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Placental growth factor (PLGF)-based testing to help diagnose suspected pre-eclampsia: a systematic review and economic evaluation

*Jonathan Shepherd, Geoff Frampton, Ben Kearns, Karen Pickett, Inês Souto-Ribeiro ,
Allan J Wailoo, Lois Woods, Keith Cooper, Lorna Hazell, Abdullah Pandor and David A Scott*





Extended Research Article

Placental growth factor (PLGF)-based testing to help diagnose suspected pre-eclampsia: a systematic review and economic evaluation

Jonathan Shepherd^{1*}, Geoff Frampton¹, Ben Kearns², Karen Pickett¹,
Inês Souto-Ribeiro¹, Allan J Wailoo², Lois Woods¹, Keith Cooper¹,
Lorna Hazell¹, Abdullah Pandor² and David A Scott¹

¹Southampton Health Technology Assessments Centre (SHTAC), University of Southampton, Southampton, UK

²Decision Support Unit, Sheffield Centre for Health and Related Research (SchARR), University of Sheffield, Sheffield, UK

*Corresponding author jps@southampton.ac.uk

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This article

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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 or the ratio of soluble fms-like tyrosine kinase-1 to placental growth factor are available (known as Triage, Elecsys, DELFIA Xpress, and BRAHMS Kryptor tests). Abnormal measurements of these biomarkers can be used as an aid to predict a diagnosis of pre-eclampsia and maternal and fetal outcomes.

Objectives: To evaluate the test accuracy, clinical effectiveness and cost-effectiveness of placental growth factor-based tests used in conjunction with standard clinical assessment for predicting pre-eclampsia and maternal and fetal outcomes in pregnant women who are referred to secondary care with suspected pre-eclampsia in weeks 20–37 of pregnancy.

Data sources and methods: A systematic review of the diagnostic/prognostic accuracy and clinical effectiveness of placental growth factor-based tests with standard clinical assessment. Database included MEDical Literature Analysis and Retrieval System, Excerpta Medica dataBASE and Cochrane Library. Other sources searched included relevant conference proceedings and websites, grey literature and research in progress. The most recent date of searching was 18 March 2021. An independent economic analysis was conducted using a decision tree model. The model includes short-term costs and quality-adjusted life-years for the management of women, maternal and neonatal outcomes and long-term outcomes for severe neonatal complications. The model compared the use of the test alongside standard clinical assessment to standard clinical assessment only. Two different estimates of standard clinical assessment were included, from the INSPIRE study and from National Institute of Health and Care Excellence Diagnostic Guidance 23.

Results: Seventeen studies were included in the systematic review. Two large, randomised trials provided the best available evidence to inform the economic model: The PARROT trial (Triage test) and the INSPIRE trial (Elecsys test). When used as rule-out tests for pre-eclampsia (with neonatal outcomes included), all four tests produced higher quality-adjusted life-years and higher costs than both types of standard clinical assessment. The incremental cost per quality-adjusted life-year ranged from £637 (DELFA test vs. standard clinical assessment from INSPIRE) to £47,393 (Triage test vs. standard clinical assessment from diagnostics guidance 23) per quality-adjusted life-year. Incremental costs and quality-adjusted life-years were always very small, with incremental costs always less than the cost of the test and incremental quality-adjusted life-years always < 0.006.

Limitations: Although the evidence for placental growth factor-based tests is advancing, there remains uncertainty for key parameters, such as diagnostic sensitivity and specificity. This particularly affects the Elecsys test.

Conclusions: Despite uncertainties from lack of data, and heterogeneity across studies, the use of placental growth factor-based tests to rule out and rule in pre-eclampsia has the potential to provide improved outcomes at reduced cost when compared with standard clinical assessment.

Future work: Future research priorities include more rigorous evaluation of the DELFIA and BRAHMS placental growth factor-based tests, more evidence for Triage and Elecsys as rule-in tests, and greater focus on Black, and Asian and Mixed ethnicity groups.

Study registration: This study is registered as PROSPERO CRD42020227085.

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List of supplementary material

Report Supplementary Material 1 Supplementary material

Supplementary material can be found on the NIHR Journals Library article page (<https://doi.org/10.3310/HDST9104>).

Supplementary material has been provided by the authors to support the article and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

The supplementary materials (which include but are not limited to related publications, patient information leaflets and questionnaires) are provided to support and contextualise the publication. Every effort has been made to obtain the necessary permissions for reproduction, to credit original sources appropriately, and to respect copyright requirements. However, despite our diligence, we acknowledge the possibility of unintentional omissions or errors and we welcome notifications of any concerns regarding copyright or permissions.

List of abbreviations

ACOG	American College of Obstetricians and Gynecologists	ISSHP	International Society for the Study of Hypertension in Pregnancy
AUC	area under the curve	IUGR	intrauterine growth restriction
CG107	clinical guideline 107	MEDLINE	MEDical Literature Analysis and Retrieval System
DAR	diagnostic assessment report	NG133	NICE guideline 133
DG23	diagnostics guidance 23	NICE	National Institute for Health and Care Excellence
EAG	External Assessment Group	NICU	neonatal intensive care unit
EMBASE	Excerpta Medica dataBASE	NPV	negative predictive value
eMiT	drugs and pharmaceutical electronic market information tool national database	PE	pre-eclampsia
EQ-5D	EuroQol-5 Dimensions	PLGF	placental growth factor
EQ-5D-3L	EuroQol-5 Dimensions, three-level version	PPV	positive predictive value
EQ-5D-5L	EuroQol-5 Dimensions, five-level version	QALY	quality-adjusted life-year
EQ-VAS	EuroQol visual analogue scale	QUADAS-2	quality assessment of diagnostic accuracy studies 2
FGR	fetal growth restriction	RCT	randomised controlled trial
FullPIERS	Preeclampsia Integrated Estimate of Risk	ROC	receiver-operator characteristics
HDU	high-dependency unit	SCBU	special care baby unit
HELLP	haemolysis, elevated liver enzymes, low platelet count	SF-6D	Short Form questionnaire-6 Dimensions
HRQoL	health-related quality of life	SF-12	Short Form questionnaire-12 items
HUI	Health Utilities Index	SF-36	Short Form questionnaire-36 items
ICER	incremental cost-effectiveness ratio	sFLT-1	soluble fms-like tyrosine kinase-1
ICU	intensive care unit	SGA	small for gestational age
		VEGFR1	vascular endothelial growth factor receptor-1

Plain language summary

Pre-eclampsia is a condition that affects some pregnant women and, if not detected or left untreated, can cause serious health complications for the mother and/or the baby.

Four tests are now available (Triage, Elecsys, BRAHMS and DELFIA) that can detect abnormal levels of certain proteins in the blood indicating that a pregnant woman may have pre-eclampsia. We investigated the use of these tests in addition to the usual tests done by doctors to diagnose pre-eclampsia. Results of the tests determine whether someone with suspected pre-eclampsia should be admitted to hospital or can be safely monitored as outpatients.

We carried out expert medical evidence searches to update our knowledge of the accuracy and cost of these tests and to find out if the tests can help doctors correctly recommend the best form of treatment for each woman. make the best decisions or impact on delivery-related outcomes for mother and baby. We developed an economic computer model that estimated costs of treatment and benefits to the mother and baby, to predict whether the tests would be good value for money for the NHS.

Economic modelling shows that placental growth factor-based tests are cost-effective compared with standard clinical assessment when used to help diagnose (rule in) or exclude (rule out) preterm pre-eclampsia. Cost-effectiveness reflects the amount of money the NHS is willing to pay for health gain. These tests would be useful to help plan safe care and a safe birth for women with pre-eclampsia, and also to identify those unlikely to develop pre-eclampsia, and therefore reduce unnecessary hospitalisation. The tests may work differently in people who are pregnant with more than one baby. There is uncertainty about how effective two of the tests are (the BRAHMS and DELFIA tests) due to lack of research, and on the usefulness and costs of testing women more than once if the previous test was negative but they still have symptoms of pre-eclampsia.

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, organ dysfunction, eclampsia, fetal growth restriction, or intrauterine death. The only cure for pre-eclampsia is to deliver the placenta (and therefore the baby); therefore, 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.

If pre-eclampsia is suspected, current practice is to assess the patient for blood pressure, proteinuria, other symptoms such as oedema or neurological disturbances, and abnormal laboratory results. 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) have been recommended by the National Institute for Health and Care Excellence (NICE) for use as an aid in predicting a diagnosis of pre-eclampsia [NICE diagnostic guidance diagnostics guidance 23 (DG23)]. A further two tests which measure these proteins (BRAHMS Kryptor and DELFIA Xpress) are available but have not yet been evaluated for diagnostic or prognostic/predictive accuracy and cost-effectiveness for the NHS. This current report was commissioned to inform an update of NICE DG23.

The four tests specified in the NICE scope for this update diagnostic assessment are: the Triage® PLGF test (QuidelOrtho, San Diego, CA, USA) San Diego; the DELFIA® Xpress PLGF 1-2-3 test™ (Revvity, Waltham, MA, USA); the Elecsys® sFlt-1 to PLGF ratio test (Roche Diagnostics Ltd, Rotkreuz, Switzerland) and the BRAHMS™ PLGF plus Kryptor™ test/BRAHMS sFlt-1 Kryptor test (ThermoFisher Scientific, Waltham, MA, USA).

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 weeks and 37 weeks pregnancy, who have received standard clinical assessment (including blood pressure and/or proteinuria assessment).

The objectives are to:

- assess any new evidence for the test accuracy and analytical validity of the BRAHMS Kryptor and DELFIA Xpress 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 on clinical decision-making (e.g. time to delivery or hospital admission), and on maternal and neonatal outcomes such as morbidity and mortality.

Methods

Systematic review of test accuracy and clinical effectiveness

A systematic review of diagnostic and prognostic accuracy and clinical effectiveness evidence was conducted according to a peer-reviewed protocol. Searches were based on a comprehensive search strategy. Bibliographic databases, including MEDical Literature Analysis and Retrieval System (MEDLINE), Excerpta Medica dataBASE (EMBASE), Web of Science, The Cochrane Library and the International Health Technology Assessment 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 weeks and 37 weeks pregnancy and reported diagnostic accuracy of at least one of the specified tests for predicting pre-eclampsia when used alongside standard clinical practice. Risks of bias and generalisability of the included test accuracy studies were assessed using the quality assessment of diagnostic accuracy studies 2 instrument. Where included studies had outcomes additional to diagnostic and prognostic/predictive accuracy, they were appraised using the Cochrane Risk of Bias tool (if a randomised trial). 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 pursued because the studies were too heterogeneous to allow for meaningful findings and conclusions.

Review of economic evaluations

A systematic review was undertaken to identify economic evaluations that compared PLGF tests, when used in addition to standard clinical assessment, against standard clinical assessment alone for women with suspected pre-eclampsia. The population, interventions and comparator inclusion criteria were the same as for the systematic review of clinical studies, but the study design and outcomes inclusion criteria were specifically relevant to health economics. Studies were included if they were full economic evaluations, assessing both costs and consequences, or were cost studies of the PLGF tests. Relevant outcomes were resource use (budget impact, cost per patient or cost per case of pre-eclampsia correctly managed) and health outcomes [life-years or quality-adjusted life-years (QALYs) gained].

Economic analysis

We developed an economic model to compare the cost-effectiveness of PLGF-based tests when used in addition to standard clinical assessment against standard clinical assessment alone, for women with suspected pre-eclampsia. The model is based on the cost-effectiveness modelling approach used in the previous NICE diagnostic assessment for suspected pre-eclampsia, extended to include maternal and fetal outcomes, and a decision tree with components for clinical management, maternal outcomes and neonatal outcomes. A single baseline population was used to which treatment effects are applied (in the form of sensitivity and specificity of the PLGF-based tests). The baseline population was informed by two of the test accuracy trials: PARROT (as used in diagnostic guidance 23) and INSPIRE. Patients were classified as having low, intermediate and high risk of pre-eclampsia, based on hypertension severity, clinical assessment, and results from the PLGF-based test. Decisions to admit women to hospital were based on their risk of pre-eclampsia and the results of the PLGF-based test.

The costs were evaluated from the perspective of the NHS and Personal Social Services. Outcomes were expressed as QALYs. A 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 NICE guidance.

A comprehensive set of cost estimates for the management of suspected pre-eclampsia were used in the model, including costs associated with:

- PLGF testing, including the cost of equipment, reagents and consumables, and the cost of staff training
- managing gestational hypertension and pre-eclampsia from presentation with suspected pre-eclampsia 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

- delivering the baby
- maternal intensive care and ward stay
- neonatal unit stay including the neonatal intensive care unit, high-dependency unit and special care baby unit
- follow-up assessment up to 6 months postpartum
- long-term costs associated with neonate complications.

We estimated the total QALYs for the index test arm (PLGF test plus standard clinical assessment) and comparator arm (standard clinical assessment alone) by considering health-related quality of life associated with delivery, maternal adverse events, postnatal care and neonatal adverse events. This included the long-term QALY loss associated with adverse events and the QALYs associated with false-positive results.

Results

Searches for test accuracy and clinical effectiveness studies identified 1974 unique bibliographic records from bibliographic databases and another 66 records were identified through searches of conference abstracts, company submissions and suggestions from study authors. After eligibility screening, the systematic review included 37 publications that reported a total of 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 10 studies evaluated the tests independently of standard clinical assessment; they include key studies that informed the previous NICE diagnostic assessment for suspected pre-eclampsia (DG23). However, in the current diagnostic assessment, these studies are less relevant given the presence of evaluations of tests used alongside standard clinical assessment.

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 clinical outcomes for maternal and neonatal morbidity and mortality were numerous and inconsistently reported across the studies.

Evidence for the Elecsys test found that a sFlt-1/PLGF test ratio cut-off of 85 had a positive predictive value (PPV) of 71% to rule in pre-eclampsia within 4 weeks in women presenting with suspected pre-eclampsia between 24 weeks and 37 weeks of pregnancy. The BRAHMS Kryptor 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 with suspected pre-eclampsia between 24 weeks and 37 weeks of pregnancy (NB. sensitivity and specificity were not reported). High negative predictive values 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 than to rule in 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 PLGF test cut-off of < 12 pg/ml and a PPV of 87% (sensitivity 95%) using a PLGF test cut-off of < 100 pg/ml.

We identified 11 economic evaluations of diagnostic tests within the scope of this assessment, that is diagnostic tests for pre-eclampsia that were administered to women between 20 weeks and 37 weeks of gestation. Six of the included studies were evaluations of the Elecsys sFlt-1/PLGF ratio test, two were evaluations of the Triage PLGF test, two assessed more than one PLGF test and the other did not report which PLGF test(s) were evaluated. Four studies were conducted in the UK. Most of the studies used a decision tree model and only one study reported QALYs. The studies suggested that including diagnostic tests alongside standard clinical assessment 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 savings when using the PLGF test, varying between £26 and £2896 per patient.

For the base-case cost-effectiveness analysis, PLGF-based tests were used to rule out pre-eclampsia, baseline test accuracy and hypertension severity were both taken from PARROT, 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 clinical assessment.

Cost-effectiveness results for the PLGF-based tests varied depending on the type of standard clinical assessment (from INSPIRE or DG23), whether testing is used to rule out or both rule out and rule in pre-eclampsia, and whether neonatal outcomes are included in the model.

When used to rule out pre-eclampsia (with neonatal outcomes included), all PLGF-based tests produced greater QALYs and higher costs than standard clinical assessment. The incremental cost-effectiveness ratios (ICERs) ranged from £637 per QALY (DELFIAXpress vs. standard clinical assessment from INSPIRE) to £47,393 per QALY (Triage PLGF test vs. standard clinical assessment from DG23). Incremental costs and QALYs were always very small, with incremental costs always less than the cost of the test and incremental QALYs always < 0.006. Excluding neonatal outcomes led to all ICERs (compared with standard clinical assessment, based on INSPIRE and DG23) exceeding £20,000.

When used to both rule out and rule in pre-eclampsia, PLGF-based tests always dominated standard clinical assessment. This dominance remained when excluding all neonatal outcomes. When compared with standard clinical assessment in INSPIRE, results became sensitive to the clinical management decisions used or which neonatal outcomes were included.

Conclusions

The use of PLGF-based tests alongside standard clinical assessment to rule out or rule in pre-eclampsia has the potential to provide improved outcomes at reduced cost when compared to standard clinical assessment alone. However, results are limited by heterogeneity in the evidence, particularly the sensitivity and specificity of the PLGF-based tests. In addition, any estimated QALY-benefits associated with PLGF-based tests were very small. There is uncertainty regarding factors such as the impact of PLGF-based tests on improving neonatal outcomes, the accuracy of standard clinical assessment, the patient population that would receive these tests in practice, and how PLGF-based tests influence clinical decision-making. These uncertainties could each have a negative impact on the incremental estimates of cost and QALYs for PLGF-based tests.

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 the clinical utility of the BRAHMS and DELFIA tests for the diagnosis of pre-eclampsia, and the impact on maternal and neonatal outcomes of the use of the Elecsys test in addition to standard clinical practice. The clinical effectiveness systematic review identified very little evidence on the use of repeat testing with PLGF-based tests, which precluded a thorough economic evaluation of this testing strategy. Further research is needed to address the long-term impact of pre-eclampsia, for example future health complications and related treatment costs and utilities. More research is also needed on the impact of adverse maternal and neonatal outcomes on long-term quality of life for mothers and neonates, particularly the lifetime costs related to intraventricular haemorrhage.

Study registration

This study is registered as PROSPERO CRD42020227085.

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Chapter 1 Background

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 (IUGR) and intrauterine death.³

Pre-eclampsia is frequently asymptomatic and, if so, may only be detected through routine antenatal testing. Symptoms can include neurological symptoms (headache, visual disturbances), epigastric or right upper quadrant pain,⁴ oedema (swelling of the hands, face or feet) and oliguria (low output of urine).⁵ Although most cases of pre-eclampsia are mild and cause no problems, the condition can worsen and be serious for both mother and baby.⁶ Pre-eclampsia is classified as early onset if it occurs before week 34 of pregnancy, or late onset if it occurs after week 34.⁷ However, pre-eclampsia is less common but often more severe if it occurs before week 34. Pre-eclampsia can also develop in women with chronic hypertension before pregnancy, a condition known as superimposed pre-eclampsia.⁷

Epidemiology

Pre-eclampsia affects up to 5% of pregnancies, and severe cases develop in about 1–2% of pregnancies.⁶ In 2012–3, there were 12,356 admissions to hospital in England for pre-eclampsia and 294 for eclampsia.⁸ Maternal deaths due to pre-eclampsia have fallen,⁹ and only nine deaths were caused directly by pre-eclampsia or eclampsia in the UK in 2010–2 (0.38 per 100,000). Fetal mortality, however, is much higher and around 1000 babies die each year as a result of pre-eclampsia, mostly due to complications associated with early delivery.¹⁰

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 the National Institute for Health and Care Excellence (NICE), the American College of Obstetricians and Gynecologists (ACOG) and the International Society for the Study of Hypertension in Pregnancy (ISSHP) overlap.^{1–3} 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 [NICE guideline 133 (NG133)]¹ 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 (FGR), 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 opinion varies on whether new-onset proteinuria alone indicates 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 increases the mother's lifetime risk of hypertension, pre-eclampsia in subsequent pregnancies,¹¹ ischaemic heart disease, stroke, type 2 diabetes and venous thromboembolism.^{9,12} Negative consequences of pre-eclampsia for the baby include FGR and preterm birth,³ which can lead to complications including intracranial haemorrhage, nutritional compromise and breathing difficulties (neonatal respiratory distress syndrome),⁶ requiring a stay in a neonatal intensive care unit (NICU).

