 20 to 33[+6] weeks)[1]	**Sensitivity**	**Specificity**
DELFIA ≥150 (Rule-out)	0.806	0.900
DELFIA <50 (Rule-in)	0.472	0.990
DELFIA ratio <50 (Rule-out)	0.556	0.980
DELFIA ratio ≥70 (Rule-in)	0.500	0.990
Giblin and colleagues (PE requiring delivery within 14 days, GA < 35 weeks)[2]	**Sensitivity**	**Specificity**
DELFIA ≥150 (Rule-out)	0.846	0.799
DELFIA <50 (Rule-in)	0.538	0.950

GA: Gestational age. PE: Pre-eclampsia.

Comparisons between the two studies is difficult due to differences in the outcome definition, time-frame, and gestational ages included. Compared with the COMPARE study, results from Bremner and colleagues for PE within seven days showed lower sensitivity and specificity values for DELFIA 123 when used to either rule-out or rule-in PE. Absolute decreases in sensitivity were 12% and 15% (rule-out and rule-in

respectively) whilst for specificity decreases were 2% and 4% respectively. Based on PE within 28 days, sensitivity values remained lower (4% and 7% respectively), but specificity was increased (10% and 4% respectively).

For use within the updated analyses, the outcome of PE within seven days was used, as this timeframe (and outcome definition) is consistent with that used in the INSPIRE trial[3] (the PARROT UK trial[4] used the same timeframe and outcome definition as COMPARE[5]).

The costs of the DELFIA ratio test were based on those calculated by the EAG, with details provided in Table 4.

Table 4: Breakdown of costs for the DELFIA ratio test

Cost component	Price	Cost per test	Rationale/Formula
Cost per reportable test	NA	£60	As informed by the manufacturer
Training			
Standard training	£0.00	£0.00	Perkin Elmer provides training for free
Staff time	£17.43	£0.43	Salary of a healthcare scientist per hour = £17.43 Time spent in training per year: 3h*3 persons = 9h Cost of training per year (£17.43*9h)/number of tests per year (n=365)
Staff			
Staff who process samples in lab	£17.43	£7.32	Salary of healthcare scientist per hour/time spent per test (0.42h)
Staff who perform device QC	£17.43	£0.19	Time spent per device QC per year: 4h Cost of device QC per year (£17.43*4h)/number of tests per year (n=365)
Other costs			
Phone calls	£3.47	£3.47	Proportion of tests processed in labs: 100% (100%*365=365 tests) Cost per year (£3.47*365)/number of tests per year (n=365)
TOTAL		**£71.41**	
NA, not applicable; QC, quality control			

Absolute sensitivity and specificity values for the DELFIA ratio test when applied to the two baselines of PARROT UK and INSPIRE are included in Table 5. To aid in

comparisons, this also includes the baseline values and the values for the DELFIA test. As before, logical constraints were included to ensure that high-risk thresholds never have better sensitivity or worse specificity than intermediate-risk thresholds. For the deterministic results, this constrained the sensitivity for the DELFIA ratio ≥70 to be = 0.839 (the sensitivity for the DELFIA ratio <50). The unconstrained value would be 0.845.

Table 5: Sensitivity and specificity values used in the economic model

Baseline = PARROT UK[4]	**Sensitivity**	**Specificity**	**Notes**
Triage <100	0.95	0.53	Absolute values from PARROT UK[4]
Triage <12	0.74	0.84	Absolute values from PARROT UK[4]
DELFIA ≥150	0.97	0.53	Relative to Triage <100, from COMPARE[5]
DELFIA <50	0.85	0.83	Relative to Triage <12, from COMPARE[5]
DELFIA ratio <50	0.84	0.67	Relative to DELFIA 123 from Bremner 2022[1]
DELFIA ratio ≥70	0.84	0.82	Relative to DELFIA 123 from Bremner 2022[1]
Baseline = INSPIRE[3]	**Sens**	**Spec**	**Notes**
Elecsys >38	0.96	0.80	Absolute values from INSPIRE 2019[3]
Elecsys >85	0.71	0.80	Relative to Elecsys >38, from INSPIRE 2021[6,7]
DELFIA ≥150	0.99	0.61	Relative to Elecsys >38, from COMPARE[5]
DELFIA <50	0.90	0.79	Relative to Elecsys >85, from COMPARE[5]
DELFIA ratio <50	0.91	0.75	Relative to DELFIA 123 from Bremner 2022[1]
DELFIA ratio ≥70	0.90	0.78	Relative to DELFIA 123 from Bremner 2022[1]

For both baselines, rule-out DELFIA ratio (<50) had lower sensitivity but increased specificity compared with rule-out DELFIA, whilst the rule-in DELFIA ratio (≥70) has very similar sensitivity and specificity values to rule-in DELFIA.

Results for both types of standard assessment, and all other PLGF-based tests previously assessed, remain unchanged. To aid in comparisons, results for DELFIA and standard assessment from both DG23 and INSPIRE are also provided. One

exception is that estimates of net health benefit are provided for all PLGF-based tests, as this information was missing in the original DSU report.

1.2. RESULTS

1.2.1. Rule-out testing: base-case analysis

Deterministic results for the base-case used in the DSU report (hypertension distribution and baseline test performance both from PARROT UK, true positives do not cost more than false negatives, PLGF-based tests used to rule-out PE) are provided in Table 6, with corresponding incremental values in Table 7. Full results are provided in the Appendix Table 14.

Table 6: Deterministic results, PLGF-based tests to rule-out PE

Rule-out testing	SA: DG23	SA: INSPIRE	DELFIA	DELFIA ratio
Total cost	£10,215	£10,223	£10,225	£10,261
Test	£0	£0	£37	£71
Clinical management	£620	£615	£604	£600
Delivery	£3,781	£3,781	£3,781	£3,781
Maternal short-term	£364	£365	£363	£363
Neonatal short-term	£4,373	£4,377	£4,362	£4,365
Neonatal long-term	£1,077	£1,084	£1,078	£1,080
Total QALYs	17.6110	17.6093	17.6137	17.6127
Clinical management	-1.41E-05	-9.18E-06	-9.16E-06	-8.72E-06
Delivery	0.035	0.035	0.035	0.035
Maternal short-term	0.384	0.384	0.384	0.384
Neonatal short-term	-0.001	-0.001	-0.001	-0.001
Maternal long-term	17.363	17.363	17.364	17.364
Neonatal long-term	-0.171	-0.172	-0.169	-0.170
True Positives	9.5%	8.0%	9.0%	8.7%
True negatives	62.7%	65.9%	65.9%	66.2%
False positives	9.2%	6.0%	6.0%	5.7%
False negatives	18.6%	20.1%	19.2%	19.5%

Table 7: Incremental base-case results, PLGF-based tests to rule-out PE

	Total costs		Total QALYs			
	DG23	INSPIRE	DG23	INSPIRE		
Standard assessment	£10,215	£10,223	17.6110	17.6093		

	Incremental costs vs		Incremental QALYs vs		Incremental cost-effectiveness ratio	
	DG23	**INSPIRE**	**DG23**	**INSPIRE**	**DG23**	**INSPIRE**
DELFIA	£10.5	£2.8	0.0027	0.0044	£3,874	£637
DELFIA Ratio	£46.4	£38.7	0.0017	0.0034	£26,604	£11,342

The DELFIA ratio test resulted in higher costs and reduced QALYs when compared with DELFIA, and so was dominated by it. The increased costs persist even if the two PLGF-based tests cost the same, although in this situation the difference in costs is very small (£2). The DELFIA ratio test led to a reduced number of admissions when compared with the DELFIA test, with both true positives and false positives reducing by 0.3%, hence there was a reduction in clinical management costs, but an increase in costs for neonatal outcomes (short-term and long-term). Similar differences were observed for QALYs.

The DELFIA ratio test results in increased costs and QALYs when compared with both types of standard assessment, with ICERs of £26,604 (standard assessment from DG23) and £11,342 (standard assessment from INSPIRE) Whilst the ICERs for the DELFIA ratio are greater than those for DELFIA, they are similar to the original range of ICERs for PLGF-based test (range £3,874 to £47,393 compared to standard assessment from DG23 and £637 to £10,777 compared to standard assessment from INSPIRE).

Table 8: Impact on base-case results of excluding neonatal outcomes

Including neonatal outcomes	**DELFIA**	**DELFIA ratio**
Absolute cost	£10,225	£10,261
Absolute QALYs	17.6137	17.6127
ICER vs SA (DG23)	£3,874	£26,604
ICER vs SA (INSPIRE)	£637	£11,342
Excluding long-term neonatal outcomes		
Absolute cost	£9,147	£9,181
Absolute QALYs	17.7825	17.7823
ICER vs SA (DG23)	£13,531	£100,946
ICER vs SA (INSPIRE)	£8,298	£52,765
Excluding all neonatal outcomes		
Absolute cost	£4,785	£4,816
Absolute QALYs	17.7831	17.7829
ICER vs SA (DG23)	£31,164	£122,176
ICER vs SA (INSPIRE)	£23,274	£68,580

ICER: Incremental cost-effectiveness ratio. SA: Standard assessment

Cost-effectiveness results with neonatal outcomes excluded are provided in Table 8. Their exclusion leads to an increase in ICER relative to both types of standard assessment; excluding either long-term or all neonatal outcomes provides ICERs in excess of £50,000 for all comparisons of the DELFIA ratio with standard assessment.

The DELFIA ratio test remains dominated by the DELFIA test even when all neonatal outcomes are excluded. However, the difference in total costs in this situation is less than the difference in tests; if the two tests cost the same and all neonatal outcomes were excluded then the DELFIA test would be more expensive and more effective than the DELFIA ratio test, with an ICER of £13,569.

Table 9: Probabilistic base-case results, PLGF-based tests to rule-out PE

			ICER vs standard assessment	
	Total cost	Total QALYs	DG23	INSPIRE
Standard assessment (DG23)	£10,219	17.4972		
Standard assessment (INSPIRE)	£10,227	17.4950		
DELFIA	£10,232	17.5003	£4,229	£1,065
DELFIA ratio	£10,277	17.4966	Dominated	£32,274

Base-case probabilistic results are provided in Table 9 (results for standard assessment and DELFIA vary from those originally presented as the probabilistic analysis was re-run). Based on the probabilistic analysis, DELFIA ratio is dominated by standard assessment from DG23. However, total QALYs are identical to three decimal places, illustrating the uncertainty in this conclusion. The ICER for the DELFIA ratio compared with standard assessment from INSPIRE is £32,274.

1.2.1. Rule-out testing: applying PLGF-based tests to the outcomes of standard assessment

The additional results of the first addendum (dated 16th February 2022), in which PLGF-based tests were applied to the outcomes of standard assessment to rule-out

PE, are extended to include the DELFIA ratio test, with results provided in Table 10, and full results available in the Appendix Table 14.