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.

Babies born early, or small-for-gestational-age (SGA), 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 if it involves hospitalisation, loss of work days. 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.

Significance for the NHS

Pregnant women are monitored 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. 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 preterm 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.

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)¹ and guidance [e.g. NICE diagnostics guidance 23 (DG23)].⁷

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 clinical assessment of clinical signs and symptoms and subsequent clinical follow-up. NICE recommend the use of placental growth factor (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 DG23 on PLGF-based testing to help diagnose pre-eclampsia (2016).⁷

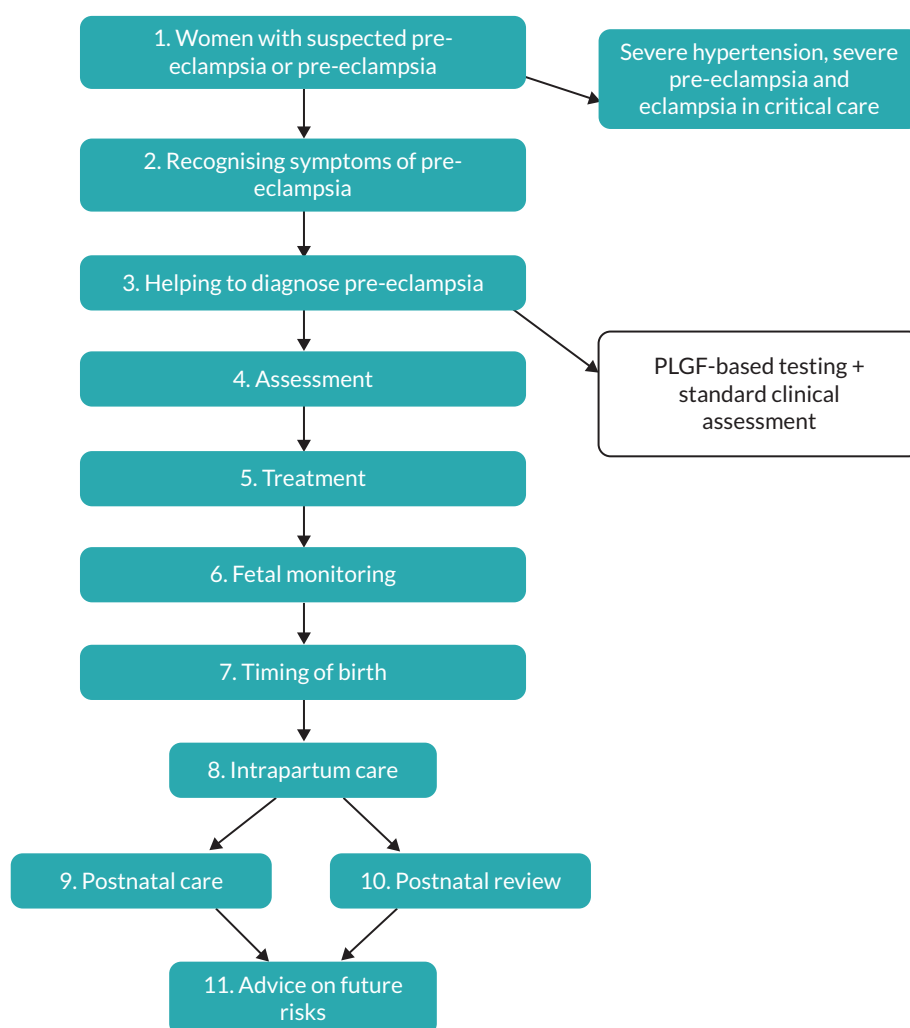


FIGURE 1 National Institute for Health and Care Excellence pathway for pre-eclampsia. Source: NICE® (2023) Hypertension in pregnancy: diagnosis and management.¹ Available from www.nice.org.uk/guidance/ng133. All rights reserved. Subject to Notice of rights (www.nice.org.uk/terms-and-conditions#notice-of-rights). NICE guidance is prepared for the National Health Service in England. All NICE guidance is subject to regular review and may be updated or withdrawn. NICE accepts no responsibility for the use of its content in this product/publication.

Women who are diagnosed with pre-eclampsia undergo clinical assessment at antenatal appointments (Step 4) to identify any concerns for their well-being 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 haematological investigations (e.g. creatinine, alanine transaminase, platelet count), signs of eclampsia, pulmonary oedema and fetal compromise among 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.

The NICE's guideline on hypertension in pregnancy (NG133)¹ proposes optional use of risk prediction models to guide decisions about maternal care. Two validated models are recommended, the fullPIERS (Preeclampsia Integrated Estimate of Risk) risk prediction model⁴ (to be used at any time during pregnancy) or the PREP-S (Prediction of complications in early-onset pre-eclampsia-survival model)⁵ (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.

Placental growth factor-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 pregnancy, reaching a plateau at 26–30 weeks gestation. Abnormally low levels of PLGF during pregnancy may indicate placental dysfunction associated with pre-eclampsia. Some PLGF-based 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.

National Institute for Health and Care Excellence DG23 includes four commercially available tests to aid diagnosis of pre-eclampsia. We describe each of these below.⁷

The **Triage® PLGF test** (QuidelOrtho, San Diego, CA, USA) is a fluorescence immunoassay to be used with the Quidel Triage Meter for the quantitative determination of PLGF in ethylenediaminetetraacetic acid anticoagulated plasma specimens. The company states that it can be used at the point of care and in the laboratory, taking < 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/ml and a measurable range of 12–3000 pg/ml.

The **Elecsys® immunoassay sFlt-1/PLGF ratio** (Roche Diagnostics Ltd, Rotkreuz, Switzerland) measures the relative amounts of PLGF to sFLT-1 [also known as vascular endothelial growth factor receptor-1 (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 pre-eclampsia (rule-out and rule-in) in pregnant women with suspicion of pre-eclampsia in conjunction with other diagnostic and clinical information.

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

The **DELFI[®] Xpress PLGF 1-2-3[™]** (Revvity, Waltham, MA, USA) can be used as a stand-alone test or in combination with the **DELFI[®] 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 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 immunoanalyser. 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 can 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/ml and a limit of quantitation of 3.3 pg/ml (measuring range 1.9–4000 pg/ml). The DELFIA Xpress sFlt-1 has a limit of detection of 3.79 pg/ml and a limit of quantitation of 7.6 pg/ml (measuring range 3.79–19,500 pg/ml).

The **BRAHMS[™] PLGF plus Kryptor[™] test** (ThermoFisher Scientific, Waltham, MA, USA) 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 pre-eclampsia ratio is formed by combining the results from two 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 pre-eclampsia 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 22–90,000 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 3.6–7000 pg/ml) and a limit of quantitation of 6.9 pg/ml.

Current service provision

NICE's 2016 diagnostic guidance⁷ 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 pre-eclampsia 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.⁷ 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 pre-eclampsia 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 2016,⁷ further research evaluating use of PLGF-based testing has been conducted, some of which has been published and some currently ongoing. 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 were also identified. An update of NICE DG23 was therefore agreed. Likewise, this report updates the diagnostic assessment report (DAR) by Frampton *et al.*⁶ which informed the 2016 NICE guidance (hereafter, we refer to this report as 'the previous DAR').

A research protocol (registered on the PROSPERO database, CRD42020227085), describes, a priori, the scope, decision problem and methods to be used in this study.

Chapter 2 Definition of the decision problem

The decision problem is based on NICE's scope for this updated diagnostic assessment. The scope is similar to that of the original diagnostic assessment (DG23)⁷ in terms of relevant diagnostic tests, population, comparator tests and outcome measures.

Decision problem

The diagnostic tests under evaluation (the index test) are:

- the Triage PLGF test
- the Elecsys immunoassay sFlt-1/PLGF ratio
- the DELFIA Xpress PLGF 1-2-3 test/DELFIA Xpress sFlt-1 kit
- the BRAHMS sFlt-1 Kryptor/BRAHMS PLGF plus Kryptor PE ratio.

Scoping work undertaken by NICE and the External Assessment Group (EAG) did not identify any other relevant PLGF-based tests 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 NICE 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 discussed later, not all studies provide clinicians with results of the PLGF-based tests to inform care decisions. We therefore categorise 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
- '**stand-alone**', 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, but we focus on the evidence for add-on testing to reflect how the test is used in clinical practice. We regard stand-alone 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, based on 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 inpatient 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 *Inclusion and exclusion criteria*.

Overall aims and objectives of assessment

The aim of this study 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 are to update the systematic review of diagnostic test evaluations, and the systematic review of cost-effectiveness studies and the decision analytic model-based economic evaluation, reported in Frampton *et al.*⁶ and which informed NICE's 2016 DG23.⁷ The results of this update inform NICE's update of the 2016 guidance.

Chapter 3 Methods

Identification of studies

The comprehensive literature search strategy used in the previous DAR⁶ 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 (see [Results of the systematic review of test accuracy and clinical effectiveness](#)) and the systematic review of cost-effectiveness (see [Systematic review of cost-effectiveness evidence](#)).

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 and 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 Health Technology Assessment 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; ISSHP; 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; AC OG; 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); ClinicalTrials.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 18 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 was not limited to any particular study type or outcome, the same search results were reviewed for the economic evaluations. In addition, a separate search for HRQoL was carried out (see [Methods for review and data extraction of health-related quality-of-life studies](#)).

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 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 $\geq 70\%$ of the study population had suspected pre-eclampsia. Since 2019, the NICE guideline NG133¹ has included suspected fetal compromise as suggestive of pre-eclampsia and clinical experts to the EAG confirmed that 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 pre-eclampsia 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 DAR⁶ 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 were therefore not eligible for inclusion in this appraisal update. To ensure continuity between the original NICE diagnostic assessment and the updated diagnostic assessment, 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 'stand-alone' test use studies. We include stand-alone 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 inpatient hospital stay; time to delivery; gestation at diagnosis of pre-eclampsia; use of antihypertensive drugs, HRQoL.
- **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 (see [Appendix 1](#)) 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 texts 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).

Data extraction strategy

Relevant data were extracted from each included study into a structured data extraction template in Microsoft Word (Microsoft Corporation, Redmond, WA, USA), 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.

Risk of bias and study critical appraisal

We critically appraised the study methods and assessed the risk of bias of the included add-on studies using criteria relevant to each respective study design and outcome measures.

- Add-on studies reporting the diagnostic/prognostic accuracy of PLGF-based testing were appraised using the quality assessment of diagnostic accuracy studies 2 (QUADAS-2) tool.¹³
- Add-on studies reporting clinical effectiveness outcomes were appraised by one of two sets of criteria as relevant to their design.
 - RCTs were appraised using the Cochrane Risk of Bias tool for randomised trials (version 1).⁸
 - Non-randomised studies (e.g. observational studies) were appraised using the Cochrane Effective Practice and Organisation of Care risk of bias criteria for non-randomised studies.⁹

(NB. Revised versions of some of these critical appraisal tools are available, but this does not negate the validity of the risk-of-bias assessments made with the older versions in this report.) Where a study reports both diagnostic/prognostic accuracy and clinical effectiveness outcomes, we appraised the evaluation of test accuracy using QUADAS-2 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 [Critical appraisal of test accuracy in the add-on studies](#).

It was not practical in the time available to critically appraise the included stand-alone studies. However, we describe the general methodological strengths and limitations of these studies, when relevant, later in this report (see [Quantity and quality of research available](#) and [Report Supplementary Material 1](#)).

Method of data synthesis

As we discuss later in this report (see [Chapter 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 including random and non-randomised data 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, as with the previous DAR,⁶ 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 [Assessment of test accuracy \(add-on studies\)](#) to [Length of stay \(neonatal\)](#). Within these sections, we also present brief key findings of the stand-alone studies, for context. The results of the stand-alone studies themselves are presented in more detail in [Report Supplementary Material 1](#).

Chapter 4 Assessment of diagnostic test and clinical effectiveness studies

Results of the systematic review of test accuracy and clinical effectiveness

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, while 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 their study met our inclusion criteria. Independent screening of the full-text reports by 2 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 18 March 2021 to identify any relevant literature published since the November 2020 search. We identified a further 130 unique references which were then independently screened by 2 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,^{10,14} and two which report studies not already identified.^{15,16}

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 2](#)). Twenty-four unique studies, reported in a total of 44 publications, met the inclusion criteria for the systematic review ([Figure 2](#)). 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](#)).

Studies excluded post hoc

As mentioned earlier, of the 24 studies which met the inclusion criteria, we subsequently excluded 7 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 stand-alone 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 address evidence gaps not already covered by the included studies in this review:

- Three studies^{50–52} employed diagnostic 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.*,⁵⁰ was included in the previous DAR.⁶
- Two studies^{53,54} 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.*¹⁶ 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 PROGNOSIS Asia study whose gestational age at enrolment was 18⁺⁰–36⁺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.

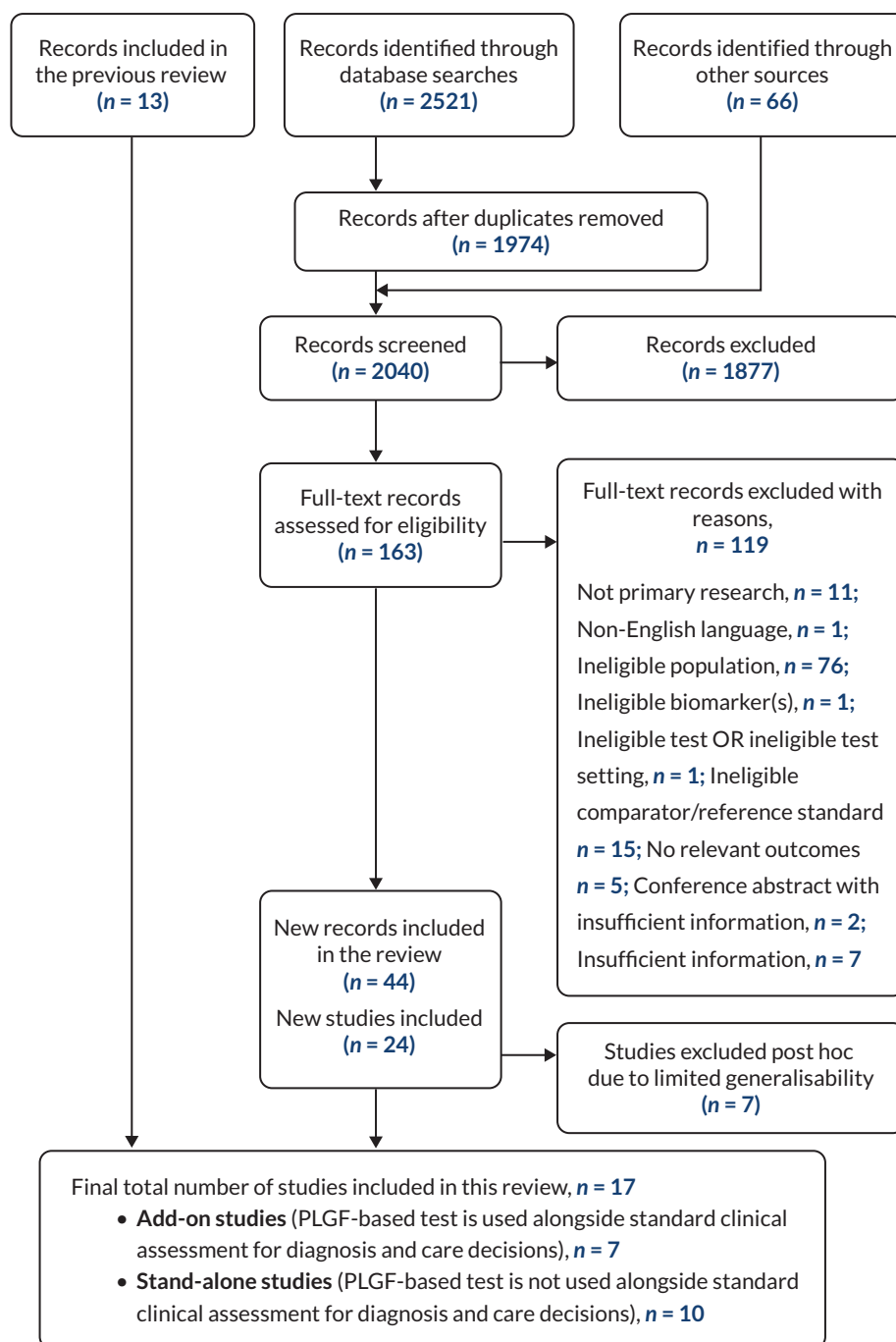


FIGURE 2 Flow chart for the identification of studies in the systematic review of test accuracy and clinical effectiveness.

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,¹⁹ MAPPLE³⁰ (Triage test) and INSPIRE³² (Elecsys sFit-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,¹⁹ INSPIRE³²) or as an indirect unadjusted comparison between a patient cohort and a separate cohort in another study (MAPPLE³⁰). 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 study⁴⁶ compares the clinicians' decisions recorded both before and after receiving the test results, at which point they could amend their original decision. All studies took place in Europe: Germany, Austria,

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)	Stand-alone test (result concealed from clinicians and used alone in statistical analyses for predicting outcomes)
Triage PLGF test	Test accuracy and comparative clinical outcomes: • <u>PARROT</u>¹⁷⁻¹⁹ (cluster RCT)^a Comparative clinical outcomes: • <u>MAPPLE</u>³⁰ (prospective cohort study, comparing to PELICAN cohort)^b Test accuracy outcomes: • <u>Ormesher 2018</u>³¹ (single group, prospective clinical evaluation; high-risk pregnancies only)	Test accuracy outcomes: • <u>PELICAN</u>^{11,12,20-22}/<u>PEACHES</u>²³ (prospective observational study; PEACHES included a cohort of from the PELICAN study) • <u>PETRA</u>²⁴⁻²⁸ (prospective cohort study) • <u>COMPARE</u>²⁹ (retrospective analysis of blood samples from three prospective cohort studies)^c
Elecsys sFlt-1/PLGF ratio	Test accuracy and comparative clinical outcomes: • <u>INSPIRE</u>^{32,33} (RCT)^a Comparative clinical outcomes: • <u>PreOS</u>⁴⁶ (before- and-after study design)^d Test accuracy outcomes: • <u>Binder 2020</u>⁴⁷ (single cohort; retrospective analysis; twin pregnancies only)^e	Test accuracy outcomes: • <u>PROGNOSIS</u>³⁴⁻⁴⁰ (prospective observational study) • <u>PROGNOSIS Asia</u>^{41,42} (prospective observational study) • <u>ROPE</u>⁴³ (prospective cohort study) • <u>Baltajian 2016</u>⁴⁴ (prospective cohort study) • <u>Wang 2021</u>¹⁵ (prospective cohort study) • <u>Salahuddin 2016</u>⁴⁵ (case-control study) • <u>Saleh 2016</u> (prospective cohort study) • <u>COMPARE</u>²⁹ (retrospective analysis of blood samples from three prospective cohort studies)^c
BRAHMS Kryptor sFlt-1/PLGF ratio	Test accuracy outcomes: • <u>Andersen 2019</u>⁴⁸ (single cohort; retrospective study)	Test accuracy outcomes: • <u>Salahuddin 2016</u>⁴⁵ (case-control study)
Delfia Xpress test	^f No studies met the inclusion criteria (Bremner <i>et al.</i> , 2022 used in economic model). ⁴⁹	Test accuracy outcomes: • <u>COMPARE</u>²⁹ (retrospective analysis of blood samples from three prospective cohort studies)^c

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 were taken into account in care decisions) and the PELICAN cohort (where clinicians were not informed of the test result).^{20,21}

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.

f Since completion of this systematic review, a study (stand-alone) has been published comparing the diagnostic accuracy of the DELFIA Xpress PLGF 1-2-3 test with the DELFIA sFlt1/PLGF ratio test.⁴⁹ We include this study in our economic evaluation (see [Chapter 5](#)).

Note

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).

Denmark and the UK (with one Australian site in the MAPPLE study³⁰). The larger comparative studies took place in the UK: PARROT¹⁹ with a total study population of 1023 and INSPIRE³² with a total study population of 370. An overview of the design of the add-on studies is in [Table 2](#).

The strongest evidence, therefore, comes from the large, UK-based RCTs: PARROT¹⁹ for the Triage test and INSPIRE³² for the Elecsys test, supported by the cohort studies MAPPLE³⁰ for Triage and PreOS⁴⁶ for Elecsys. The Binder 2020⁴⁷ study provides data on multiple pregnancies and is discussed as a subgroup of interest in [Subgroups of interest](#) of this report. The evidence for the BRAHMS Kryptor test is limited to a retrospective cohort study, conducted outside of the UK, available only as a conference abstract when the systematic review was completed.⁴⁸ (Subsequent to the review the

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 ¹⁹	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 ³⁰	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 ³¹	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 randomised, 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 ⁴⁶	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 ⁴⁷	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
N/A, not application.					

study appears to have been published in a scientific journal).⁵⁵ There are 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 stand-alone test – the COMPARE²⁹ study (see the next subsection and also the [Report Supplementary Material 1](#)).

Characteristics of the stand-alone test studies

The stand-alone 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^{20,21} study (also a comparator arm for the MAPPLE³⁰ add-on study, as noted above).

All, except one study, were prospective cohort studies with the main difference between them being whether they were small single-centre studies (Baltajian 2016,⁴⁴ Saleh 2016⁵⁶), or were large multicentre studies (PELICAN,^{20,21} PETRA,^{24,26} PROGNOSIS,^{34–40} PROGNOSIS Asia⁴¹).

The only stand-alone study providing data on the BRAHMS Kryptor test (Salahuddin 2016⁴⁵) is also the only case-control study, using the remaining evaluable samples from a defined recruitment period in the ROPE⁴³ cohort (a

different recruitment period to the one reported in ROPE)⁴³ 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 receiver–operator characteristics (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 are derived from a single cohort. The test concordance aspect of the study (BRAHMS/Elecsys) is discussed in [Assessment of concordance between tests](#) of this report.

An overview of the design of the stand-alone studies is in [Table 3](#).

In summary, the stand-alone test studies mainly report test accuracy results and to a lesser extent test concordance data. Notably, stand-alone studies provide data for tests where evidence from add-on studies was limited: BRAHMS Kryptor test⁴⁵ and the DELFIA Xpress PLGF 1-2-3 test (COMPARE).²⁹

Classification of included studies as add-on (test results revealed) or stand-alone (test results concealed)

We categorised the 17 studies included in the systematic review (see [Table 1](#)) according to whether the results of the tests were used alongside standard clinical assessment to inform care decisions, referred to as ‘**add-on studies**’ $n = 7$ or studies in which the test results did not inform diagnosis or care decisions alongside standard clinical assessment, referred to as ‘**stand-alone**’ studies $n = 10$.

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 stand-alone tests, though not directly relevant to the scope, provide the next best evidence for the diagnostic/prognostic accuracy of the tests. The stand-alone set of studies features three key studies included in the previous DAR⁶ and thus which informed the original NICE guidance on this topic (NICE DG23) (PETRA,^{24,26} PELICAN^{20,21} and PROGNOSIS^{34–40}).

In the following subsections, 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 addition, we provide a narrative description of two of the add-on studies: the PARROT study (Triage PLGF test) and the INSPIRE study (Elecsys sFlt-1/PLGF ratio test) (see [Appendix 4](#)). These are two large UK-based RCTs which, as will become apparent in [Chapter 5](#) of this report, inform the base case in our economic evaluation.

TABLE 3 Overview of the included studies of stand-alone tests (result concealed)

Study	Location (centres)	Design	Total population analysed	Outcome types
<i>Triage PLGF test</i>				
PELICAN ^{20,21}	UK and Ireland (7 centres)	Prospective observational study	Enrolled: 649 Analysed: 625	Test accuracy; test concordance (PEACHES validation cohort)
PEACHES – validation cohort ²³	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 ^{24,26}	USA and Canada (24 centres)	Prospective single cohort	20 ⁺⁰ –35 ⁺⁰ weeks: Enrolled: $N = 757$ Analysed: $N = 753$ 35 ⁺⁰ –36 ⁺⁶ weeks: Enrolled: $N = 224$ Analysed: $N = 224$	Test accuracy

TABLE 3 Overview of the included studies of stand-alone tests (result concealed) (*continued*)

Study	Location (centres)	Design	Total population analysed	Outcome types
Elecsys sFlt-1/PLGF ratio				
PROGNOSIS ^{34–40}	Argentina, Australia, Austria, Belgium, Canada, Chile, Germany, the Netherlands, New Zealand, Norway, Peru, Spain, Sweden, UK (30 centres; 1 centre in the UK)	Prospective, multicentre, observational study	Total: 1050 Development cohort: 500 Validation cohort: 550	Test accuracy
PROGNOSIS Asia ⁴¹	China, Hong Kong, Japan, Singapore, Republic of Korea and Thailand (25 centres)	Prospective, multicentre, blinded, non-interventional study	Enrolled: 764 Analysed: 700 evaluable for the primary end-point analysis. Analysed: 690 evaluable for analysis of fetal adverse outcomes.	Test accuracy
ROPE ⁴³	USA (1 centre)	Prospective cohort study	Total: 402	Test accuracy
Baltajian 2016 ⁴⁴	USA (1 centre)	Prospective cohort study	Enrolled: 103 Analysed: 100	Test accuracy
Saleh 2016 ⁵⁶	The Netherlands (1 centre) ^a	Prospective cohort study	Total: 107	Test accuracy
Wang 2021 ¹⁵	China (1 centre)	Prospective cohort study	Enrolled: 200 Analysed: 196	Test accuracy
BRAHMS Kryptor sFlt-1/PLGF ratio				
Salahuddin 2016 ⁴⁵	USA (1 centre)	Case-control study using evaluable participants from a different recruitment period (to that reported above in Rana 2018 ⁴³) within the ROPE cohort and normative controls.	Available samples from previous cohort: 412 Normative controls: 434	Test accuracy; test concordance
DELFIAXpress PLGF 1-2-3				
COMPARE ²⁹	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

^a Study centre location(s) not reported, based on author affiliations.

Further detail of the characteristics of the stand-alone studies can be found in [Report Supplementary Material 1](#).

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-off 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,¹⁹ MAPPLE,³⁰ Ormesher 2018³¹), to 24⁺⁰ weeks (INSPIRE,³² PreOS,⁴⁶ Andersen 2019⁴⁸), and in one study testing was performed on a population with a gestational age within an interquartile range (IQR) of 30–35 weeks (Binder 2020⁴⁷). 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 2020⁴⁷ study additionally investigated ratio cut-offs of > 80 and > 67 and intermediate values of 38–80 and 38–67 as it was investigating different sFlt-1/PLGF ratio measures in twin pregnancies. However, only the cut-off of 38 in the Binder 2020⁴⁷ study is assessed in this review because the others do not match the cut-offs recommended by the

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 ¹⁹	20 ⁺⁰ –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. ⁵⁷
MAPPLE ³⁰	20 ⁺⁰ –34 ⁺⁶	Derived from PELICAN ²⁰ study: < 12 pg/ml (very low) 12–100 pg/ml (low; representing < fifth 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 ^a
Ormesher 2018 ³¹	20 ⁺⁰ –36 ⁺⁶	PLGF was classified as either normal (> 100 pg/ml), intermediate (13–100 pg/ml) or low (< 12 pg/ml).	A care pathway was developed incorporating standard clinical management guidelines (NICE CG107 ⁵⁸ and RCOG Greentop Guideline no. 31) ⁵⁹ with inclusion of the PLGF result.	ISSHP 2014 ⁵⁷ and ACOG 2013 ⁶⁰ criteria.
Elecsys sFlt-1/PLGF ratio				
INSPIRE ³²	24 ⁺⁰ –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 ⁵⁷ and ACOG 2013 ⁶⁰ criteria.
PreOS ⁴⁶	24 ⁺⁰ –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-1/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 ⁴⁷	IQR 30–35	Cut-off < 38 assessed for ruling out delivery within 1 and 2 weeks Cut-offs of > 80 and > 67 and intermediate values of 38–80 and 38–67 also assessed for predicting delivery within 1 and 2 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. ⁵⁷
BRAHMS Kryptor sFlt-1/PLGF ratio				
Andersen 2019 ⁴⁸	24 ⁺⁰ –37 ⁺⁰	33 and 85 (rationale and purpose not reported)	Women had had a sFlt1/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.

CG107, clinical guideline 107.

^a MAPPLE was not a diagnostic accuracy study, comparison of clinical outcomes only.

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 2 weeks; the cut-off of 33 correlates with the Elecsys sFlt-1/PLGF ratio to rule out pre-eclampsia in the short term.

- **Use of test results to inform care.** Four studies (PARROT,¹⁹ MAPPLE,³⁰ Ormesher 2018,³¹ INSPIRE³²) incorporated test results into local clinical care algorithms; one study (PreOS⁴⁶) 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 2020,⁴⁷ Andersen 2019⁴⁸) 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,¹⁹ Binder 2020⁴⁷) used the ISSHP 2014 criteria;⁵⁷ one study (Andersen 2019⁴⁸) used the Danish guidelines based on the ISSHP criteria, which version is not reported; two studies (INSPIRE,³² Ormesher 2018³¹) referred to both ISSHP 2014⁵⁷ and ACOG 2013⁶⁰ criteria; one study (PreOS⁴⁶) referred to their protocol definitions which reference ISSHP 2001⁶¹ criteria for pre-eclampsia and ACOG 2002⁶² for severe pre-eclampsia.

The updated ISSHP 2014⁵⁷ criteria and ACOG 2013⁶⁰ criteria include proteinuria, but its concomitant presence alongside other criteria is not required. Therefore, the PreOS study,⁴⁶ and potentially the Andersen 2019 study,⁴⁸ used a narrower definition of pre-eclampsia than the other studies.

Approach to stand-alone test use

An overview of the diagnostic test aspects of the stand-alone studies is in [Table 5](#).

- **Gestational age at testing.** Testing was performed from 20⁺⁰ weeks in three studies (PELICAN,^{20,21} PETRA,^{24,26} PROGNOSIS Asia⁴¹), and slightly later in other studies, from 22 weeks (Saleh 2016⁵⁶), and from 24 weeks (PROGNOSIS^{34–40}).
- **Test cut-off values.** All the stand-alone 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 time points across the studies: in one study (PELICAN^{20,21}), the tests were run, but the results were masked from the clinicians and participants; for most studies (PROGNOSIS,^{34–40} PROGNOSIS Asia,⁴¹ ROPE,⁴³ Baltajian 2016,⁴⁴ Salahuddin 2016⁴⁵), the tests were not run until after all deliveries and clinical outcomes were measured.
- **Diagnostic criteria.** Criteria used to define pre-eclampsia varied more than for the add-on studies, including the earlier ACOG 2002⁶² and ISSHP 2001⁶¹ criteria and/or the updated ACOG 2013 criteria⁶⁰ and ISSHP 2014 statement⁵⁷ (likely due to study start date). This indicates less consistency in the use of proteinuria as a diagnostic criterion across the studies.

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,¹⁹ MAPPLE,³⁰ Ormesher 2018,³¹ INSPIRE,³² PreOS,⁴⁶ Binder 2020.⁴⁷ ([Table 6](#)) This list contains MAPPLE³⁰ and Ormesher 2018³¹ which included suspected FGR as a presenting condition, which in itself is a sign of suspected pre-eclampsia as the current NICE guidance includes 'suspected fetal compromise'.¹ 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 the stand-alone studies comprised only women with suspected pre-eclampsia ([Table 7](#)).

TABLE 5 Overview of the approach to stand-alone 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 ^{20,21}	20 ⁺⁰ –34 ⁺⁶ 35 ⁺⁰ –36 ⁺⁶	Normal: PLGF ≥ 5th centile for gestational age. Positive, low: < 5th centile. Positive, very low: < 12 pg/ml.	All test meters were programmed to produce a masked result, indicating 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.	ACOG practice bulletin 2002 ⁶² for pre-eclampsia, severe pre-eclampsia and super-imposed pre-eclampsia. ISSHP 2001 ⁶¹ for atypical pre-eclampsia.
PEACHES – validation cohort ²³	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 categorised according to outcome at delivery. Plasma samples were tested without awareness of clinical outcomes.	As above for PELICAN
PETRA ^{24,26}	20 ⁺⁰ –34 ⁺⁶ 35 ⁺⁰ –36 ⁺⁶	Preterm pre-eclampsia: 12 pg/ml Preterm 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 ⁶² and 2013, ⁶⁰ and pre-specified in the protocol.
Elecsys sFlt-1/PLGF ratio				
PROGNOSIS ^{34–40}	24 ⁺⁰ –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, ⁶¹ ACOG Practice Bulletin 2002. ⁶²
PROGNOSIS Asia ⁴¹	20 ⁺⁰ –36 ⁺⁶	sFlt-1/PLGF ratio cut-off of 38	The maternal serum samples were analysed retrospectively at two 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 ⁶¹ diagnostic criteria to align with the PROGNOSIS study.
ROPE ⁴³	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, ⁶⁰ including ACOG criteria for diagnosing pre-eclampsia with severe features.
Baltajian 2016 ⁴⁴	< 37 (IQR 31–35)	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 analysed 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. ⁶⁰
Saleh 2016 ⁵⁶	22–36	Cut-off of ≥ 85 for diagnosing pre-eclampsia and for predicting adverse outcomes and prolongation of pregnancy.	Blood samples were taken at time of admission, centrifuged and stored at –80 °C until analysis. Values of sFlt-1 and PLGF were determined after delivery to prevent any influence on clinician decision making.	Pre-eclampsia was defined according to the ISSHP 2001 ⁶¹ criteria and based on clinical judgement and routine laboratory findings.

TABLE 5 Overview of the approach to stand-alone test use (continued)

Study	Timing of the tests (GA weeks)	Test diagnostic cut-off(s)	Use of the test	Reference standard diagnostic criteria
Wang 2021 ¹⁵	20–36	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 ⁶³
BRAHMS Kryptor sFlt-1/PLGF ratio				
Salahuddin 2016 ⁴⁵	IQR 28.7–33 (< 34 group) IQR 33.6–38.0 (total)	sFlt-1/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. ⁶⁰
DELTA Xpress PLGF 1-2-3				
COMPARE ²⁹	20 ⁺⁰ –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 ⁵⁷

Characteristics of participants in the add-on studies

The key demographic and maternal health characteristics of the participants are shown in [Tables 8](#) and [9](#), except for Andersen *et al.*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 *et al.*⁴⁷ 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 PreOS⁴⁶ 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 *et al.*⁴⁷ which had a slightly greater proportion of nulliparous participants at 55%, 60% or 71% depending on the outcome group. Binder *et al.*⁴⁷ also report a slightly lower BMI for participants and the range does not reach 30 kg/m^2 , whereas participants in the other studies reached 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: PARROT¹⁹ (66% revealed arm, 65% concealed arm), MAPPLE³⁰ (91% revealed arm, 66% concealed arm) and INSPIRE³² (89% revealed arm, 90% concealed arm). Other ethnicities are not reported consistently across studies. The PreOS study,⁴⁶ 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 *et al.*⁴⁷ did not report ethnicity.

Only MAPPLE³⁰ and INSPIRE³² 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;⁴⁷ some studies had a mixture of singleton and multiple pregnancies (MAPPLE,³⁰ PreOS⁴⁶) (although in MAPPLE³⁰ women with twin pregnancies were excluded from the adjusted comparison with PELICAN²⁰), while other studies included singleton pregnancies only (PARROT,¹⁹ INSPIRE³²). A recent study demonstrated that maternal plasma PLGF in twin pregnancy follows the same gestational pattern as described in singletons and therefore

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 ¹⁹	(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, FGR, or abnormal maternal blood tests that indicated disease. Proportions are reported in participant characteristics.
MAPPLE ³⁰	(All.) Suspected pre-eclampsia or FGR < 35 weeks gestation.	Symptoms/signs included headache, visual disturbances, epigastric or right upper quadrant pain, hypertension, dipstick proteinuria, or suspected FGR.
Ormesher 2018 ³¹	(All.) High-risk pregnant women with suspected pre-eclampsia or FGR.	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, oedema or right upper quadrant pain or any other suspicion of pre-eclampsia.
PreOS ⁴⁶	(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 ⁴⁷	(All.) Presenting condition was suspected pre-eclampsia.	Symptoms of pre-eclampsia including epigastric pain, new-onset oedema, 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 ($\geq$ 140/90 mmHg), dyspnoea, 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, stand-alone studies (result concealed)

Study	Proportion of population with suspected pre-eclampsia	Reasons for suspected pre-eclampsia
Triage PLGF test		
PELICAN ^{20,21}	(All.) Inclusion criteria were 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 ²³	(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 ^{24,26}	(All.) Inclusion criteria required signs or symptoms of pre-eclampsia.	Not stated which of the signs and symptoms listed in the population baseline characteristics raised suspicion of pre-eclampsia.