For both types of standard assessment, applying the DELFIA ratio to the results of standard assessment to rule-out PE leads to a cost-saving and increased QALYs, and hence is dominant. However, the DELFIA ratio is itself dominated by DELFIA.

Table 10: Deterministic results, PLGF-based tests to rule-out PE compared with standard assessment

	Standard assessment (SA) from DG23			SA from INSPIRE		
Rule-out testing	**SA: DG23**	**DELFIA**	**DELFIA ratio**	**SA: INSPIRE**	**DELFIA**	**DELFIA ratio**
Total cost	£10,724	£10,402	£10,445	£10,239	£10,104	£10,149
Test	£0	£37	£71	£0	£37	£71
Clinical management	£1,238	£1,016	£1,014	£844	£711	£710
Delivery	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781
Maternal short-term	£361	£347	£347	£349	£345	£346
Neonatal short-term	£4,357	£4,236	£4,241	£4,257	£4,218	£4,226
Neonatal long-term	£987	£986	£990	£1,007	£1,011	£1,015
Total QALYs	17.6217	17.6539	17.6521	17.6461	17.6561	17.6539
Clinical management	-0.00109	-0.00005	-4.37E-05	-0.00041	-0.00002	-1.83E-05
Delivery	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352
Maternal short-term	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841
Neonatal short-term	-0.0006	-0.0005	-0.0005	-0.0005	-0.0005	-0.0005
Maternal long-term	17.3660	17.3733	17.3729	17.3715	17.3738	17.3733
Neonatal long-term	-0.1618	-0.1381	-0.1394	-0.1437	-0.1364	-0.1381
True Positives	27.6%	25.6%	24.80%	21.7%	20.2%	19.50%
True negatives	17.1%	41.9%	43.30%	49.0%	59.4%	60.00%
False positives	54.8%	30.0%	28.50%	22.9%	12.5%	11.90%
False negatives	0.6%	2.5%	3.30%	6.5%	8.0%	8.60%

1.2.2. Rule-out and rule-in tests

Results of using PLGF-based tests to both rule-out and rule-in PE are summarised in Table 11. Use of the DELFIA ratio always dominated standard assessment from DG23. Hence the results here only include standard assessment from INSPIRE. As before, three options for ruling-in PE were considered ('standard' rule-in, 'cautious' rule-in [both from survey results], and use of PreOS trial results[8]). As results for 'standard' rule-in and 'cautious' rule-in were very similar, only the former is displayed here. Full results for all three options are included in the Appendix Table 14.

With standard rule-in testing, the DELFIA ratio dominated standard assessment from INSPIRE. This dominance held when excluding long-term neonatal outcomes. When all neonatal outcomes were excluded, the DELFIA ratio had an ICER of £1,174. With rule-in testing from PreOS, the DELFIA ratio had an ICER of £1,174, which increased to £23,815 when excluding long-term neonatal outcomes and £39,084 when excluding all neonatal outcomes. As with rule-out testing, the DELFIA ratio was dominated by the DELFIA test.

Table 11: Deterministic base-case results, PLGF-based tests to rule-out and rule-in PE

	Rule-out and standard rule-in			Rule-out and rule-in from PreOS		
	SA: INSPIRE	**DELFIA**	**DELFIA ratio**	**SA: INSPIRE**	**DELFIA**	**DELFIA ratio**
Total cost	£10,724	£10,402	£10,445	£10,239	£10,104	£10,149
Test	£0	£37	£71	£0	£37	£71
Clinical management	£1,238	£1,016	£1,014	£844	£711	£710
Delivery	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781
Maternal short-term	£361	£347	£347	£349	£345	£346
Neonatal short-term	£4,357	£4,236	£4,241	£4,257	£4,218	£4,226
Neonatal long-term	£987	£986	£990	£1,007	£1,011	£1,015
Total QALYs	17.6217	17.6539	17.6521	17.6461	17.6561	17.6539
Clinical management	-0.00109	-0.00005	-4.37E-05	-0.00041	-0.00002	-1.83E-05
Delivery	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352
Maternal short-term	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841
Neonatal short-term	-0.0006	-0.0005	-0.0005	-0.0005	-0.0005	-0.0005
Maternal long-term	17.3660	17.3733	17.3729	17.3715	17.3738	17.3733
Neonatal long-term	-0.1618	-0.1381	-0.1394	-0.1437	-0.1364	-0.1381
True Positives	27.6%	25.6%	24.80%	21.7%	20.2%	19.50%
True negatives	17.1%	41.9%	43.30%	49.0%	59.4%	60.00%
False positives	54.8%	30.0%	28.50%	22.9%	12.5%	11.90%
False negatives	0.6%	2.5%	3.30%	6.5%	8.0%	8.60%

1.2.3. Scenario analyses

Table 12 provides incremental results of scenario analyses when PLGF-based tests are used to rule-out PE. With use of PLGF-based tests to both rule-out PE and (standard) rule-in PE, the DELFIA ratio always dominated both types of standard assessment, with one exception. This is when using INSPIRE for baseline test performance, for which the ICER relative to standard assessment from INSPIRE was £11,841. Full details are provided in the Appendix Table 15 and Table 16.

With one exception, DELFIA dominated DELFIA ratio in all the scenario analyses. The exception was when using INSPIRE for baseline test performance, for which the ICER for DELFIA ratio was £1,705 compared with DELFIA. The typical dominance of DELFIA over DELFIA ratio is likely to be because cost-effectiveness outcomes are primarily driven by the sensitivity of the rule-out threshold and the specificity of the rule-in threshold. When using PARROT UK for the baseline, for DELFIA these values are 0.97 and 0.83 respectively, whilst for DELFIA ratio they are 0.84 and 0.82, respectively.