TABLE 7 Reasons for suspecting pre-eclampsia, stand-alone studies (result concealed) (*continued*)

Study	Proportion of population with suspected pre-eclampsia	Reasons for suspected pre-eclampsia
Elecsys sFlt-1/PLGF ratio		
PROGNOSIS ³⁴⁻⁴⁰	(All.) Inclusion criteria specify 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 oedema/severe swelling (face, hands, feet), headache, visual disturbances, sudden weight gain (> 1 kg/week in the third trimester, low platelets, elevated liver transaminases, (suspected) IUGR, 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 ⁴¹	(All.) Inclusion criteria specify women with suspected pre-eclampsia.	One or more of the following, new onset of hypertension [systolic blood pressure (BP) ≥ 140 mmHg or diastolic BP ≥ 90 mmHg, single measurement], aggravation of pre-existing hypertension (systolic BP ≥ 160 mmHg or diastolic BP ≥ 110 mmHg, 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 ⁴³	(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 oedema.
Baltajian 2016 ⁴⁴	(All.) Women admitted for evaluation of pre-eclampsia.	Reasons for suspecting pre-eclampsia were not reported.
Saleh 2016 ⁵⁶	(All.) Women were recruited at time of admission for suspected pre-eclampsia.	Patients were suspected of pre-eclampsia 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 ¹⁵	(All.) Women presenting with suspected pre-eclampsia.	At least one of the following: new onset of hypertension (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, oedema, visual impairment, abnormal weight gain (> 1 kg/week), decreased platelets (< 150 × 10 ⁹ /l), elevated liver transaminase (alanine transferase > 55 U/l or aspartate transaminase > 34 U/l), FGR (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 ⁴⁵	(All.) As above for the ROPE study.	As above for the ROPE study.
DELTA Xpress PLGF 1-2-3		
COMPARE ²⁹	(All.) As above for the PELICAN and PEACHES studies.	As above for the PELICAN and PEACHES studies.

TABLE 8 Characteristics of participants in the Triage add-on test studies

Population characteristic	PARROT ¹⁹ revealed arm	PARROT ¹⁹ concealed arm	MAPPLE ³⁰ revealed arm	MAPPLE ³⁰ concealed arm	Ormesher 2018 ³¹
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 (23 ⁺⁰ –40) PE: 31 (23–41) SGA: 32 (23–38)
Parity, n (%)	0 : 317 (55) 1 : 133 (23) 2 : 59 (10) ≥ 3 : 67 (12)	0 : 211 (47) 1 : 120 (27) 2 : 65 (15) ≥ 3 : 51 (11)	0 : 208 (52.7)	0 : 164 (57.1)	Not reported
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	^a PreOS ⁴⁶	Binder 2020 ⁴⁷
Measure (variance)	Median (IQR)		Median (minimum–maximum)	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 weeks due to PE: 36.0 (31.2–38.0) Delivery > 2 weeks 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 ^a	Delivery ≤ 1 week due to PE: 35.0 (33.0–36.1) Delivery ≤ 2 weeks due to PE: 34.3 (32.9–36.0) Delivery > 2 weeks 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 weeks due to PE: 0 : 25 (59.5) Delivery > 2 weeks 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 weeks due to PE: 25.1 (21.9–29.1) Delivery > 2 weeks 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

TABLE 9 Characteristics of the participants in the Elecsys add-on test studies (*continued*)

Population characteristic	INSPIRE ³² revealed arm	INSPIRE ³² concealed arm	^a PreOS ⁴⁶	Binder 2020 ⁴⁷
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

^a Data shown here for the full analysis population of the PreOS study, except for gestational age which was only reported for the safety population.

we need not discount evidence from studies including multiple pregnancies in the population.⁶⁴ 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.^{65–68} A clinical expert 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.

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,¹⁹ MAPPLE³⁰) and two of the Elecsys test studies (PreOS⁴⁶ and Binder *et al.* 2020⁴⁷) (Table 10).

All four studies reported 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 PreOS⁴⁶ (14%) than in PARROT¹⁹ (52% revealed arm) or MAPPLE³⁰ (80% revealed arm); however, PreOS⁴⁶ 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 PARROT¹⁹ study at 59% (both study arms) compared to 4% in PreOS.⁴⁶ The PreOS study⁴⁶ 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 (3–15.9%). 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 FGR. All other prognostic characteristics were only reported by one or two studies (see Table 10). Ormesher *et al.* (2018),³¹ which only reports suspected FGR (51%) and both suspected pre-eclampsia and suspected FGR (20%), is not included in Table 10.

The studies report differing aspects of medical history relevant to pre-eclampsia. (NB. INSPIRE³² does not report any.) These include:

- previous pre-eclampsia, range 7–39% (PARROT,¹⁹ MAPPLE,³⁰ PreOS⁴⁶)
- previous hypertensive disorder of pregnancy (excluding pre-eclampsia), range 2–6% (MAPPLE³⁰)
- previous eclampsia, 1% (PreOS⁴⁶)
- previous HELLP, 4% (PreOS⁴⁶)
- family history of pre-eclampsia, 1% (PreOS⁴⁶)
- chronic hypertension, range 14–16% (PARROT,¹⁹ MAPPLE³⁰)
- pre-existing hypertension, range 14–55% (Ormesher 2018³¹)
- pre-existing renal disease, range 4–7% (PARROT,¹⁹ MAPPLE³⁰)
- diabetes, range 2–17% (PARROT,¹⁹ MAPPLE,³⁰ Ormesher 2018³¹)
- gestational diabetes, range 12%/12% (PARROT¹⁹)
- being prescribed prophylactic aspirin, range 41–40% (PARROT¹⁹)
- antihypertensive medication, 14% (Binder 2020⁴⁷)
- systemic lupus erythematosus/antiphospholipid syndrome, range 2–4% (MAPPLE³⁰)
- early pregnancy proteinuria, range 4–23% (Ormesher 2018³¹).

TABLE 10 Prognostic characteristics of participants in the Triage and Elecsys add-on studies

Prognostic characteristic	Triage		Elecsys	
	PARROT ¹⁹	MAPPLE ³⁰	^a PreOS ⁴⁶	Binder 2020 ⁴⁷
New-onset hypertension, <i>n</i> (%)	Revealed: 299 (52) Concealed: 209 (47)	Revealed: 314 (79.5) Concealed: 155 (54.0)	27 (14.1)	Not reported
Worsening of existing hypertension, <i>n</i> (%)	Revealed: 100 (17) Concealed: 79 (18)	Not reported	24 (12.5)	Not reported
New onset of elevated blood pressure, <i>n</i> (%)	Not reported	Not reported	69 (35.9)	Delivery ≤ 1 week due to PE: 25 (86.2) Delivery ≤ 2 weeks due to PE: 38 (90.5) Delivery > 2 weeks due to PE or other: 71 (58.2)
New-onset proteinuria, <i>n</i> (%)	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 weeks due to PE: 18 (42.8) Delivery > 2 weeks due to PE or other: 19 (15.6)
Epigastric or right upper-quadrant pain, <i>n</i> (%)	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 weeks due to PE: 2 (4.7) Delivery > 2 week due to PE or other: 16 (13.1)
Neurological symptoms, <i>n</i> (%)	Revealed: 187 (32) Concealed: 150 (34)	Not reported	Not reported	Delivery ≤ 1 week due to PE: 4 (13.8) Delivery ≤ 2 weeks due to PE: 6 (14.3) Delivery > 2 weeks due to PE or other: 9 (7.4)
New-onset oedema	Not reported	Not reported	Not reported	Delivery ≤ 1 week due to PE: 16 (55.2) Delivery ≤ 2 weeks due to PE: 24 (57.1) Delivery > 2 weeks due to PE or other: 36 (29.5)
Dyspnoea, <i>n</i> (%)	Not reported	Not reported	Not reported	Delivery ≤ 1 week due to PE: 0 (0.0) Delivery ≤ 2 weeks due to PE: 0 (0.0) Delivery > 2 weeks due to PE or other: 5 (4.1)
Abnormal blood test results, <i>n</i> (%)	Revealed: 19 (3) Concealed: 8 (2)	Not reported	Low platelets: 14 (8.5) Elevated liver transaminases: 12 (7.3)	Delivery ≤ 1 week due to PE: Low platelets: 3 (10.3) Elevated liver enzymes: 2 (6.9) Delivery ≤ 2 weeks due to PE: Low platelets: 3 (7.1) Elevated liver enzymes: 3 (7.1) Delivery > 2 weeks due to PE or other: Low platelets: 6 (4.9) Elevated liver enzymes: 6 (4.9)
Suspected FGR, <i>n</i> (%)	Revealed: 103 (18) Concealed: 62 (14)	Revealed: 66 (16.7) Concealed: 25 (8.7)	49 (29.9)	Not reported
Reduced fetal movement, <i>n</i> (%)	Revealed: 6 (1) Concealed: 5 (1)	Not reported	Not reported	Not reported

PE, pre-eclampsia.

^a A further breakdown of prognostic characteristics by PLGF level and trial arm is also reported for this study.¹⁴^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.**Note**Andersen 2019⁴⁸ for the BRAHMS Kryptor test is a conference abstract and did not report prognostic characteristics. It is therefore not included in this table.The INSPIRE study³² and Ormesher 2018³¹ did not report prognostic characteristics of participants and are not included in this table.

Three of the studies report blood pressure levels at baseline, but they use different measures of variance so it is difficult to compare (PARROT,¹⁹ INSPIRE,³² Binder *et al.* 2020⁴⁷), and two studies report proteinuria at baseline, either the proportion of participants with proteinuria (MAPPLE³⁰), or by level of proteinuria (PARROT¹⁹).

Critical appraisal of test accuracy in the add-on studies

We applied the QUADAS-2¹³ critical appraisal tool to assess the risk of bias and applicability of test accuracy data in the add-on studies (see [Table 42](#), [Appendix 1](#)). 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 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 individual pregnant women were enrolled in the study, resulting in an unclear risk of bias. Across the other domains of bias, our judgements are that the studies are low risk of bias.

In terms of applicability of the studies' findings to our systematic 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 stand-alone test only; thus, the test accuracy results have limited applicability to the decision problem. However, the clinical outcomes, measured in the concealed and revealed arms of the trial, are relevant.

We note that the purpose of the Binder *et al.* study was to identify cut-offs in twin pregnancies that optimised positive predictive values (PPVs) and negative predictive values (NPVs) for this population, and by default the cut-offs were not pre-specified. The paper also did not clearly report the cut-offs for which the test accuracy findings were presented, so the applicability of the findings to this review were unclear.

Although we did not identify any applicability issues in how the PLGF test was used in the Ormesher *et al.* study, we note that the test was used in a slightly different way to the other studies. Specifically, 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. In the other studies, the PLGF test was done once and not repeated.

Critical appraisal of risk of bias of clinical effectiveness outcomes in randomised controlled trials (add-on)

We used the Cochrane risk of bias tool for randomised trials (version 1)⁸ 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 low risk of bias, with a couple of exceptions in each trial (see [Table 42](#), [Appendix 1](#)).

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, while for PARROT it was not explicitly stated whether the assessment of clinical outcomes (all of which were secondary outcomes) was without knowledge of assignment. Detection bias is less likely for those clinical outcomes which, by their nature, are indisputable 'hard' end points (e.g. mortality, hospitalisation, delivery, stillbirth).

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 the outcome measures the authors intended to measure (as stated in the trial protocol).

A narrative summary of the PARROT and INSPIRE studies is given in [Appendix 4](#).

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 (stand-alone studies) are summarised briefly (further data for these studies are in the [Report Supplementary Material 1](#)).

An overview of the test accuracy data available from the seven included add-on studies is summarised in [Appendix 5](#).

Testing to predict pre-eclampsia

Triage placental growth factor test

Ormesher *et al.*³¹ 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 11](#)).

Two stand-alone studies (PETRA, PELICAN)^{22,24} 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 pre-eclampsia at any time point (see [Report Supplementary Material 1](#)).

Elecsys soluble fms-like tyrosine kinase-1/placental growth factor ratio test

In the original INSPIRE published manuscript,³² test accuracy data are provided only for the use of the test cut-off of < 38 for ruling out pre-eclampsia within 1 week, with a NPV of 0.992 ([Table 12](#)). A post hoc analysis of the INSPIRE study with women who presented with suspected pre-eclampsia from 24⁺⁰ to 36⁺⁶ weeks reported the NPVs using a sFlt-1/PLGF ratio cut-off of < 38 for ruling out pre-eclampsia within 1, 2, 3 weeks and 4 weeks.⁶⁹ 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 high, exceeding 0.96, and with relatively narrow 95% confidence intervals (CIs; lower limit exceeding 0.92) (data not shown here).

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 (see [Table 12](#)).

Similarly, high NPVs (> 0.9) were reported at a cut-off of 38 for prediction of pre-eclampsia at various time points in stand-alone studies: PROGNOSIS^{34,37,70} (within 1, 2, 3 and 4 weeks), PROGNOSIS Asia⁴¹ (within 1 and 4 weeks), Wang¹⁵ (within 4 weeks) and ROPE⁴³ (pre-eclampsia with severe features within 2 weeks). At the lower cut-off (< 38), PPVs

TABLE 11 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
<i>Ormesher et al.³¹ Triage PLGF test, result concealed, after 20 and < 37 weeks' gestation</i>							
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

CI, confidence interval.

^a 95% CI not reported.^b Calculated by reviewer.**TABLE 12** Prediction of pre-eclampsia by time point (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)
<i>INSPIRE,³² Elecsys ratio (result revealed arm, using test result only), 24⁺⁰–37⁺⁰ weeks</i>							
Within 1 week	> 38	186	0.958 (0.789 to 0.999)	0.796 (0.726 to 0.855)	0.411 (0.281 to 0.550)	0.992 (0.958 to 1.000)	12.90 ^a (8.45 to 18.59)
<i>INSPIRE,³³ Elecsys ratio plus standard clinical interpretation (result revealed arm), 24⁺⁰–37⁺⁰ weeks</i>							
Within 4 weeks (rule in) ^b	≥ 85	186	0.571 (0.394 to 0.737)	0.947 (0.898 to 0.977)	0.714 (0.513 to 0.868)	NR	NR
<i>INSPIRE,³² Elecsys ratio (result concealed arm), 24⁺⁰–37⁺⁰ weeks</i>							
Within 4 weeks (rule in) ^b	≥ 85	184	0.643 (0.441 to 0.814)	0.955 (0.910 to 0.982)	0.720 (0.506 to 0.879)	NR	NR
<i>Andersen et al.,⁴⁸ BRAHMS Kryptor sFlt-1/PLGF ratio used alongside clinical care, 24⁺⁰–37⁺⁰ weeks</i>							
Within 1 week	33	300	NR	NR	NR	0.960	20 ^a
	85	300	NR	NR	0.460	NR	20 ^a
Within 4 weeks	33	300	NR	NR	NR	0.940	20 ^a
	85	300	NR	NR	0.620	NR	20 ^a

NR, not reported.

^a Calculated by reviewer.^b Author emphasis.

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 < 34 weeks gestation (see [Report Supplementary Material 1](#)). Saleh et al.⁵⁶ reported high PPVs (> 0.9) at a test cut-off > 85 for the diagnosis/prediction of pre-eclampsia at study inclusion and at final diagnosis (see [Report Supplementary Material 1](#)).

BRAHMS Kryptor soluble fms-like tyrosine kinase-1sFlt-1/placental growth factor 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 (see [Table 12](#)).

DELFIA Xpress placental growth factor test

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

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.*³⁴ (a stand-alone study) conducted a post hoc analysis of the PROGNOSIS validation cohort ($N = 550$), 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).

Assessment of concordance between tests

The previous DAR⁶ found no studies which compared the predictive accuracy of the four tests in a relevant population who had suspected pre-eclampsia. Our literature search identified 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 (see [Appendix 3](#)). 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.*⁷¹ identified intertest 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 pre-eclampsia. 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.*²⁹ conducted a secondary analysis, called the COMPARE study, which utilised PLGF samples from women in the PEACHES study²³ and in parts 1 and 2 of the PELICAN study^{20,21} who had presented with suspected pre-eclampsia 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 a SGA infant.] McCarthy *et al.* compared the commercially recommended cut-offs for the Triage PLGF test (< 100 pg/ml), the Elecsys test sFlt-1/PLGF ratio (> 38) and an optimally derived cut-off for the 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 similar among the tests (full test accuracy statistics for the three tests are provided in the publication²⁹). 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 diagnostic assessment since it comprises women suspected of having pre-eclampsia as well as those suspected of having a SGA infant.

Giblin *et al.*⁷² conducted a further secondary analysis of PLGF samples from women in the PELICAN and PEACHES studies who presented with suspected pre-eclampsia or a suspected SGA infant (as assessed in the COMPARE study²⁹). 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, Elecsys and DELFIA Xpress tests. They concluded that the Triage and Elecsys tests have slightly different sensitivities and specificities, but area under the curve (AUC) was similar and the test had similar clinical applicability for prediction of delivery. That said, there was a threefold 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, for example by converting biomarker concentrations to multiples of the median, to reduce the possibility of confusion.

Assessment of clinical effectiveness outcomes

Numerous clinical effectiveness outcome measures are reported across the included studies, with variation in their assessment and reporting. 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^{31,48,73} 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. Similarly, the stand-alone studies included in this review also lack control groups and they 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 (Elecsys sFlt-1/PLGF ratio test).^{14,19,30,32,46} 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 economic evaluation (see [Chapter 5](#)).

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

Assessment of time-to-event outcomes

Time to pre-eclampsia diagnosis

In the PARROT study, use of the Triage PLGF test alongside standard clinical assessment ('result revealed') was associated with a 64% reduction in time to diagnosis of pre-eclampsia (95% CI 13% to 85%, $p = 0.027$).^{14,19} Time to diagnosis was numerically shorter in the revealed trial arm in all three PLGF level subgroups (see [Table 54](#), [Appendix 5](#)).

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 (see [Appendix 5](#)).³² Time to pre-eclampsia diagnosis was not reported in the MAPPLE or PreOS studies.^{30,46}

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 vs. 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 13](#)).^{14,19} In general, time to delivery was longer in women at < 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 (see [Table 13](#)).³⁰

Time to delivery was not reported in the INSPIRE or PreOS studies.^{32,46}

Assessment of maternal outcomes

Pre-eclampsia diagnosis

Triage placental growth factor test

In the PARROT study, a slightly higher proportion of women were diagnosed with pre-eclampsia (one percentage point higher) or severe eclampsia (three percentage points higher) in the test revealed arm compared to the concealed arm, with the highest numerical differences observed in women with very low PLGF levels (see [Table 55](#), [Appendix 5](#)).^{14,19} In contrast, the MAPPLE study observed a lower proportion of women diagnosed with pre-eclampsia in the revealed arm compared to the concealed arm (difference of 8.4 percentage points) with larger differences between the study arms observed when stratified by PLGF level (see [Table 55](#), [Appendix 5](#)).³⁰

TABLE 13 Time to delivery, test result revealed vs. 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 to 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 –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
^c MAPPLE ³⁰	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

SD, standard deviation.

^a n not reported for subgroups.^b pg/ml.^c Unadjusted indirect comparison.

Elecsys soluble fms-like tyrosine kinase-1/placental growth factor 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 (see [Table 55](#), [Appendix 5](#)).³² Of those with a pre-eclampsia diagnosis, a higher proportion of the test revealed group (nine percentage points higher) were diagnosed with severe pre-eclampsia than the test concealed group (see [Table 56](#), [Appendix 5](#)). Klein *et al.*⁴⁶ 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.

Severe maternal adverse outcomes

Triage placental growth factor test

The PARROT trial reported the composite outcome of severe maternal adverse outcomes.^{14,19} This outcome is defined by the fullPIERS consensus⁴ and includes the number of women with one or more events including maternal death, eclampsia, stroke, myocardial ischaemia or myocardial infarction. 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 14](#)).

The PARROT study also reported separate results for each individual component of the fullPIERS composite outcome of severe maternal adverse outcomes.^{14,19} The majority of these outcomes were reported in < 1% of women in both trial arms. The exceptions were the need for blood transfusion(s) 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%).

TABLE 14 Severe maternal adverse outcomes: composite, test result revealed vs. concealed

Study	Outcome	Group	Revealed	Concealed	Difference (as reported in study)
Triage PLGF test					
PARROT ^{14,19}	Severe maternal adverse outcomes (defined by the fullPIERS consensus), % (n/N)	Total	3.8 (22/573)	5.4 (24/446)	1.0; ^a aOR 0.32, 95% CI 0.11 to 0.96, <i>p</i> = 0.043
		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)	aOR: 0.29 (0.02 to 4.34)
MAPPLE ³⁰	Adverse maternal outcomes, % (n/N)	Total	11.9 (47/396)	10.1 (29/287) (10.1)	Risk ratio (95% CI) 1.17 (0.76 to 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.

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 arm (risk ratio: 1.17; 95% CI 0.76 to 1.82).³⁰ Although not explicitly stated by the study authors, we have assumed that this composite includes the fullPIERS-defined outcomes⁴ since many of the individual fullPIERS outcomes were also reported separately in the MAPPLE study. The majority of these individual outcomes were reported in < 1% of women in both trial arms with the following exceptions: hepatic dysfunction was reported at a higher frequency in the revealed arm (*n* = 38; 9.6%) compared to the concealed arm (*n* = 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 soluble fms-like tyrosine kinase-1/placental growth factor 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 vs. concealed) and are therefore not presented in this report.⁴⁶ The INSPIRE study reported the frequency of selected outcomes with severe hypertension and hepatic dysfunction the most frequently reported of these outcomes (Table 15).³² No statistically significant differences were observed between trial arms; however, 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 of each other.

Assessment of fetal outcomes

Fetal mortality

Rates of intrauterine fetal death (including pre-viable and viable stillbirths) were similar for the revealed and concealed arms of Triage PLGF test in the PARROT study^{14,19} 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 16).³⁰ The PreOS and INSPIRE studies did not report this outcome for the Elecsys sFlt-1/PLGF ratio test.^{32,46}

Assessment of neonatal/perinatal outcomes

Gestational age at delivery

Triage placental growth factor 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) (see [Table 57](#), [Appendix 5](#)).^{14,19} 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) (see [Table 57](#), [Appendix 5](#)).³⁰

Elecsys soluble fms-like tyrosine kinase-1/placental growth factor ratio test

No statistically significant difference in gestational age at delivery was observed between revealed and concealed arms in the INSPIRE study (see [Table 57](#), [Appendix 5](#)).³² Klein *et al.* (PreOS study)⁴⁶ performed an analysis of intended clinical decisions made before and after sFlt-1/PLGF ratio test results were revealed to the clinical team. 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 (e.g. to hospitalise, to use steroids to induce fetal lung maturity) compared to those women where the clinical decision was reversed (not to hospitalise or induce lung maturity).

Perinatal and neonatal mortality

Data were available for this outcome for the Triage PLGF test only. Perinatal deaths (defined to include deaths from 24 weeks of gestation, including 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 study³⁰ but at similar frequencies (1.0%) in both arms of the PARROT study (see [Table 58](#), [Appendix 5](#)).^{14,19}

Overall, < 1% of women experienced early or late neonatal death in the MAPPLE and PARROT studies, respectively (see [Table 59](#), [Appendix 5](#)). Late neonatal deaths were reported at the highest frequency in 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.

TABLE 15 Maternal adverse outcomes: individual; test result revealed vs. 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; <i>p</i> = 0.994
	Placental abruption, % (n/N)	1.1 (2/186)	2.7 (5/184)	1.6; <i>p</i> = 0.246
	Severe hypertension (in women with a PE diagnosis only), % (n/N)	46.8 (22/47)	52.6 (20/38)	5.8; <i>p</i> = 0.59
	Creatinine > 97, % (n/N)	4.8 (9/186)	4.4 (8/184)	0.4; <i>p</i> = 0.822
	Platelets < 100, % (n/N)	2.2 (4/186)	3.8 (7/184)	1.6; <i>p</i> = 0.349
	ALT double the normal, % (n/N)	17.7 (33/186)	12.5 (23/184)	5.2; <i>p</i> = 0.159
	Eclampsia, % (n/N)	0 (0/186)	0 (0/184)	Not applicable

ALT, alanine transaminase; PE, pre-eclampsia.

^a Absolute % difference as calculated by reviewer.

TABLE 16 Fetal mortality, test results revealed vs. concealed

Study	Outcome	Group	Revealed	Concealed	Difference ^a
<i>Triage PLGF test</i>					
PARROT ¹⁹	Intrauterine death, % (n/N) ^b	Total	1.2 (7/573)	1.3 (6/446)	0.1
		PLGF < 12 ^c	3.1 (4/130)	3.8 (4/106)	0.7
		PLGF 12–100 ^c	0.5 (1/212)	1.2 (2/173)	0.7
		PLGF > 100 ^c	0 (0/229)	1.3 (2/156)	1.3
MAPPLE ³⁰	Stillbirth, % (n/N) ^b	Total	0.2 (1/433)	2.3 (7/299)	2.1
		PLGF < 12 ^c	0.8 (1/124)	5.8 (4/69)	5.0
		PLGF 12–100 ^c	0 (0/158)	2.9 (3/105)	2.9
		PLGF > 100 ^c	0 (0/151)	0 (0/125)	Not applicable

^a Absolute % difference as calculated by reviewer.
^b Number of infants.
^c pg/ml.

Neonatal and perinatal mortality was not reported in the INSPIRE or PreOS studies.^{32,46}

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^{14,19} 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) (see [Appendix 5](#)). In contrast, the composite perinatal adverse outcome (assumed by the 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% vs. 18.9%) reported for the subgroup with singleton pregnancies only.³⁰ The composite including neonatal outcomes only was reported at a higher frequency in the revealed arm than in the concealed arm, both in the 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.

Neonatal adverse outcomes: individual components

The PARROT and MAPPLE studies report the frequencies of the individual components of the composite adverse neonatal outcome ([Table 17](#)).^{14,19,30} 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 lower than that of individual subgroups.

TABLE 17 Neonatal outcomes: individual components

Outcome	Group (pg/ml)	PARROT ^{14,19}		MAPPLE ³⁰	
		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)
	PLGF 12–100	0.5 (1/212)	0.6 (1/173)	2.6 (4/158)	0.0 (0/105)
	PLGF > 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)
	PLGF < 12	NR	NR	1.6 (2/124)	0.0 (0/69)
	PLGF 12–100	NR	NR	1.3 (2/158)	0.0 (0/105)
	PLGF > 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)
	PLGF < 12	3.2 (4/130)	4.8 (5/106)	3.4 (4/124)	4.3 (3/69)
	PLGF 12–100	1.4 (3/212)	0.6 (1/173)	1.3 (2/158)	0.0 (0/105)
	PLGF > 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)
	PLGF < 12	0.0 (0/130)	0.0 (0/106)	6.0 (7/124)	7.2 (5/69)
	PLGF 12–100	0.0 (0/212)	0.6 (1/173)	1.9 (3/158)	1.0 (1/105)
	PLGF > 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.

Assessment of delivery and related perinatal outcomes

Magnesium sulphate

Use of magnesium sulphate was reported in the PARROT study only.^{14,19} Magnesium was more frequently used by those with lower PLGF levels (PLGF < 12 pg/ml); however, the proportions in the revealed and concealed arms were similar across all PLGF subgroups (Table 18).

Onset of labour

Onset of labour was reported in the PARROT study only.^{14,19} A higher proportion of women had a pre-labour caesarean section in the revealed arm (40%) compared to the concealed arm (35%) (Table 19).

Mode of delivery

In the PARROT study, the proportion of women delivered by emergency caesarean section was higher in the revealed arm compared to the concealed arm (26% vs. 21%). The highest rates were reported in women with very low PLGF levels (PLGF < 12 pg/ml) (Table 20).^{14,19}

TABLE 18 Use of magnesium sulphate, test result revealed vs. concealed

Study	Outcome	Group	Revealed	Concealed	Difference (as reported in study)
Triage PLGF test					
PARROT ^{14,19}	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.					

TABLE 19 Onset of labour, test result revealed vs. concealed

Study	Outcome	Group	Revealed	Concealed	Difference ^a
<i>Triage PLGF test</i>					
PARROT ^{14,19}	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.					

TABLE 20 Mode of delivery, test result revealed vs. concealed

Study	Outcome	Group	Revealed	Concealed	Difference (as reported in study)
Triage PLGF test					
PARROT ^{14,19}	Spontaneous vaginal cephalic, % (n/N)	Total	37 (210/573)	41 (182/446)	aOR 1.05, 95% CI 0.59 to 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 to 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% vs. 64.5%; risk ratio (95% CI) 1.14 (1.03 to 1.26)].³⁰

No data on delivery mode were reported in the INSPIRE or PreOS studies.^{32,46}

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 (see [Table 62](#), [Appendix 5](#)).^{14,19,30} No data for this outcome was available from the INSPIRE or PreOS studies.^{32,46}

Admission to hospital or specialist care unit

Maternal admissions

No statistically significant difference in maternal admissions was observed at any time point measured in the INSPIRE study (see [Table 63](#), [Appendix 5](#)), 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 ($n = 98$ women, 83.1%) were unchanged after the sFlt-1/PLGF ratio test result was revealed. However, in seven mothers (5.9%) the decision changed in favour of hospitalisation compared to 13 mothers (11.0%) where the decision was changed in favour of not hospitalising the mother.⁴⁶

No data on maternal admissions were reported in the PARROT or MAPPLE studies.^{14,19,30} The INSPIRE study³² did not report on the proportion of women admitted to different levels of care, for example intensive care units (ICUs) or other critical care units.

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 21](#)).^{14,19,30} 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 (see [Table 21](#)).³²

Length of stay in hospital or unit

Length of stay (maternal)

There was no difference in the mean number of inpatient nights in women admitted to hospital between the revealed and concealed arms in the PARROT study ([Table 22](#)).^{14,19}

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 NICU or high-dependency unit (HDU) was 10.6 days shorter in the revealed arm than for the concealed arm ([Table 23](#)).¹⁹

Subgroups of interest

Subgroups of interest to this diagnostic assessment, as specified in 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.

TABLE 21 Admission to neonatal unit, test result revealed vs. concealed

Study	Outcome	Group	Revealed	Concealed	Difference (as reported in study)
Triage PLGF test					
PARROT ^{14,19}	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 to 7.92)
		PLGF 12–100 ^a	34.4 (73/212)	31.2 (54/173)	aOR (95% CI): 2.37 (0.76 to 7.37)
		PLGF > 100 ^a	12.7 (29/229)	17.3 (27/156)	Not reported
MAPPLE ³⁰	Neonatal unit admission, % (n/N) ^b	Total	45.5 (190/433)	39.8 (117/299)	Risk ratio (95% CI) 1.14 (0.95 to 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)	<i>p</i> = 0.430
aOR, adjusted odds ratio. a pg/ml. b Number of infants.					

TABLE 22 Inpatient nights, test result revealed vs. concealed, by test cut-off

Study	Outcome	Revealed	Concealed	Difference
Triage PLGF test				
PARROT ¹⁹	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
SE, standard error. a Effect measure not specified.				

TABLE 23 Nights in neonatal unit, test result revealed vs. concealed

Study	Outcome	Revealed	Concealed	Difference
Triage PLGF test				
PARROT ^{14,19}	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)
SE, standard error. a Level of neonatal care not specified.				

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

- Test accuracy data are reported by **gestational age group** in the ROPE, PELICAN and McCarthy (COMPARE)^{22,29,43} stand-alone studies for prediction of delivery-related outcomes (see [Report Supplementary Material 1](#)).
- Test accuracy data are reported for subgroups of participants with **chronic kidney disease and/or hypertension** in the PEACHES (PELICAN cohort) stand-alone study²³ for the prediction of delivery within 2 weeks due to pre-eclampsia or superimposed pre-eclampsia (see [Report Supplementary Material 1](#)).
- Time to delivery outcomes are stratified by **gestational age** (and PLGF level) in the add-on PARROT study^{14,19} (see [Time to delivery](#)).
- All results for the Elecsys sFlt-1/PLGF ratio in the add-on study Binder *et al.*⁴⁷ are **for twin pregnancies only** [see [Assessment of test accuracy \(add-on studies\)](#)].

Summary of the results of the systematic review of test accuracy and clinical effectiveness

Seventeen studies were included in the systematic review, reporting a wide range of outcomes, including test accuracy to predict or rule out pre-eclampsia and clinical effectiveness and safety outcomes. The economic analysis (see [Independent economic evaluation](#) below) primarily uses data from studies of add-on tests. The results of studies conducted on stand-alone tests are presented in [Report Supplementary Material 1](#).

Overall, high PPVs for the Triage PLGF test, Elecsys sFlt-1/PLGF ratio and BRAHMS Kryptor sFlt-1/PLGF ratio test from add-on test studies indicate that these tests could have good accuracy for predicting pre-eclampsia at various time points and gestational periods when used to supplement existing clinical decision-making (see [Testing to predict pre-eclampsia](#)). However, no evidence is available on the diagnostic accuracy of the DELFIA Xpress PLGF test for predicting pre-eclampsia. Furthermore, no data are available from the add-on test studies to determine whether repeat testing could accurately rule in or rule out pre-eclampsia (see [Repeat testing to rule in/out pre-eclampsia](#)).

In terms of clinical effectiveness outcomes, time to pre-eclampsia diagnosis was shorter when using the Triage PLGF test or Elecsys sFlt-1/PLGF ratio in addition to standard clinical assessment (see [Time to pre-eclampsia diagnosis](#)). Time to delivery (data from the Triage PLGF test only) varied with gestational age and PLGF cut-off, being shortest when using the lowest PLGF cut-off (< 12 pg/ml) (see [Time to delivery](#)). The proportion of women diagnosed with pre-eclampsia using the Triage PLGF test varied according to the study (PARROT or MAPPLE), while the Elecsys sFlt-1/PLGF ratio test when used alongside clinical practice increased the proportion of women who were diagnosed with pre-eclampsia (see [Pre-eclampsia diagnosis](#)).

Maternal adverse outcomes

The fullPIERS composite outcome from the PARROT trial indicated a slightly lower frequency of adverse events when the Triage PLGF test was used in addition to standard clinical assessment. Comparable data were not available for the Elecsys sFlt-1/PLGF ratio test. No maternal deaths were reported in the studies (see [Severe maternal adverse outcomes](#)). Use of magnesium sulphate to reduce maternal seizures was only reported in the PARROT study and was not affected by adding the Triage PLGF test to standard clinical assessment (see [Magnesium sulphate](#)).

Fetal adverse outcomes

Fetal mortality rates were generally unaffected by using the Triage PLGF test in addition to standard clinical assessment, except for a slight reduction in stillbirths in the MAPPLE study at the lowest PLGF cut-off (< 12 pg/ml) (see [Fetal mortality](#)). Perinatal mortality was marginally reduced (by 0.5%) when the Triage PLGF test was used in addition to clinical practice in MAPPLE but not in PARROT (see [Perinatal and neonatal mortality](#)). Fetal and perinatal mortality data were not available for the Elecsys sFlt-1/PLGF ratio test, while late neonatal mortality was a rare event. Composite outcomes for perinatal and neonatal adverse events were available only for the Triage PLGF test and occurred at higher frequency when the test was used in addition to clinical practice in the MAPPLE study, but with no influence of the test evident in the PARROT study (see [Perinatal and neonatal adverse composite outcomes](#)). The same pattern (i.e. when the Triage PLGF test was used in MAPPLE but not PARROT) was evident for the individual neonatal adverse event

components (respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular haemorrhage, necrotising enterocolitis, retinopathy of prematurity) (see [Neonatal adverse outcomes: individual components](#)).

Labour and delivery outcomes

Gestational age at delivery was, on average, earlier at the lowest PLGF cut-off and around 1.4 weeks earlier when the Triage PLGF test was used in addition to standard clinical assessment in the MAPPLE study. But no change in age at delivery was seen in the PARROT study or when using the Elecsys sFlt-1/PLGF ratio test in addition to clinical practice (see [Gestational age at delivery](#)).

Modes of delivery were reported only for the Triage PLGF test. When used in addition to standard clinical assessment, this test increased the proportion of women who had a pre-labour caesarean section (PARROT and MAPPLE) and the proportion of women who had an emergency caesarean section (only reported in PARROT) (see [Onset of labour](#) and [Mode of delivery](#)). The rate of preterm delivery (< 37 weeks gestation) was available for the Triage PLGF test only. When used in addition to standard clinical assessment, this test resulted in an increase in the proportion of women experiencing preterm delivery in MAPPLE but with no effect in PARROT (see [Preterm and early preterm delivery](#)).

Maternal hospital admissions and length of stay

The proportion of mothers admitted did not differ significantly when the Elecsys sFlt-1/PLGF ratio test was used in addition to clinical practice, although in the PreOS study the proportion of clinical decisions which were revised to not hospitalise the mother (11%) exceeded the proportion of revised clinical decisions to hospitalise the mother (5.9%). No maternal admission data were available for the Triage PLGF test (see [Maternal admissions](#)). The mean number of women's inpatient nights was only reported in PARROT and did not change when the Triage PLGF test was added to standard clinical assessment [see [Length of stay \(maternal\)](#)].

Neonate hospital admissions and length of stay

Where reported, admission to a neonatal unit did not change significantly when the Triage PLGF test was used in addition to clinical practice, and admission to a SCBU did not change significantly when the Elecsys sFlt-1/PLGF ratio test was used in addition to clinical practice [see [Length of stay \(neonatal\)](#)]. Neonate length of stay, reported only in PARROT, in the neonatal unit or SCBU did not change when the Triage PLGF test was added to standard clinical assessment, but the length of stay in the NICU was 10.6 days shorter [see [Length of stay \(neonatal\)](#)].

Health-related quality of life

The effect of PLGF testing on HRQoL of mothers was not reported in any of the included studies but was subsequently available in the PARROT-Ireland study which informs the updated economic analysis (see [Independent economic evaluation](#)).