Table 12: Scenario results for DELFIA ratio, rule-out testing

Incremental cost-effectiveness ratios	**Vs SA (DG23)**	**Vs SA (INSPIRE)**
Base-case*	£26,604	£11,342
INSPIRE for baseline test performance	£7,945	£27,234
True positive test results cost more than false negative results	£25,171	£11,884
Hypertension distribution from PARROT Ireland	£66,004	£31,478
Hypertension distribution from PELICAN	£38,648	£17,497
Hypertension distribution from EAG DAR (Triage, PE)	£3,554	-£438

1.2.4. Net-health benefits: all treatments

In response to consultation comments, estimates of net health benefit, using a willingness to pay threshold of £20,000 are provided for all PLGF-based tests and both standard assessments in Table 13. These are given for the base-case analysis of rule-out testing as well as rule-out with standard rule-in testing. For both analyses, largest estimates of net health benefit were generally observed for the BRAHMS and Elecsys add-on tests, with standard assessment having some of the lowest estimates. Values for the DELFIA ratio were always lower than for the DELFIA test, consistent with the analyses presented in previous sub-sections.

Table 13: Deterministic estimates of net health benefit (at a willingness to pay of £20,000)

	Rule-out testing	Rule-out and rule-in testing
Standard assessment (DG23)	£342,005	£341,710
Standard assessment (INSPIRE)	£341,963	£342,683
Triage test	£341,985	£342,934
Elecsys	£342,015	£343,282
Elecsys as add-on	£342,045	£343,363
DELFIA	£342,048	£343,153
DELFIA ratio	£341,993	£343,113
BRAHMS	£342,073	£343,287

APPENDIX

A.1 ADDITIONAL COST-EFFECTIVENESS RESULTS

Table 14: Deterministic results: DELFIA ratio

	Rule out (base-case)	Rule out applied to SA (DG23)	Rule out applied to SA (INSPIRE)	Rule out and standard rule-in	Rule out and cautious rule-in	Rule out and rule-in based on PreOS
Total cost	£10,261	£10,445	£10,149	£10,163	£10,183	£10,248
Test	£71	£71	£71	£71	£71	£71
Clinical management	£600	£1,014	£710	£785	£674	£628
PE: True positive	£84	£241	£190	£225	£155	£112
PE: False negative	£178	£32	£78	£37	£107	£150
No PE: True negative	£263	£365	£285	£215	£244	£225
No PE: False positive	£75	£376	£157	£309	£168	£141
Delivery	£3,781	£3,781	£3,781	£3,781	£3,781	£3,781
PE: True positive	£362	£1,036	£814	£1,010	£686	£488
PE: False negative	£813	£139	£361	£165	£489	£687
No PE: True negative	£2,399	£1,571	£2,174	£1,904	£2,203	£2,236
No PE: False positive	£206	£1,034	£432	£701	£403	£369
Maternal short-term	£363	£347	£346	£342	£351	£360
PE: True positive	£33	£93	£73	£91	£62	£44
PE: False negative	£113	£19	£50	£23	£68	£95
No PE: True negative	£197	£129	£178	£156	£181	£183
No PE: False positive	£21	£106	£44	£72	£41	£38
Neonatal short-term	£4,365	£4,241	£4,226	£4,194	£4,271	£4,343
PE: True positive	£627	£1,793	£1,409	£1,748	£1,187	£845
PE: False negative	£1,728	£296	£768	£351	£1,039	£1,460
No PE: True negative	£1,819	£1,191	£1,648	£1,444	£1,670	£1,695
No PE: False positive	£191	£961	£401	£651	£374	£343
Neonatal long-term	£1,080	£990	£1,015	£989	£1,034	£1,063
PE: True positive	£241	£689	£541	£672	£456	£325
PE: False negative	£664	£114	£295	£135	£400	£561
No PE: True negative	£158	£104	£144	£126	£145	£148
No PE: False positive	£17	£84	£35	£57	£33	£30
Total QALYs	17.6127	17.6521	17.6539	17.6638	17.6406	17.6197
Clinical management	-8.72E-06	-4.37E-05	-1.83E-05	-3.32E-04	-1.37E-04	-5.56E-05
PE: True positive	0	0	0	0	0	0
PE: False negative	0	0	0	0	0	0
No PE: True negative	0	0	0	0	0	0
No PE: False positive	-8.72E-06	-4.37E-05	-1.83E-05	-3.32E-04	-1.37E-04	-5.56E-05
Delivery	0.0352	0.0352	0.0352	0.0352	0.0352	0.0352
PE: True positive	0.003	0.008	0.007	0.008	0.006	0.004
PE: False negative	0.007	0.001	0.003	0.001	0.004	0.006

No PE: True negative	0.024	0.015	0.021	0.019	0.022	0.022
No PE: False positive	0.002	0.010	0.004	0.007	0.004	0.004
Maternal short-term	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841
PE: True positive	0.033	0.095	0.075	0.093	0.063	0.045
PE: False negative	0.075	0.013	0.033	0.015	0.045	0.063
No PE: True negative	0.254	0.166	0.230	0.202	0.233	0.237
No PE: False positive	0.022	0.110	0.046	0.074	0.043	0.039
Neonatal short-term	-0.0006	-0.0005	-0.0005	-0.0005	-0.0005	-0.0006
PE: True positive	-4.24E-05	-1.21E-04	-9.53E-05	-1.18E-04	-8.03E-05	-5.71E-05
PE: False negative	-4.06E-04	-6.96E-05	-1.80E-04	-8.24E-05	-2.44E-04	-3.43E-04
No PE: True negative	-1.19E-04	-7.78E-05	-1.08E-04	-9.42E-05	-1.09E-04	-1.11E-04
No PE: False positive	-4.61E-05	-2.31E-04	-9.64E-05	-1.57E-04	-9.00E-05	-8.25E-05
Maternal long-term	17.3637	17.3729	17.3733	17.3757	17.3702	17.3653
PE: True positive	1.504	4.303	3.381	4.196	2.850	2.028
PE: False negative	3.356	0.575	1.491	0.682	2.019	2.836
No PE: True negative	11.516	7.541	10.434	9.139	10.573	10.732
No PE: False positive	0.988	4.954	2.067	3.359	1.928	1.769
Neonatal long-term	-0.1696	-0.1394	-0.1381	-0.1303	-0.1482	-0.1642
PE: True positive	-0.016	-0.045	-0.035	-0.044	-0.030	-0.021
PE: False negative	-0.106	-0.018	-0.047	-0.021	-0.064	-0.089
No PE: True negative	-0.038	-0.025	-0.034	-0.030	-0.035	-0.035
No PE: False positive	-0.010	-0.052	-0.022	-0.035	-0.020	-0.018
True Positives	8.7%	24.8%	19.5%	24.2%	16.4%	11.7%
True negatives	66.2%	43.3%	60.0%	52.5%	60.8%	61.7%
False positives	5.7%	28.5%	11.9%	19.3%	11.1%	10.2%
False negatives	19.5%	3.3%	8.6%	4.0%	11.7%	16.4%

SA: Standard assessment

Table 15: Deterministic sensitivity analysis results: DELFIA ratio (rule-out testing)

	INSPIRE baseline test performance	True positive test results cost more than false negatives	Hypertension distribution from PARROT Ireland	Hypertension distribution from PELICAN	Hypertension distribution from EAG DAR (Triage, PE)
Total cost	£10,249	£10,287	£9,924	£10,552	£11,238
Test	£71	£71	£71	£71	£71
Clinical management	£598	£626	£520	£561	£790
PE: True positive	£88	£110	£40	£22	£172
PE: False negative	£174	£178	£185	£265	£191
No PE: True negative	£261	£263	£258	£255	£273
No PE: False positive	£75	£75	£36	£19	£153
Delivery	£3,781	£3,781	£3,762	£3,792	£3,834
PE: True positive	£379	£362	£174	£94	£740
PE: False negative	£796	£813	£859	£1,165	£834
No PE: True negative	£2,399	£2,399	£2,631	£2,480	£1,839
No PE: False positive	£206	£206	£99	£53	£421
Maternal short-term	£362	£363	£360	£379	£376

PE: True positive	£34	£33	£16	£8	£66
PE: False negative	£110	£113	£119	£161	£116
No PE: True negative	£197	£197	£216	£203	£151
No PE: False positive	£21	£21	£10	£5	£43
Neonatal short-term	£4,359	£4,365	£4,211	£4,567	£4,838
PE: True positive	£656	£627	£300	£162	£1,280
PE: False negative	£1,692	£1,728	£1,825	£2,475	£1,772
No PE: True negative	£1,819	£1,819	£1,995	£1,880	£1,394
No PE: False positive	£192	£191	£92	£50	£391
Neonatal long-term	£1,078	£1,080	£998	£1,182	£1,329
PE: True positive	£252	£241	£115	£62	£492
PE: False negative	£650	£664	£701	£951	£681
No PE: True negative	£158	£158	£174	£164	£121
No PE: False positive	£17	£17	£8	£4	£34
Total QALYs	17.6146	17.6127	17.6180	17.5764	17.5851
Clinical management	-8.72E-06	-8.72E-06	-4.18E-06	-2.26E-06	-1.78E-05
PE: True positive	0	0	0	0	0
PE: False negative	0	0	0	0	0
No PE: True negative	0	0	0	0	0
No PE: False positive	-8.72E-06	-8.72E-06	-4.18E-06	-2.26E-06	-1.78E-05
Delivery	0.0352	0.0352	0.0352	0.0351	0.0350
PE: True positive	0.003	0.003	0.001	0.001	0.006
PE: False negative	0.006	0.007	0.007	0.009	0.007
No PE: True negative	0.024	0.024	0.026	0.024	0.018
No PE: False positive	0.002	0.002	0.001	0.001	0.004
Maternal short-term	0.3841	0.3841	0.3841	0.3841	0.3841
PE: True positive	0.035	0.033	0.016	0.009	0.068
PE: False negative	0.073	0.075	0.079	0.107	0.077
No PE: True negative	0.254	0.254	0.279	0.263	0.195
No PE: False positive	0.022	0.022	0.010	0.006	0.045
Neonatal short-term	-0.0006	-0.0006	-0.0006	-0.0007	-0.0007
PE: True positive	-4.44E-05	-4.24E-05	-2.03E-05	-1.10E-05	-8.66E-05
PE: False negative	-3.97E-04	-4.06E-04	-4.28E-04	-5.81E-04	-4.16E-04
No PE: True negative	-1.19E-04	-1.19E-04	-1.30E-04	-1.23E-04	-9.10E-05
No PE: False positive	-4.61E-05	-4.61E-05	-2.21E-05	-1.19E-05	-9.41E-05
Maternal long-term	17.3641	17.3637	17.3649	17.3552	17.3572
PE: True positive	1.575	1.504	0.721	0.390	3.073
PE: False negative	3.286	3.356	3.544	4.808	3.442
No PE: True negative	11.516	11.516	12.627	11.902	8.824
No PE: False positive	0.988	0.988	0.473	0.256	2.017
Neonatal long-term	-0.1681	-0.1696	-0.1656	-0.1973	-0.1905
PE: True positive	-0.016	-0.016	-0.008	-0.004	-0.032
PE: False negative	-0.103	-0.106	-0.112	-0.151	-0.108
No PE: True negative	-0.038	-0.038	-0.042	-0.039	-0.029
No PE: False positive	-0.010	-0.010	-0.005	-0.003	-0.021
True Positives	9.1%	8.7%	4.2%	2.2%	17.7%