Overall summary

Overall, the Triage PLGF test, Elecsys sFlt-1/PLGF ratio and BRAHMS Kryptor sFlt-1/PLGF ratio are promising for predicting pre-eclampsia when used as add-on tests, for a range of gestational time points and test positivity cut-offs. The Triage PLGF test and Elecsys sFlt-1/PLGF ratio can also reduce the time to pre-eclampsia diagnosis when added to standard clinical practice. For clinical effectiveness outcomes, most data are available for the Triage PLGF test (from the PARROT and MAPPLE studies), while relatively limited outcomes were available for the Elecsys sFlt-1/PLGF ratio and none for the BRAHMS Kryptor sFlt-1/PLGF ratio at the time that the review was completed. However, we have incorporated a subsequently published study evaluating the diagnostic accuracy of the BRAHMS test in our economic evaluation, allowing us to estimate incremental cost-effectiveness.

Chapter 5 Economic analysis

This chapter assesses the evidence on the cost-effectiveness of the PLGF-based tests when used in addition to standard clinical assessment. This is based on a systematic review of economic analyses we conducted and an independent economic model which we developed for this topic. Input parameters for the model were identified from the systematic review of test accuracy and clinical effectiveness (in particular the PARROT^{14,19} and INSPIRE³² RCTs for the base case), the systematic review of economic studies (see [Methods for the systematic review of economic studies](#)), a review of health utility estimates (see [Methods for review and data extraction of health-related quality-of-life studies](#)) and targeted searches for data on relevant costs and resource use.

Systematic review of cost-effectiveness evidence

Methods for the systematic review of economic studies

The same methods used to conduct the systematic review of test accuracy and clinical effectiveness (as reported earlier in [Chapter 3](#)) were used in the systematic review of economic studies. The relevant population, interventions and comparators were the same in both reviews (as described in [Inclusion and exclusion criteria](#)), but the relevant study design and outcomes differed. Thus, studies were eligible if they were full economic evaluations, assessing both costs and consequences, or cost studies for the specified index tests. Relevant outcomes 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 quality-adjusted life-years (QALYs) gained]. Each step of the review was completed by two health economists and any disagreements were resolved by discussion.

Methods for data extraction and critical appraisal of economic studies

Data extraction was performed using the standard data extraction form we used in the previous DAR.⁶ The included economic evaluations were critically appraised using the same checklist that was used in the previous DAR.⁶ This was based on criteria in checklists proposed by Drummond *et al.*,⁷⁴ Philips *et al.*⁷⁵ and the NICE reference case.⁷⁶

Results of the systematic review of economic studies

Starting with the $n = 1953$ potentially relevant references identified in the original and updated searches, we applied a filter for the word 'cost' appearing anywhere in the title and/or abstract study report to reduce the number of references to a manageable level.

- Application of the filter identified $n = 119$ references of which $n = 26$ ^{6,10,77–99} were retrieved for full-text screening.
- After inspection of the full texts $n = 15$ references were excluded:
 - $n = 13$ were conference abstracts^{77–86,88–90}
 - $n = 1$ was a duplicate of the previous DAR⁶
 - $n = 1$ was a protocol for a study in [clinicaltrials.gov](#).⁸⁷
- The excluded references and the reason for exclusion are shown in [Appendix 2](#).

The 11 remaining full texts met the inclusion criteria for the systematic review of economic studies.^{6,10,91–99} [Table 65](#), [Appendix 6](#) provides an overview of the characteristics of the 11 included economic studies and a summary of their base-case results. Six of the included studies are evaluations of the Elecsys sFit-1/PLGF ratio test,^{10,93,94,96,98,99} two are evaluations of the Triage PLGF test,^{91,92} two assess more than one PLGF-based test (Elecsys sFit-1/PLGF ratio test, Triage PLGF test and BRAHMS Kryptor sFit-1/PLGF ratio test)^{6,97} and the other did not report which PLGF-based test(s) were evaluated.⁹⁵ We categorised five studies as cost-effectiveness analyses,^{6,10,92,98,99} three as cost analyses,^{91,93–95} one as a budget impact analysis,⁹⁴ one as cost-effectiveness and budget impact analysis,⁹⁷ and one as a cost and budget impact analysis.⁹⁶ One study did not use a model;⁹⁵ 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,^{6,10,91,93,94,96–99} and one study used a decision tree with a Monte Carlo simulation.⁹² Only one model measured the effects in QALYs,⁶ two considered maternal and neonatal outcomes,^{6,92} and the other nine concentrated on potential savings due to more appropriate management.^{6,10,91,93–99}

The results of the studies suggest that including PLGF-based diagnostic tests alongside standard clinical assessment has the potential to reduce maternal adverse events and decrease the number of women who receive inappropriate treatment (mainly hospitalisation) due to false-positive diagnoses. Six studies^{91–93,95,96,99} reported a cost saving within a range of £94–2896 per woman tested due to the introduction of a first PLGF test in addition to standard clinical assessment versus standard clinical assessment alone. Five studies^{93,94,96,98,99} reported a cost saving between £26 and £607 for women who have received a retest. The study by Myrhaug *et al.*⁹⁷ reported £3710 as the cost per additional correctly identified case of pre-eclampsia.

Assessment of the quality and relevance of the economic studies

The studies used a similar comparator (standard clinical assessment 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 *et al.*⁹⁵ and Hodel *et al.*⁹⁶ where there are some uncertainties about the patient population as explained above. It is uncertain how relevant the studies conducted for different healthcare systems and settings^{10,93–98} are for the UK NHS.

One study did not use a model.⁹² The remaining 10 studies used appropriate models, although Duhig *et al.*⁹² did not clearly describe the modelling methodology, structure and assumptions. Moreover, the data inputs were not fully described and justified in four studies.^{93,95,98,99} Of the 10 published studies, only 2 based estimates of clinical effectiveness on a systematic review,^{6,97} and only 1 measured the health benefits in QALYs using standardised and validated generic instruments for assessment of quality of life.⁶ The studies described and justified the resource costs used, except for Giardini *et al.*⁹⁵ Most of the studies assessed uncertainty through deterministic sensitivity and scenario analyses^{6,10,91,93,94,96,98,99} but Duhig *et al.*⁹² used a probabilistic sensitivity analysis, and Giardini *et al.*⁹⁵ and Myrhaug *et al.*⁹⁷ did not assess uncertainty at all. Model validation was only reported by Frampton *et al.*⁶

Methods for review and data extraction of health-related quality-of-life studies

The EAG undertook searches to identify data on HRQoL in gestational hypertension, pre-eclampsia and general pregnancy. The aim of these searches was to identify utility values suitable for use in the economic model. The following HRQoL measures were eligible for inclusion: EuroQol-5 Dimensions (EQ-5D) [3- (EQ-5D-3L) or 5-level (EQ-5D-5L) version], Short Form questionnaire-36 items (SF-36) (using all subscales), Short Form questionnaire-12 items (SF-12), Short Form questionnaire-6 Dimensions (SF-6D), Health Utilities Index (HUI) 1, 2 and 3 and 15D questionnaire. All of these are general preference-based utility measures or can be mapped to the EQ-5D using published algorithms, in line with the NICE reference case.⁷⁶ 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 relevant HRQoL studies:

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 searches were conducted by an information specialist and screening of references was done by two health economists, with any disagreements resolved through discussion.

The systematic searches were carried out separately in MEDLINE (Ovid), including Epub Ahead of Print, In-Process and 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 DAR,⁶ 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 72](#), [Appendix 8](#). 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.

Data extraction was performed using a pre-designed standard data extraction form which we used in the previous DAR.⁶

Results of the review of health-related quality-of-life studies

The systematic searches identified 133 potentially relevant studies (see [Figure 10](#), [Appendix 6](#)):

- 125 were identified directly from database searches and the remaining 8 were identified from ad hoc searches.
- 32 were retrieved for full-text screening.
- 5 studies¹⁰⁰⁻¹⁰⁴ were included after full-text screening.

Of the 27 excluded full texts,

- 12 were conference abstracts¹⁰⁵⁻¹¹⁶
- design¹¹⁷⁻¹²⁸
- 2 studies were excluded on population^{129,130}
- 1¹³¹ was excluded on HRQoL measure.

The excluded references and reasons for exclusion are shown in [Appendix 2](#). The flow chart for the identification of HRQoL studies is shown in [Figure 10](#), [Appendix 8](#).

The five included studies are described in [Appendix 8](#). Only two studies^{100,103} reported EQ-5D, while three^{101,102,104} reported SF-36. Four studies were done with European populations, but none were from the UK.^{100,101,103,104} Three studies had samples sizes > 200.^{100,103,104} Only the study Seppänen *et al.*¹⁰⁰ provided better-utility estimates than those used in the previous DAR⁶ and were used in our current model.

Independent economic evaluation

To evaluate the cost-effectiveness of PLGF-based tests for the assessment of pre-eclampsia, we developed, de novo, a decision tree model. The decision tree builds on the model reported in the previous DAR by Frampton *et al.*⁶ which informed NICE DG23.⁷

The tests under evaluation (the index test) are:

- the Triage PLGF test
- the Elecsys immunoassay sFlt-1/PLGF ratio
- the DELFIA Xpress PLGF 1-2-3 test/DELFIA Xpress sFlt-1 kit
- the BRAHMS sFlt-1 Kryptor/BRAHMS PLGF plus Kryptor pre-eclampsia ratio.

The PLGF-based tests were compared to each other and to standard clinical assessment only, comprising blood pressure measurement, urinalysis and fetal monitoring among other things. Standard clinical assessment is assumed to follow NICE guidelines for managing hypertension and pre-eclampsia [clinical guideline 107 (CG107),⁵⁸ and updated in 2019 (NG133)¹⁷], in addition to the clinician's judgement. The population modelled is pregnant women, between gestation week 20 and gestation week 36 plus 6 days, who, based on screening tests and clinical symptoms, are suspected of having pre-eclampsia.

The model was developed in accordance with the scope of the diagnostic assessment issued by NICE.¹³² 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 methods guide. A shorter time horizon of up to 6 months postpartum was tested in a scenario analysis.

Similar to the model in the study by Frampton *et al.*,⁶ which informed NICE DG23,⁷ 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 6 months postpartum. The model also estimates the long-term impact of complications on the HRQoL of children and their mothers; longer-term costs of respiratory distress syndrome and intraventricular haemorrhage; and the impact of false-positive results on the HRQoL of women who are misdiagnosed.

The model structure includes four main components:

- **Risk stratification** of women into subcohorts depending on the risk of suspected pre-eclampsia (low, intermediate, or high) based on the results of standard clinical assessment with or without PLGF testing.
- **Delivery 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 four model components are illustrated in [Figures 3–5](#) and further described below. The model components are structurally similar to the submodels used in the previous DAR⁶ with the exception of the risk stratification component.

In the current diagnostic assessment, NICE requested substantial changes to the cost-effectiveness model when the first version was submitted. In the revised version, presented here, the main changes have been made to the methods for the risk stratification component (reported in [Risk stratification](#)). Also, we included a further study – the PARROT IRELAND study⁶⁴ – which was published after the systematic review of test accuracy and clinical effectiveness was completed (and so is not included within that review).

PARROT IRELAND was a cluster RCT comparing usual care plus the addition of point-of-care PLGF testing to usual care only, in seven maternity hospitals in Ireland. It did not provide evidence on the sensitivity and specificity for standard clinical assessment and use of the Triage test and so it could not be used to inform estimates of test performance. Instead, the study was used to inform estimates of hypertension severity of the baseline model population (see [Clinical management decision](#)).

Risk stratification

The risk stratification component determines whether patients are high risk, intermediate or low risk of pre-eclampsia. The health economic model was structured to use estimates of relative test performance (sensitivity and specificity) applied to a single baseline population to determine the level of monitoring of patients and the likelihood that they will be admitted to hospital. An overview of the model is provided in [Figure 3](#). The modelling of maternal and neonatal outcomes is described in the following sections.

The model required information on the following clinical effectiveness parameters:

- distribution of hypertension categories
- prevalence of pre-eclampsia by hypertension category
- test sensitivity and specificity
- clinical management decisions conditional on the original decision to admit to hospital, and the test result.

These are discussed in [Model parameters](#). Throughout, information on the steps taken to make the model probabilistic is also provided. For probabilistic analyses, 10,000 iterations were used.

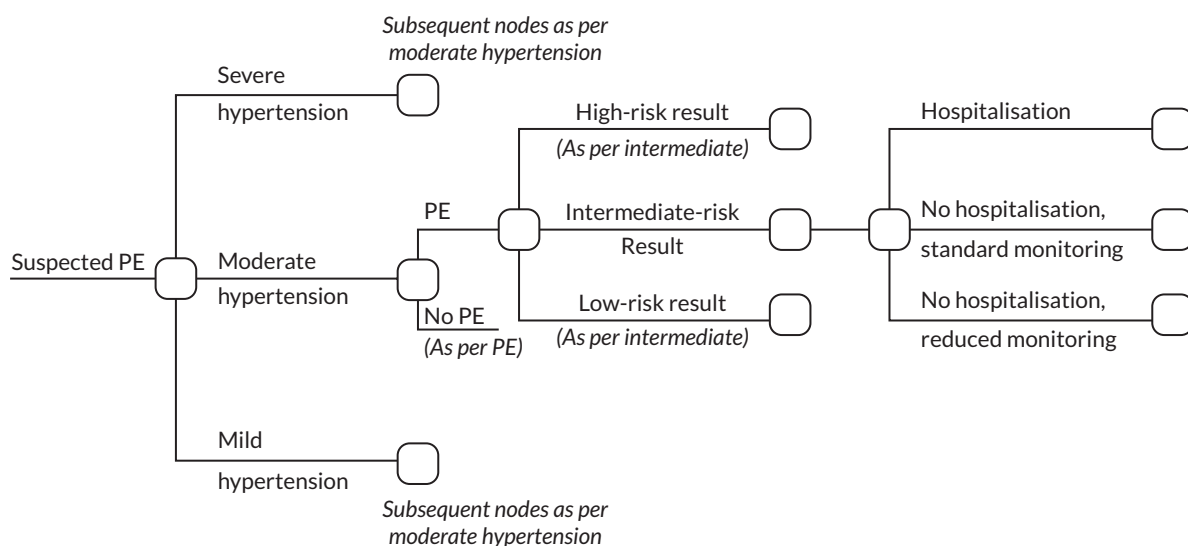


FIGURE 3 Model structure (risk stratification and pregnancy management). PE, pre-eclampsia.

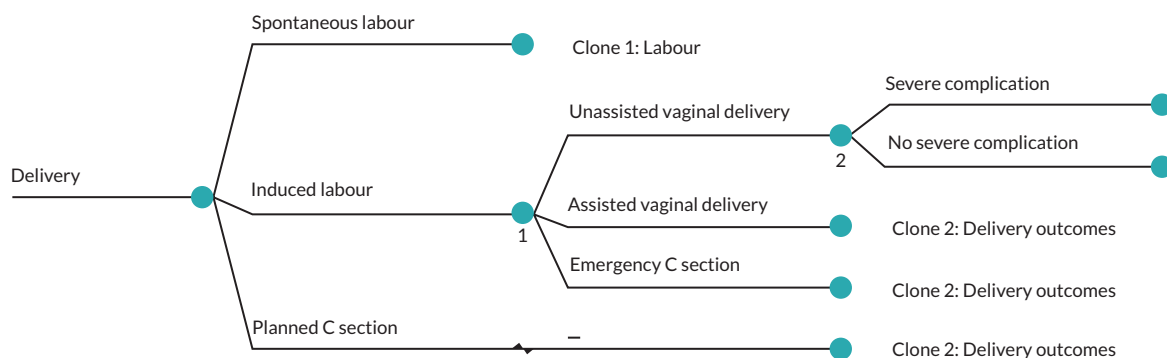


FIGURE 4 Delivery management and maternal outcomes model subtree.

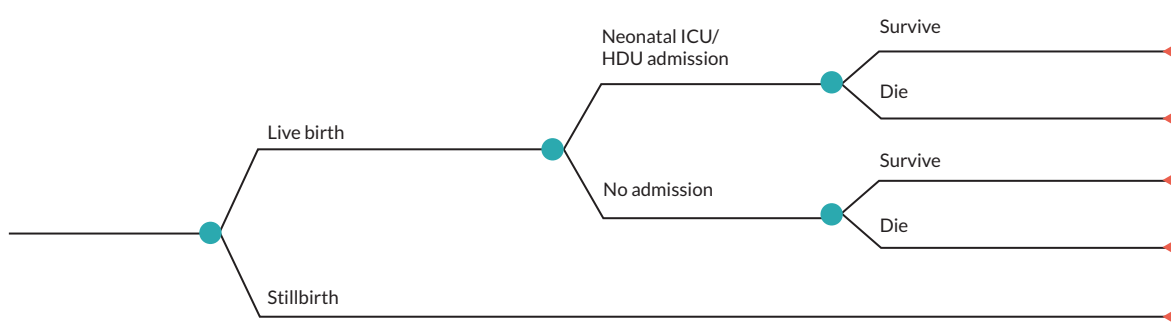


FIGURE 5 Fetal and neonatal outcome subtree.

Delivery management and maternal outcomes

[Figure 4](#) shows a subtree for the delivery and maternal outcome component of the model. This model structure was adopted from the previous DAR for NICE DG23.⁶ This subtree begins with delivery of the child, 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 anticonvulsive 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.

Fetal and neonatal outcomes

[Figure 5](#) shows the structure for the fetal and neonatal outcome subtree, adopted from the previous DAR.⁶ 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. ICU or HDU). As stated in the previous DAR,⁶ 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 submodel establishes whether the labour results in a live birth or stillbirth. The following branch relates to admission to neonatal HDU or ICU 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 [Resource use and costs associated with management of suspected pre-eclampsia](#) and [Utilities](#)).

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 include:

- 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 NICU, HDU and SCBU
- long-term costs associated with complications in neonates.

These cost components are further described in [Resource use and costs](#).

The costs of managing gestational hypertension and pre-eclampsia are driven by the time to delivery 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;⁵⁸ hypertension or severe hypertension in the current NICE guideline NG133¹) and can be higher in women with pre-eclampsia (as shown in [Table 24](#)). As explained above, the cost of delivery depends on the mode of delivery and is significantly higher for assisted and emergency deliveries (see [Table 84](#), [Appendix 8](#)). Therefore, such differences were considered when estimating the costs accrued in the test and comparator arms (see [Resource use and costs](#)).

Estimation of quality-adjusted life-years

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 [Utilities](#).

TABLE 24 Total costs for managing women with high, intermediate and low risk of pre-eclampsia

Population group		Total cost			
		Up to 35 weeks		Between 35 and 37 weeks	
		Intervention (£)	Comparator (£)	Intervention (£)	Comparator (£)
Severe hypertension					
PE	High-risk test result	1717.95	1717.95	895.61	895.61
	Intermediate	1089.40	1089.40	875.40	875.40
	Low-risk test result	1089.40	1089.40	875.40	875.40
No PE	High-risk test result	1814.97	1814.97	895.61	895.61
	Intermediate	1487.22	1487.22	922.02	922.02
	Low-risk test result	1487.22	1487.22	922.02	922.02
Intermediate hypertension					
PE	High-risk test result	1717.95	1717.95	895.61	895.61
	Intermediate	1089.40	1089.40	875.40	875.40
	Low-risk test result	1089.40	1089.40	875.40	875.40
No PE	High-risk test result	1814.97	1814.97	1665.13	1664.13
	Intermediate	825.55	825.55	260.35	260.35
	Low-risk test result	465.85	465.85	193.01	193.01
Mild hypertension					
PE	High-risk test result	1717.95	1717.95	895.61	895.61
	Intermediate	1089.40	1089.40	875.40	875.40
	Low-risk test result	1089.40	1089.40	875.40	875.40
No PE	High-risk test result	1814.97	1814.97	1665.13	1664.13
	Intermediate	825.55	825.55	260.35	260.35
	Low-risk test result	465.85	465.85	193.01	193.01
PE, pre-eclampsia.					
Note					
Time to deliveries based on data from the PARROT study. ¹⁴					

Induced labour, planned caesarean section and admission to an 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 postpartum), emergency and non-emergency caesarean section (from birth to 3 weeks postpartum), and admission to ICU (from admission to 6 weeks postpartum).

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 some 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 the long-term impact of adverse outcomes in neonates on the quality of life of the mother and baby.

Model parameters

Clinical management decision

There is uncertainty on how patient management decisions are influenced by PLGF test results. We contacted seven specialist committee members appointed by NICE for this diagnostic assessment, and other relevant clinical contacts in this field. A short survey was developed that focused on the following estimates:

- The proportion of women who 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 who 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 assessed as moderate and high risk and less surveillance for those assessed as 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 25](#).

The following issues were also highlighted during responses to the survey:

- Several respondents indicated that women assessed as needing to be admitted to hospital who 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 while 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 25](#).

1. Testing is only used to rule out pre-eclampsia. 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.

TABLE 25 Survey responses

Respondent ID	Clinical decision: hospital			Clinical decision: not hospital		
	High	Moderate	Low	High	Moderate	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

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 study⁴⁶ and is reproduced in [Table 26](#).

The PreOS study³³ was used to derive evidence for the model based on the following assumptions:

- The 11 women admitted following a high-risk test result includes the 9 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 27](#) 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 clinical assessment.

For women who are not admitted, it is assumed that under standard clinical assessment resource use follows the expectant management pathway (stratified by hypertension severity). Resource use with PLGF-based tests was the same as for standard clinical assessment, with the exception 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.

TABLE 26 Numbers of women admitted before and after testing, by test result

Numbers admitted	High risk	Intermediate risk	Low risk
<i>Before test result</i>			
Admit	9	8	23
Do not admit	12	14	52
<i>After test result</i>			
Admit	11	8	15
Do not admit	10	14	60
Source PreOS study. ³³			

TABLE 27 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
Do not admit	High risk	0	100	50	17
Do not admit	Int. risk	0	30	0	0
Do not admit	Low risk	0	0	0	0

Distribution of hypertension categories

The distribution of hypertension categories (mild, moderate, severe) was estimated based on PARROT¹ in the base-case analysis, which reported an average highest systolic blood pressure of 143.56 mmHg [standard deviation (SD) 20]. A normal distribution was assumed, with hypertension categories (mmHg) based on cut-offs of > 160 for severe hypertension, 150–160 for moderate hypertension, and < 150 for mild hypertension.

In addition, hypertension categories were derived from PARROT IRELAND¹³⁸ (mean 136.29 mmHg, SD 18.38) in scenario analyses using the same approach as for the base case. For PELICAN^{91,139} values by category were directly available. The distribution of hypertension categories are shown in [Table 28](#). For probabilistic analyses, a Dirichlet distribution was used.

Prevalence of pre-eclampsia by hypertension status

The PELICAN study was the only identified source of evidence on the distribution of pre-eclampsia by hypertension status. This is reproduced in [Table 29](#). For probabilistic analyses, a Dirichlet distribution was used, with the total counts set to 60 (the number of participants in PELICAN⁹¹).

Test sensitivity and specificity

Based on our systematic review of test accuracy and clinical effectiveness (see [Results of the systematic review of test accuracy and clinical effectiveness](#)), four studies^{29,32,140,141} were identified that reported on the sensitivity and specificity of at least two assessment methods (PLGF-based and standard clinical assessment), and therefore provided relative estimates of test accuracy. Relative estimates were used as it was assumed that these would generalise across studies (unlike absolute estimates of test accuracy, relative estimates would not be affected by differences in study populations). These relative effects were then applied to baseline (absolute) sensitivity and specificity values for a single test (based on INSPIRE or PARROT) to generate absolute estimates of sensitivity and specificity for each test (including standard clinical assessment).

TABLE 28 Distributions of hypertension categories in the economic evaluation

Hypertension category	Study		
	PARROT (base case) (%)	PARROT IRELAND (%)	PELICAN (%)
Severe	20.56	9.85	5.32
Moderate	16.82	12.93	58.40
Mild	62.62	77.21	36.27

TABLE 29 Distribution of pre-eclampsia by hypertension status

Hypertension category	Pre-eclampsia status	Per cent of whole sample (%)	Per cent 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

PE, pre-eclampsia.

Source

[Figure 1](#) of PELICAN.⁹¹

An overview of the four studies is shown in [Figure 6](#). The studies vary in the population included (in particular, gestational age), the tests considered, how tests were used (as stand-alone or add-ons to standard clinical assessment), and the definition of a positive result (see [Quantity and quality of research available](#)). (NB. Standard clinical assessment is labelled clinical judgement in [Figure 6](#).)

Two of the studies (INSPIRE and Schnettler *et al.*) provided evidence for standard clinical assessment compared to the Elecsys test. However, relative test accuracy estimates were very different between the two studies. When applied to the PARROT trial, standard clinical assessment from INSPIRE had sensitivity and specificity values of 0.74 and 0.72, respectively. In contrast, standard clinical assessment from Schnettler¹⁴⁰ (as used in NICE DG23) had values of 0.98 and 0.25, respectively. Clinical advice noted that the INSPIRE trial may not be wholly representative of UK hospitals, particularly those which have limited accessibility or less experience of managing suspected pre-eclampsia. Hence, the clinical experts suggested that standard clinical assessment from Schnettler, as used in DG23, may be more representative. For this current economic evaluation, estimates of standard clinical assessment from INSPIRE and Schnettler *et al.*¹⁴⁰ were included and presented as separate assessment methods for purposes of comparison.

Of the four studies comparing the tests with each other, only one (INSPIRE) provided evidence on performance 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 clinical assessment (from INSPIRE)
2. standard clinical assessment (from DG23)
3. Triage test
4. Elecsys
5. Elecsys (add-on)
6. DELFIA
7. BRAHMS.

We considered PARROT,¹⁹ and INSPIRE³² to be the most relevant sources of evidence for this diagnostic assessment. Hence, two analyses were considered, one where absolute test performance values (sensitivity and specificity) were derived from PARROT,¹⁹ and one where INSPIRE³² was used. Resulting values are provided in [Table 30](#), along with details of how they were derived. Base-case analyses use the PARROT trial population, as this was deemed to be more relevant to the NHS than INSPIRE (PARROT is a multicentre trial, while INSPIRE is a single-centre trial). The ROPE

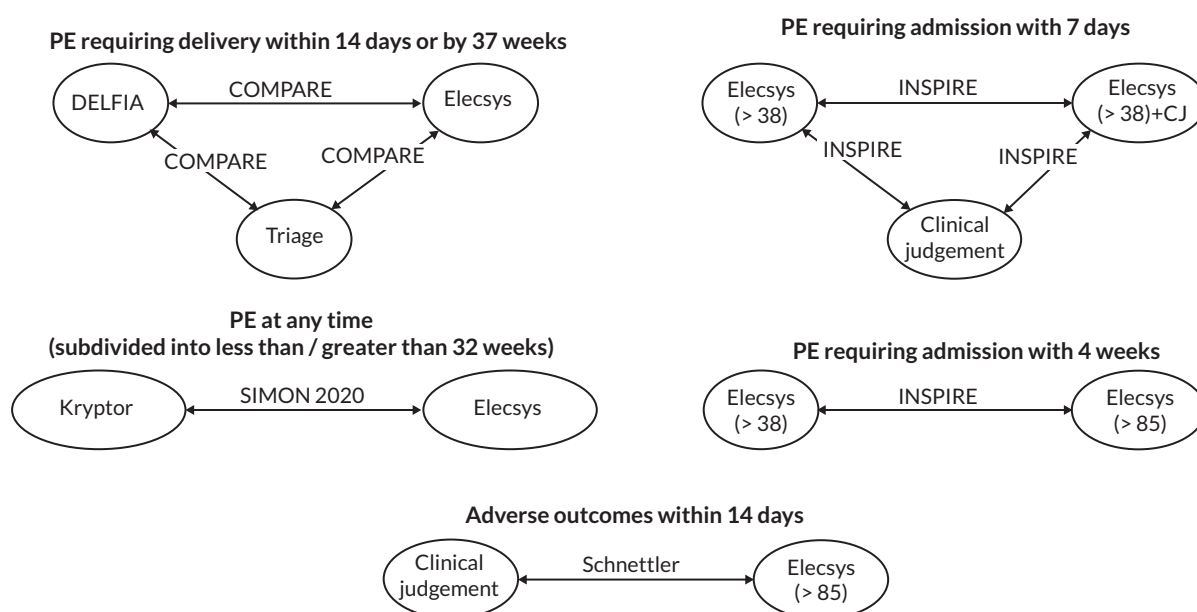


FIGURE 6 Overview of studies providing comparisons of test performance.

TABLE 30 Diagnostic sensitivity and specificity values used in the economic model

PLGF test, baseline = PARROT	Sensitivity	Specificity	Notes
Triage < 100	0.95	0.53	Absolute values from PARROT ¹⁹
Triage < 12	0.74	0.84	Absolute values from PARROT ¹⁹
Elecsys > 38	0.91	0.72	Relative to Triage < 100, from COMPARE ²⁹
Elecsys > 85	0.85	0.84	Relative to Triage < 12, from COMPARE ²⁹
DELFI A > 150	0.97	0.53	Relative to Triage < 100, from COMPARE ²⁹
DELFI A > 50	0.85	0.83	Relative to Triage < 12, from COMPARE ²⁹
BRAHMS > 38	0.96	0.67	Relative to Elecsys > 38, from Simon 2020 ¹⁴¹
BRAHMS > 85	0.92	0.77	Relative to Elecsys > 85, from Simon 2020 ¹⁴¹
Elecsys + CJ > 38	0.95	0.70	Relative to Elecsys > 38, from INSPIRE 2019 ³²
Elecsys + CJ > 85	0.90	0.82	Assume same relative effect as above
Clinical judgement (INSPIRE)	0.74	0.72	Relative to Elecsys > 38, from INSPIRE 2019 ³²
Clinical judgement (Schnettler)	0.98	0.25	Relative to Elecsys > 85, from Schnettler 2013 ¹⁴⁰
PLGF test, Baseline = INSPIRE	Sensitivity	Specificity	Notes
Triage < 100	0.98	0.61	Relative to Elecsys > 38, from COMPARE ²⁹
Triage < 12	0.90	0.80	Relative to Elecsys > 85, from COMPARE ²⁹
Elecsys > 38	0.96	0.80	Absolute values from INSPIRE 2019 ³²
Elecsys > 85	0.71	0.80	Relative to Elecsys > 38, from INSPIRE 2021 ^{69,142}
DELFI A > 150	0.99	0.61	Relative to Elecsys > 38, from COMPARE ²⁹
DELFI A > 50	0.90	0.79	Relative to Elecsys > 85, from COMPARE ²⁹
BRAHMS > 38	0.99	0.75	Relative to Elecsys > 38, from Simon 2020 ¹⁴¹
BRAHMS > 85	0.82	0.75	Relative to Elecsys > 85, from Simon 2020 ¹⁴¹
Elecsys + CJ > 38	0.98	0.78	Relative to Elecsys > 38, from INSPIRE 2019 ³²
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 ³²
Clinical judgement (Schnettler)	0.92	0.22	Relative to Elecsys > 85, from Schnettler 2013 ¹⁴⁰

study⁴³ provided estimates of the sensitivity and specificity of the BRAHMS test. While there were no estimates of relative test accuracy, we could have used as a source of absolute test performance values. However, we did not pursue this as the ROPE study is US-based, and the relevance to the UK NHS is unclear.

An overview of the test sensitivity and specificity values is provided in [Table 30](#). 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 COMPARE²⁹) and applying this to the PARROT¹⁹ 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 population sensitivity (Triage high-risk result, from PARROT): 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.¹⁴¹ 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 clinical assessment.^{19,138} Evidence from PROGNOSIS³⁷ includes Elecsys and standard clinical assessment (use of the ACOG criteria), but this was not included as it was assumed to be superseded by the INSPIRE trial,³² for which standard clinical assessment was based on observed clinical decision-making. Similarly, it was assumed that the PELICAN trial¹³⁹ was superseded by PARROT.¹⁹

Note the study by Simon *et al.*¹⁴¹ was not included in our systematic review of test accuracy and clinical effectiveness as it had an ineligible population according to our review inclusion criteria. Nevertheless, it was informative for the cost-effectiveness modelling.

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,¹³⁹ which showed very similar performance for the Triage test by hypertension category.

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 CG107⁵⁸ and expert opinion.

Costs associated with placental growth factor-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, we are 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 7](#). The cost components and the total cost of the PLGF-based tests are shown in [Table 31](#).

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

Resource use for management of women with suspected pre-eclampsia

The costs associated with the care of women with suspected pre-eclampsia are based on NICE CG107.⁵⁸ This guideline defines the management of pre-eclampsia and gestational hypertension and its associated resource use by hypertension category (mild, moderate or severe hypertension).

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 CG107,⁵⁸ 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.

Time to delivery

In accordance with CG107,⁵⁸ all women at high risk of pre-eclampsia are admitted to hospital. Based on clinical guidelines,⁵⁸ women are expected to have varying lengths of monitoring according to their disease status and gestational age. We used time to delivery estimates from the PELICAN study¹³⁹ as this study provided evidence on the time to delivery by both gestational age and the women's true pre-eclampsia status. The PELICAN study reports delivery times of 19 and 5 days for women with pre-eclampsia and gestational ages of < 35 and 35–37 weeks, respectively. Values for women without pre-eclampsia were estimated to be 45 days and 8 days. For women in the immediate delivery pathway, birth occurred within 2 days after admission.⁵⁸

TABLE 31 Cost components and total cost of PLGF-based 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	
Machine 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

a Triage PLGF test.

b Elecsys sFit-1/PLGF ratio test.

c BRAHMS Kryptor sFit-1/PLGF ratio test.

d Cost per reportable test including capital, maintenance and equipment costs.

Source

Based on companies' submissions, expert opinion and assumptions.

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 CG107.⁵⁸ We assumed that women receive oral labetalol until delivery, in line with the previous DAR.⁶ NICE CG107⁵⁸ 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 8](#) 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 CG107.⁵⁸ 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. The length of stay for women with severe hypertension was informed by the previous DAR.⁶ [Appendix 8](#) shows the recommended resource use to manage women at intermediate and low risk of pre-eclampsia for each hypertension category.

According to the previous DAR,⁶ we 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 been 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 2018–9 for NHS Trusts and NHS Foundation Trusts,¹⁴³ NHS Payment by Results Tariff 2020–1¹⁴⁴ and the 2020 version of drugs and pharmaceutical electronic market information tool (eMIT) national database.¹⁴⁵ [Table 84](#), [Appendix 8](#) presents the unit costs required for the NICE CG107 pathways.⁵⁸ Payment by Results Tariff 2020–1¹⁴⁴ was 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 2020–1¹⁴⁴ assesses stays of 0–5 days and 0–9 days and provides the costs for additional days.

We 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 is negligible. Similarly, for women managed in an inpatient setting, the cost of these tests is included within the cost of hospitalisation.

We assumed that women with pre-eclampsia would require hospitalisation at some point for monitoring and treatment. For those women whose pre-eclampsia was not identified, we assumed that this hospitalisation cost was equal to that for managing gestational severe hypertension (£662; based on an NHS Payment by Results Tariff¹⁴⁴ stay of up to 3 days). In addition, we assumed that women without pre-eclampsia who were hospitalised to manage suspected pre-eclampsia incurred a fixed NHS Payment by Results Tariff 2020–1¹⁴⁴ (NZ18A), which covers stays of up to 8 days (£1465).

Gestational age

For gestational age, we used data from the PELICAN study¹³⁹ as this provided the proportion of women with a gestational age < 35 weeks (287/625 = 46%). This proportion was varied via a beta distribution.

Evidence from PARROT 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).¹⁹ Hence, a weighted average of 7.36 was used for admitted women (with the exception of admitted women with pre-eclampsia or severe hypertension and a gestational age > 35 weeks, for whom 2 days was used). The corresponding cost for this admission is taken from the NHS Payment by Results Tariff 2020–1,¹⁴⁴ which is a fixed cost for stays of up to 8 days. Hence, variation in length of stay was not modelled.

[Table 24](#) 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 pathways⁵⁸ and the length of monitoring and resources described above. The total costs were calculated by multiplying the frequency of use of

each resource component by their unit costs (see [Appendix 7](#)) and by the length of time those resources were used. 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 (see [Table 24](#)).

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.^{14,19} [Table 82](#), [Appendix 8](#) 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 4 g as a bolus over 5–15 minutes followed by a maintenance dose of 1 g per hour for at least 24 hours.⁵⁸ The proportion of patients taking magnesium sulphate was sourced from PARROT¹⁴ and is also presented in [Appendix 7](#).

The costs for the different types of deliveries were based on the *National Schedule of Reference Costs 2018–9 for NHS Trusts and NHS Foundation Trusts*¹⁴³ and are shown in [Appendix 7](#). The cost of magnesium sulphate were sourced from the *British National Formulary* (accessed March 2021).¹⁴⁶ 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 study¹⁴ and for the Elecsys sFlt-1/PLGF ratio test were informed by data from INSPIRE study³² when available. For example, length of stay in SCBUs for Elecsys were informed by PARROT¹⁴ since no data from INSPIRE or other studies assessing Elecsys were available. Where no data were available for Elecsys, we assumed there were no differences in outcomes between the intervention and comparator arms. None of the studies reported maternal death.^{14,32}

The differences in the maternal outcomes were not reported directly by the studies, 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 placental growth factor test

[Table 82](#), [Appendix 8](#) 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 ICU and HDU and the remaining were admitted to the SCBU, as reported in the Phoenix study.¹⁴⁷

Maternal and neonatal outcomes for the Elecsys soluble fms-like tyrosine kinase-1/placental growth factor ratio test

The maternal severe/major complications for the Elecsys test were taken from INSPIRE³² and include pulmonary oedema, abruption and eclampsia. We assumed that each woman experienced only one of the adverse outcomes. [Table 82](#), [Appendix 8](#) shows the parameters associated with maternal, fetal and neonatal outcomes used in the model for the Elecsys sFlt-1/PLGF ratio test. INSPIRE³² reported the number of neonates admitted to the SCBU. However, it is not clear if this refers to ICU admissions. For the base case, we assumed that SCBU admissions were different from ICU and HDU 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 ICU and HDU.¹⁴⁷

Costs associated with maternal and neonatal complications

Mothers who did not experience major complications were managed with standard postnatal care. We considered that women and babies with severe outcomes were likely to be managed in maternal and neonatal ICUs, neonatal HDUs 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 (see [Table 82](#), [Appendix 8](#)). The unit cost of stay in neonatal ICUs and HDUs were calculated as the average of ICU and HDU costs (see [Table 82](#), [Appendix 8](#)).