True negatives	66.2%	66.2%	72.6%	68.4%	50.7%
False positives	5.7%	5.7%	2.7%	1.5%	11.6%
False negatives	19.1%	19.5%	20.5%	27.9%	20.0%

Table 16: Deterministic sensitivity analysis results: DELFIA ratio (rule-out and rule-in testing)

	INSPIRE baseline test performance	True positive test results cost more than false negatives	Hypertension distribution from PARROT Ireland	Hypertension distribution from PELICAN	Hypertension distribution from EAG DAR (Triage, PE)
Total cost	£10,131	£10,244	£9,837	£10,282	£11,044
Test	£71	£71	£71	£71	£71
Clinical management	£790	£866	£735	£754	£903
PE: True positive	£240	£306	£192	£242	£317
PE: False negative	£21	£37	£34	£45	£47
No PE: True negative	£211	£215	£205	£190	£231
No PE: False positive	£317	£309	£304	£278	£308
Delivery	£3,781	£3,781	£3,762	£3,792	£3,834
PE: True positive	£1,079	£1,010	£878	£1,062	£1,370
PE: False negative	£97	£165	£155	£197	£204
No PE: True negative	£1,887	£1,904	£2,062	£1,935	£1,513
No PE: False positive	£719	£701	£668	£598	£746
Maternal short-term	£339	£342	£338	£343	£352
PE: True positive	£97	£91	£79	£95	£123
PE: False negative	£13	£23	£21	£27	£28
No PE: True negative	£155	£156	£169	£159	£124
No PE: False positive	£74	£72	£69	£61	£77
Neonatal short-term	£4,170	£4,194	£4,031	£4,278	£4,645
PE: True positive	£1,866	£1,748	£1,518	£1,838	£2,371
PE: False negative	£206	£351	£329	£418	£434
No PE: True negative	£1,431	£1,444	£1,563	£1,467	£1,147
No PE: False positive	£667	£651	£620	£555	£693
Neonatal long-term	£979	£989	£900	£1,043	£1,238
PE: True positive	£717	£672	£584	£706	£911
PE: False negative	£79	£135	£126	£161	£167
No PE: True negative	£125	£126	£136	£128	£100
No PE: False positive	£58	£57	£54	£48	£60
Total QALYs	17.6708	17.6638	17.6720	17.6616	17.6419
Clinical management	-3.43E-04	-3.32E-04	-3.76E-04	-3.58E-04	-2.30E-04
PE: True positive	0	0	0	0	0
PE: False negative	0	0	0	0	0
No PE: True negative	0	0	0	0	0
No PE: False positive	-3.43E-04	-3.32E-04	-3.76E-04	-3.58E-04	-2.30E-04
Delivery	0.0352	0.0352	0.0352	0.0351	0.0350
PE: True positive	0.009	0.008	0.007	0.009	0.011

PE: False negative	0.001	0.001	0.001	0.002	0.002
No PE: True negative	0.019	0.019	0.020	0.019	0.015
No PE: False positive	0.007	0.007	0.007	0.006	0.007
Maternal short-term	0.3841	0.3841	0.3841	0.3841	0.3841
PE: True positive	0.099	0.093	0.081	0.098	0.126
PE: False negative	0.009	0.015	0.014	0.018	0.019
No PE: True negative	0.200	0.202	0.218	0.205	0.160
No PE: False positive	0.076	0.074	0.071	0.063	0.079
Neonatal short-term	-0.0004	-0.0005	-0.0004	-0.0005	-0.0005
PE: True positive	-1.26E-04	-1.18E-04	-1.03E-04	-1.24E-04	-1.60E-04
PE: False negative	-4.84E-05	-8.24E-05	-7.72E-05	-9.81E-05	-1.02E-04
No PE: True negative	-9.34E-05	-9.42E-05	-1.02E-04	-9.58E-05	-7.49E-05
No PE: False positive	-1.61E-04	-1.57E-04	-1.49E-04	-1.34E-04	-1.67E-04
Maternal long-term	17.3773	17.3757	17.3776	17.3752	17.3705
PE: True positive	4.479	4.196	3.645	4.411	5.690
PE: False negative	0.400	0.682	0.639	0.812	0.842
No PE: True negative	9.057	9.139	9.895	9.288	7.263
No PE: False positive	3.441	3.359	3.199	2.864	3.575
Neonatal long-term	-0.1250	-0.1303	-0.1241	-0.1320	-0.1470
PE: True positive	-0.047	-0.044	-0.038	-0.046	-0.059
PE: False negative	-0.013	-0.021	-0.020	-0.026	-0.026
No PE: True negative	-0.030	-0.030	-0.033	-0.031	-0.024
No PE: False positive	-0.036	-0.035	-0.033	-0.030	-0.037
True Positives	25.8%	24.2%	21.0%	25.4%	32.8%
True negatives	52.1%	52.5%	56.9%	53.4%	41.7%
False positives	19.8%	19.3%	18.4%	16.5%	20.6%
False negatives	2.3%	4.0%	3.7%	4.7%	4.9%

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PLGF-BASED TESTING TO HELP DIAGNOSE SUSPECTED PRE-ECLAMPSIA (UPDATE OF DG23)

ERRATUM TO THE DECISION SUPPORT UNIT REPORT

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ABOUT THE DECISION SUPPORT UNIT

The Decision Support Unit (DSU) External Assessment Centre is based at the University of Sheffield with members at York, Bristol, Leicester and the London School of Hygiene and Tropical Medicine. The DSU is commissioned by The National Institute for Health and Care Excellence (NICE) to provide a research and training resource to support the Institute's Centre for Health Technology Evaluation Programmes. Please see our website for further information www.nicedsu.org.uk.

The production of this document was funded by the National Institute for Health and Care Excellence (NICE) through its Decision Support Unit. The views, and any errors or omissions, expressed in this document are of the authors only. NICE may take account of part or all of this document if it considers it appropriate, but it is not bound to do so.

This report should be referenced as follows:

Kearns B., Wailoo A., Abdullah P., PLGF-Based Testing to Help Diagnose Suspected Pre-Eclampsia (Update of DG23): Erratum. NICE DSU Report 2022.

In response to the consultation responses dated 15th February, the DSU provide the following erratum to their original report. None of the amendments changed the overall conclusions of the report

Page 19, Section 2.1.2.
Original text: “For the COMPARE study the main concern was the lack of a pre-specified threshold for the BRAHMS test.”
The reference to ‘BRAHMS’ is incorrect, this should be to ‘DELFIA’.
New text: “For the COMPARE study the main concern was the lack of a pre-specified threshold for the DELFIA test”

Appendix Section titles (Pages 74 and 82):
The original titles “A.3 ADDITIONAL COST-EFFECTIVENESS RESULTS FOR RULE-IN TESTING” and “A.4 ADDITIONAL COST-EFFECTIVENESS RESULTS FOR RULE-OUT TESTING” are incorrect.
The correct titles are: “A.3 ADDITIONAL COST-EFFECTIVENESS RESULTS FOR RULE-OUT TESTING” and “A.4 ADDITIONAL COST-EFFECTIVENESS RESULTS FOR RULE-IN TESTING”

Appendix Section Tables (Pages 74 and 82).
For Tables 34 and 40, column headings were in the wrong order. The correct headings are provided as part of the corrected versions of pages.

Corrected versions of pages 19, 74, and 82 are provided below.

Page 19:

Figure 2. The list of studies that were ongoing at the time of the EAG DAR (Appendix 6) was also checked. Studies that did not use the test cut-offs recommended in the final scope for DG23 were excluded.

Within the EAG DAR there was no quality assessment for the Simon and COMPARE studies. This is provided in Table 4 for risk of bias and Table 5 for applicability. The main concerns for the Simon study are the non-UK setting, and the definition of a case (which includes fetal growth restriction as well as PE, with measurements restricted to 24 to 28 weeks gestation). For the COMPARE study the main concern was the lack of a pre-specified threshold for the DELFIA test. The EAG DAR did not provide study details for the Simon study; these are provided in Table 6.

Page 74:

A.3 ADDITIONAL COST-EFFECTIVENESS RESULTS FOR RULE-OUT TESTING

Table 34: Base-case probabilistic results

Rule-out PLGF testing	SA (DG23)	SA (INSPIRE)	Triage test	Elecsys	Elecsys (add-on)	DELFIA	BRAHMS
Total cost	£10,238	£10,247	£10,267	£10,286	£10,281	£10,252	£10,260
Test	£0	£0	£50	£79	£79	£37	£52
Clinical management	£621	£617	£605	£600	£601	£605	£602
PE: True positive	£91	£77	£83	£84	£86	£84	£85
PE: False negative	£173	£187	£180	£180	£177	£179	£178
No PE: True negative	£236	£274	£263	£264	£263	£262	£261
No PE: False positive	£121	£79	£79	£72	£74	£79	£77
Delivery	£3,787	£3,787	£3,787	£3,787	£3,787	£3,787	£3,787
PE: True positive	£390	£329	£358	£361	£371	£362	£367
PE: False negative	£794	£855	£826	£823	£812	£822	£817
No PE: True negative	£2,270	£2,386	£2,387	£2,404	£2,400	£2,386	£2,391
No PE: False positive	£334	£218	£216	£199	£204	£218	£213
Maternal short-term	£371	£372	£370	£369	£369	£370	£369
PE: True positive	£33	£28	£30	£31	£31	£31	£31
PE: False negative	£121	£130	£126	£126	£124	£125	£125
No PE: True negative	£181	£190	£190	£192	£191	£190	£191
No PE: False positive	£35	£23	£23	£21	£22	£23	£23
Neonatal short-term	£4,379	£4,383	£4,371	£4,367	£4,364	£4,370	£4,367
PE: True positive	£672	£566	£616	£622	£640	£624	£632
PE: False negative	£1,679	£1,808	£1,747	£1,740	£1,718	£1,738	£1,727
No PE: True negative	£1,719	£1,807	£1,808	£1,821	£1,817	£1,807	£1,810
No PE: False positive	£310	£202	£201	£185	£189	£202	£197
Neonatal long-term	£1,081	£1,088	£1,084	£1,083	£1,081	£1,083	£1,082
PE: True positive	£258	£218	£237	£239	£246	£240	£243
PE: False negative	£646	£695	£672	£669	£661	£668	£664
No PE: True negative	£150	£157	£157	£159	£158	£157	£158
No PE: False positive	£27	£18	£17	£16	£16	£18	£17
Total QALYs	17.4789	17.4763	17.4811	17.4828	17.4841	17.4817	17.4829
Clinical management	-1.59E-05	-1.03E-05	-1.03E-05	-9.47E-06	-9.69E-06	-1.03E-05	-1.01E-05
PE: True positive	0	0	0	0	0	0	0
PE: False negative	0	0	0	0	0	0	0
No PE: True negative	0	0	0	0	0	0	0
No PE: False positive	-1.59E-05	-1.03E-05	-1.03E-05	-9.47E-06	-9.69E-06	-1.03E-05	-1.01E-05
Delivery	0.0349	0.0349	0.0349	0.0349	0.0349	0.0349	0.0349
PE: True positive	0.003	0.003	0.003	0.003	0.003	0.003	0.003
PE: False negative	0.006	0.007	0.007	0.007	0.006	0.007	0.007
No PE: True negative	0.022	0.023	0.023	0.024	0.024	0.023	0.023
No PE: False positive	0.003	0.002	0.002	0.002	0.002	0.002	0.002
Maternal short-term	0.3840	0.3840	0.3840	0.3840	0.3840	0.3840	0.3840

PE: True positive	0	0	0	0	0	0	0
PE: False negative	0	0	0	0	0	0	0
No PE: True negative	0	0	0	0	0	0	0
No PE: False positive	-1.87E-05	-1.87E-05	-1.72E-05	-1.87E-05	-1.85E-05	-1.76E-05	-2.88E-05
Delivery	0.0350	0.0350	0.0350	0.0350	0.0350	0.0350	0.0350
PE: True positive	0.006	0.006	0.006	0.006	0.006	0.006	0.007
PE: False negative	0.007	0.007	0.007	0.007	0.006	0.006	0.006
No PE: True negative	0.018	0.018	0.018	0.018	0.018	0.018	0.016
No PE: False positive	0.004	0.004	0.004	0.004	0.004	0.004	0.007
Maternal short-term	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841	0.3841
PE: True positive	0.063	0.067	0.069	0.070	0.073	0.072	0.075
PE: False negative	0.081	0.078	0.075	0.074	0.072	0.073	0.070
No PE: True negative	0.192	0.193	0.196	0.193	0.193	0.195	0.167
No PE: False positive	0.047	0.047	0.043	0.047	0.046	0.044	0.072
Neonatal short-term	-0.0007	-0.0007	-0.0007	-0.0007	-0.0007	-0.0007	-0.0007
PE: True positive	-8.04E-05	-8.53E-05	-8.83E-05	-8.96E-05	-9.24E-05	-9.13E-05	-9.49E-05
PE: False negative	-4.43E-04	-4.22E-04	-4.09E-04	-4.03E-04	-3.91E-04	-3.96E-04	-3.81E-04
No PE: True negative	-8.99E-05	-9.00E-05	-9.17E-05	-8.99E-05	-9.02E-05	-9.13E-05	-7.81E-05
No PE: False positive	-9.90E-05	-9.85E-05	-9.08E-05	-9.89E-05	-9.77E-05	-9.28E-05	-1.52E-04
Maternal long-term	17.3556	17.3567	17.3578	17.3577	17.3584	17.3584	17.3564
PE: True positive	2.854	3.028	3.134	3.180	3.280	3.239	3.369
PE: False negative	3.660	3.488	3.382	3.336	3.237	3.278	3.149
No PE: True negative	8.718	8.729	8.896	8.721	8.747	8.852	7.576
No PE: False positive	2.123	2.112	1.945	2.120	2.094	1.989	3.263
Neonatal long-term	-0.1958	-0.1921	-0.1887	-0.1890	-0.1867	-0.1868	-0.1932
PE: True positive	-0.030	-0.032	-0.033	-0.033	-0.034	-0.034	-0.035
PE: False negative	-0.115	-0.110	-0.106	-0.105	-0.102	-0.103	-0.099
No PE: True negative	-0.029	-0.029	-0.029	-0.029	-0.029	-0.029	-0.025
No PE: False positive	-0.022	-0.022	-0.020	-0.022	-0.022	-0.021	-0.034
True Positives	16.4%	17.4%	18.1%	18.3%	18.9%	18.7%	19.4%
True negatives	50.1%	50.2%	51.1%	50.1%	50.3%	50.9%	43.5%
False positives	12.2%	12.2%	11.2%	12.2%	12.1%	11.5%	18.8%
False negatives	21.2%	20.2%	19.6%	19.3%	18.8%	19.0%	18.3%

A.4 ADDITIONAL COST-EFFECTIVENESS RESULTS FOR RULE-IN TESTING

Table 40: Base-case probabilistic results

Rule-out PLGF testing	**SA (DG23)**	**SA (INSPIRE)**	**Triage test**	**Elecsys**	**Elecsys (add-on)**	**DELFIA**	**BRAHMS**
Total cost	£10,734	£10,251	£10,193	£10,128	£10,127	£10,176	£10,162
Test	£0	£0	£50	£79	£79	£37	£52
Clinical management	£1,235	£845	£813	£761	£777	£818	£807
PE: True positive	£250	£196	£218	£223	£233	£223	£228
PE: False negative	£12	£66	£43	£39	£29	£39	£34