Long-term costs

We included the long-term costs associated with complications for neonates. A study by Khan *et al.*¹⁴⁸ estimated the costs for preterm birth for the first 2 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 weeks and 36 weeks, there were costs of £1037 (after inflating the costs to the year 2020 using the Hospital and Community Health Service Index¹⁴⁹). 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 haemorrhage, we assumed the lifetime costs to be the same as for cerebral palsy, as used by Varley-Campbell.¹³⁶ Kruse *et al.*¹⁵⁰ 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,¹³⁶ we assumed that the costs after 2 years would be the same for those born preterm without intraventricular haemorrhage and those born full term.

Utilities

Of the five studies in our review of HRQoL studies (see [Results of the review of health-related quality-of-life studies](#)), only one study¹⁰⁰ provided better utility estimates, in our judgement, than those used in the previous DAR.⁶ Seppänen *et al.*¹⁰⁰ provides estimates of a decrement in utility for women admitted to an ICU due to pregnancy complications.

The studies identified suggest that women largely recovered to pre-pregnancy HRQoL scores by 6 months postpartum. We model short-term HRQoL outcomes until 6 months postpartum, 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 in a study by Prosser *et al.*¹³³ who assessed the HRQoL losses perceived by parents due to a false-positive result obtained within a newborn screening programme 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 between admission and delivery. We assumed this period was 31 days (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 *et al.*¹³³ 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's acting as proxies.

[Appendix 7](#) shows the utility scores used in the economic model for the short-term HRQoL. All of them, except for the decrements for women and babies admitted to an ICU and women with false-positive results, were used in the previous DAR.⁶ Based on the results from Seppänen *et al.*,¹⁰⁰ we assumed:

- A utility decrement of 0.039 in HRQoL for women admitted to an ICU.
- After 6 weeks postpartum, women who were admitted to ICU would have the same HRQoL as those women not admitted to the ICU as they are expected to have mostly recovered from adverse effects (as reported in Bijlenga *et al.*¹³⁵).
- 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.

Quality-adjusted life-years were calculated by multiplying the utility scores and decrements by the time spent in each health state.

Long-term estimation of quality-adjusted life-years in children

The QALYs accrued up to hospital discharge in neonates 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,¹⁴ we consider respiratory distress syndrome and intraventricular haemorrhage to be a proxy for preterm birth.

In PARROT,¹⁴ 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 respiratory distress syndrome was slightly higher in the revealed arm (13.8%) versus concealed arm (12.2%). The proportion of babies reported in PARROT with intraventricular haemorrhage was 1.2% in the revealed arm and 2.5% in the concealed arm. More details on the incidence of these adverse effects per level of risk of pre-eclampsia in [Appendix 7](#). INSPIRE³² does not report on these outcomes nor any other study in our systematic review of test accuracy and clinical effectiveness that assessed the Elecsys sFlt-1/PLGF ratio test.

Varley-Campbell *et al.*¹³⁶ estimated total discounted QALY loss for children for respiratory distress syndrome and intraventricular haemorrhage compared to preterm survivors. They used survival estimates from Office for National Statistics life tables,¹⁵¹ age-related disutilities from Ara and Brazier¹³⁷ and discounted at 3.5% per annum. For respiratory distress syndrome and intraventricular haemorrhage, they used lower utilities of 0.85 and 0.76, respectively. Varley-Campbell *et al.*¹³⁶ 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 respiratory distress syndrome and 70% for intraventricular haemorrhage. 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 Brazier¹³⁷ and discounting at 3.5% per annum.

Long-term estimation of quality-adjusted life-years in mothers

The longer-term HRQoL of mothers of children with and without adverse child outcomes are also taken from Varley-Campbell *et al.*¹³⁶ The estimates are derived assuming the average age at birth of 30 years (as reported by Office for National Statistics 2015¹⁵¹). Varley-Campbell *et al.* estimated the average discounted QALYs to be 17.42 for mothers whose child survived. For mothers whose child died, they either assumed 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 0.644.¹³⁶ We assume the average lifetime discounted QALYs of 13.45 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 of children who had respiratory distress syndrome or intraventricular haemorrhage of 2 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 postpartum.

[Table 83](#), [Appendix 8](#) shows the long-term QALYs used in the economic model.

Results of the economic evaluation

Base-case analysis

Since this report was written, a (stand-alone) study has been published comparing the diagnostic accuracy of the DELFIA Xpress PLGF 1-2-3 test with the DELFIA sFlt1/PLGF ratio test.⁴⁹ For the BRAHMS test, further evidence

has become available from Andersen *et al.*⁵⁵ (see [Quantity and quality of research available](#)). This study evaluated the performance of the BRAHMS test for diagnosing pre-eclampsia for differing thresholds: 33, 66 and 85. This new evidence means that it is possible to evaluate use of the BRAHMS test with a rule-out threshold of 66 and rule-in threshold of 85. We provide updated cost-effectiveness results for the DELFIA ratio test and the BRAHMS test in [Appendix 9](#).

Rule-out testing

Deterministic base-case results (which use PLGF-based tests to rule out pre-eclampsia) are presented in [Table 32](#). Incremental results (compared with the two definitions of standard clinical assessment) are provided in [Table 33](#), while the impact of excluding either long-term or all neonatal costs is demonstrated in [Table 34](#).

There was relatively little variation in total costs and QALYs between the diagnostic approaches. Costs were highest for the use of Elecsys (either stand-alone or as an add-on test) and lowest for the two standard clinical 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 clinical assessments.

Standard clinical assessment from DG23 had the highest percentage of true positives, but also the highest percentage of false positives (and hence the lowest percentage of false negatives), reflecting a conservative approach to managing pre-eclampsia. The largest percentage of true negatives was observed for the Elecsys test.

It should be noted that [Table 32](#) shows the results of using assessment methods (both standard clinical assessment and PLGF-based) to rule out pre-eclampsia, 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, while rates of false

TABLE 32 Deterministic base-case results, PLGF-based tests to rule out pre-eclampsia

Rule-out testing	SCA: DG23	SCA: INSPIRE	Triage test	Elecsys	Elecsys add-on	DELFLIA	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 (£)	3781	3781	3781	3781	3781	3781	3781
Maternal short term (£)	364	365	364	363	362	363	362
Neonatal short term (£)	4373	4377	4369	4361	4357	4362	4357
Neonatal long term (£)	1077	1084	1081	1079	1077	1078	1077
Total QALYs	17.6110	17.6093	17.6117	17.6139	17.6151	17.6137	17.6151
Clinical management	0.0	0.0	0.0	0.0	0.0	0.0	0.0
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
SCA, standard clinical assessment							

TABLE 33 Incremental base-case results, PLGF-based tests to rule out pre-eclampsia

Test	Total costs		Total QALYs			
	DG23 (£)	INSPIRE (£)	DG23	INSPIRE		
Standard clinical assessment	10,215	10,223	17.6110	17.6093		
	Incremental costs		Incremental QALYs		ICER (£/QALY)	
	DG23	INSPIRE	DG23	INSPIRE	DG23	INSPIRE
Triage	33.2	25.5	0.0007	0.0024	£47,393	£10,777
Elecsys	47.0	39.3	0.0029	0.0046	£16,290	£8638
Elecsys add-on	41.2	33.6	0.0041	0.0058	£10,099	£5834
DELFLA	10.5	2.8	0.0027	0.0044	£3874	£637
BRAHMS	14.6	6.9	0.0042	0.0058	£3508	£1183
ICER, incremental cost-effectiveness ratio.						

TABLE 34 Impact on base-case results of excluding neonatal outcomes

Including neonatal outcomes	Triage test	Elecsys	Elecsys add-on	DELFLA	BRAHMS
<i>Compared with DG23 standard clinical assessment</i>					
Incremental cost (£)	33	47	41	10	15
Incremental QALYs	0.0007	0.0029	0.0041	0.0027	0.0042
ICER (£/QALY) (£)	47,393	16,290	10,099	3874	3508
<i>Excluding long-term neonatal outcomes</i>					
Incremental cost (£)	29	45	41	9	15
Incremental QALYs	0.0002	0.0007	0.0010	0.0007	0.0010
ICER (£/QALY) (£)	162,565	64,239	41,617	13,531	14,797
<i>Excluding all neonatal outcomes</i>					
Incremental cost (£)	33	57	57	20	31
Incremental QALYs	0.0002	0.0007	0.0010	0.0006	0.0010
ICER (£/QALY) (£)	191,698	83,026	59,067	31,164	31,593
<i>Compared with INSPIRE standard clinical assessment</i>					
Incremental cost (£)	26	39	34	3	7
Incremental QALYs	0.0024	0.0046	0.0058	0.0044	0.0058
ICER (£/QALY) (£)	10,777	8638	5834	637	1183
<i>Excluding long-term neonatal outcomes</i>					
Incremental cost (£)	29	45	41	9	15
Incremental QALYs	0.0006	0.0011	0.0014	0.0010	0.0014
ICER (£/QALY) (£)	50,952	41,212	29,739	8298	10,518
<i>Excluding all neonatal outcomes</i>					
Incremental cost (£)	37	61	61	24	35
Incremental QALYs	0.0006	0.0011	0.0013	0.0010	0.0014
ICER (£/QALY) (£)	66,568	56,909	45,167	23,274	25,553
ICER, incremental cost-effectiveness ratio.					

positives and false negatives were 10.9% and 18.5%, respectively. Hence, the use of additional assessment methods to rule out pre-eclampsia leads to a decrease in the number of false positives, but at the expense of also reducing the number of true positives. Results from INSPIRE demonstrated a specificity of 80.1% for standard clinical assessment, 77.8% for Elecsys add-on and 79.6% for Elecsys stand-alone.³² The increased specificity for standard clinical assessment (compared with PLGF-based tests) observed in INSPIRE is not reflected in fewer false positives for standard clinical assessment because this trial comparison was based on use of Elecsys with a single threshold.

All the PLGF-based tests resulted in increased costs and QALY gains when compared with standard clinical assessment. Incremental QALYs were all very small (always < 0.006), so even though the largest cost increase was £47, incremental cost-effectiveness ratios (ICERs; per QALY) ranged from £637 to £47,393 (see [Table 33](#)). Incremental costs were always lower than the cost of a test, which ranged from £37 for DELFIA to £79 for Elecsys.

As anticipated, excluding neonatal costs led to increases in the ICERs for all the PLGF-based tests (see [Table 34](#)). The largest increases occurred when all neonatal outcomes were excluded whereby all PLGF-based tests had ICERs above £20,000.

The probabilistic results ([Table 35](#)) are similar to the deterministic results. The incremental QALYs (compared with standard clinical assessment) are very small, but there is less variation in the ICERs than the deterministic results and all ICERs are all below £12,500 per QALY. As with the deterministic results, the lowest ICERs are observed for DELFIA and the highest for the Triage test. 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 clinical assessments.

Rule out and rule in tests

Three options for the use of tests to both rule out and rule in pre-eclampsia were explored. Two contrasting options were derived from the short survey of clinical experts: (see [Test sensitivity and specificity](#)) 'standard' rule-in and 'cautious' rule-in. The third option is based on the PreOS trial which provides insights into how testing is used to rule out and rule in pre-eclampsia. The results from the two survey options were very similar to each other, so for brevity only results for the 'standard rule-in' survey and the PreOS study are provided here. [Table 89](#), [Appendix 9](#) shows deterministic results for rule-out and rule-in using the survey results, while results using PreOS evidence are provided in [Table 90](#), [Appendix 9](#). Summary cost-effectiveness results are provided in [Table 36](#).

The results are generally similar for all tests for both approaches, except for standard clinical 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.

TABLE 35 Probabilistic base-case results, PLGF-based tests to rule out pre-eclampsia

PLGF test	Total cost (£)	Total QALYs	ICER vs. standard clinical assessment (£/QALY)	
			DG23 (£)	INSPIRE (£)
Standard clinical assessment (DG23)	10,238	17.4789	–	–
Standard clinical assessment (INSPIRE)	10,247	17.4763	–	–
Triage test	10,267	17.4811	12,478	4091
Elecsys	10,286	17.4828	12,254	6040
Elecsys as add-on	10,281	17.4841	8150	4380
DELFIA	10,252	17.4817	4852	999
BRAHMS	10,260	17.4829	5294	1957

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 standard clinical 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 clinical assessment as used in DG23. For standard clinical assessment based on the INSPIRE trial, results varied depending on if 'standard rule-in' or 'cautious rule-in' was used, as summarised in [Table 37](#).

For clinical management decisions based on the PreOS trial, PLGF-based tests always dominated standard clinical assessment as used in DG23. This held for deterministic and probabilistic analyses, and when all neonatal outcomes were excluded. DELFIA and BRAHMS dominated standard clinical 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 £2561 when used as stand-alone and £1826 when used as an add-on. Similar ICERs were observed for the probabilistic results.

TABLE 36 Incremental base-case results, PLGF-based tests to rule out and rule in pre-eclampsia (based on survey responses and PreOS evidence)

Rule-out and rule-in testing based on survey responses	Total cost (£)	Total QALYs	ICER vs. standard clinical assessment	
			DG23	INSPIRE
Standard clinical assessment (DG23)	10,734	17.510		
Standard clinical 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
Rule-out and rule-in testing based on PreOS	Total cost (£)	Total QALYs	ICER vs. standard clinical assessment	
			DG23	INSPIRE
Standard clinical assessment (DG23)	10,302	17.494		
Standard clinical assessment (INSPIRE)	10,224	17.499		
Triage test	10,219	17.506	Dominates	Dominates
Elecsys	10,239	17.508	Dominates	£1715
Elecsys as add-on	10,238	17.509	Dominates	£1477
DELFIA	10,207	17.507	Dominates	Dominates
BRAHMS	10,223	17.507	Dominates	Dominates

TABLE 37 Incremental cost-effectiveness ratio vs. standard clinical assessment (INSPIRE) when excluding all neonatal outcomes

PLGF test	Survey: rule-out and rule-in	Survey: rule-out and cautious rule-in	PreOS: rule-out and rule-in (£)
Triage test	£5503	Dominates	20,679
Elecsys	Dominates	£2039	30,064
Elecsys as add-on	Dominates	£3246	27,390
DELFIA	£314	Dominates	6390
BRAHMS	£2037	£2753	17,796

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 underestimate their cost-effectiveness.

Comparison of rule-out and rule-in tests

In general, the use of PLGF-based tests for both ruling-out and ruling-in pre-eclampsia provides more favourable estimates of cost-effectiveness than when just used to rule out pre-eclampsia. A comparison of the incremental costs and QALYs is provided in [Figure 7](#). For illustration, this compares the Elecsys (add-on) test with standard clinical 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 8](#). This illustrates that cost savings are largest for the clinical management of pre-eclampsia, 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 clinical assessment from DG23 (25%), which leads to a large increase in false-positive results when used to rule in pre-eclampsia; 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%.

Scenario analyses

For the included scenario analyses, deterministic ICERs are presented here. Results are shown for both the strategy of using testing to only rule out pre-eclampsia and using testing to both rule out and rule in pre-eclampsia. 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 38](#) provides ICERs relative to standard clinical assessment as used in DG23, while for [Table 39](#) standard clinical assessment is based on that in INSPIRE.

For both definitions of standard clinical assessment, use of PLGF-based testing to rule out and rule in pre-eclampsia nearly always dominated standard clinical assessment, for all five PLGF-based tests considered. The two exceptions were when using INSPIRE for both baseline test performance and standard clinical assessment; for this, ICERs for the Triage test and DELFIA were both approximately £15,000.

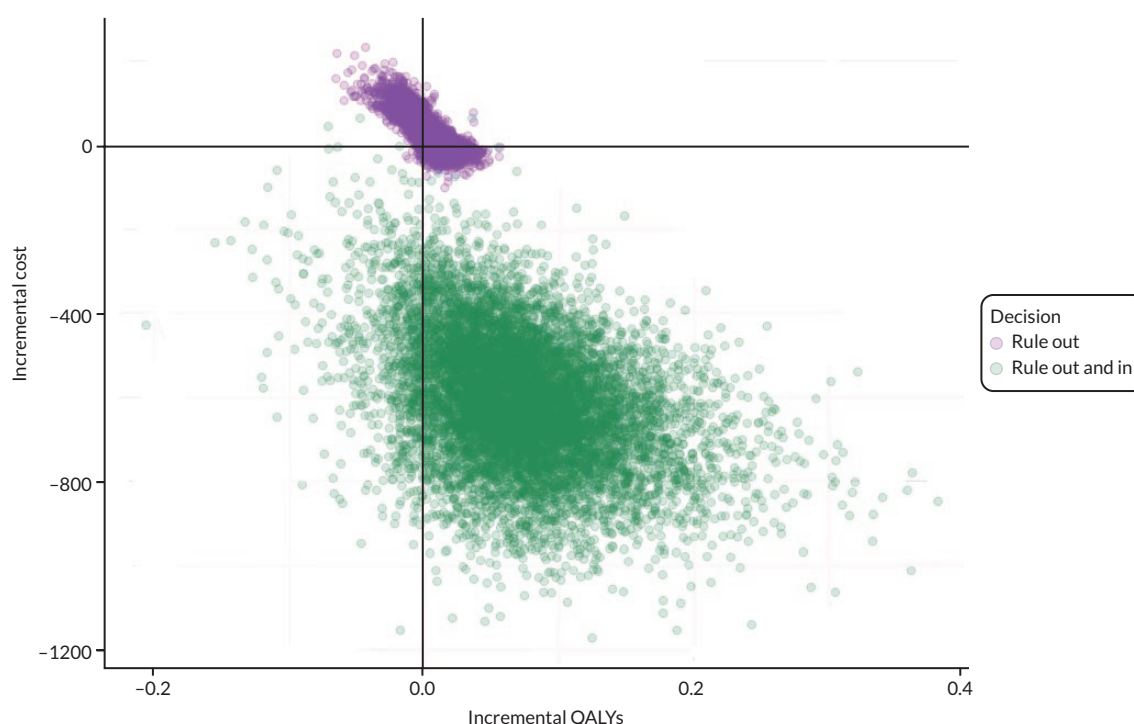


FIGURE 7 Incremental costs and QALYs for the Elecsys (add-on) test compared with standard clinical assessment from DG23, and rule-in based on the survey responses.

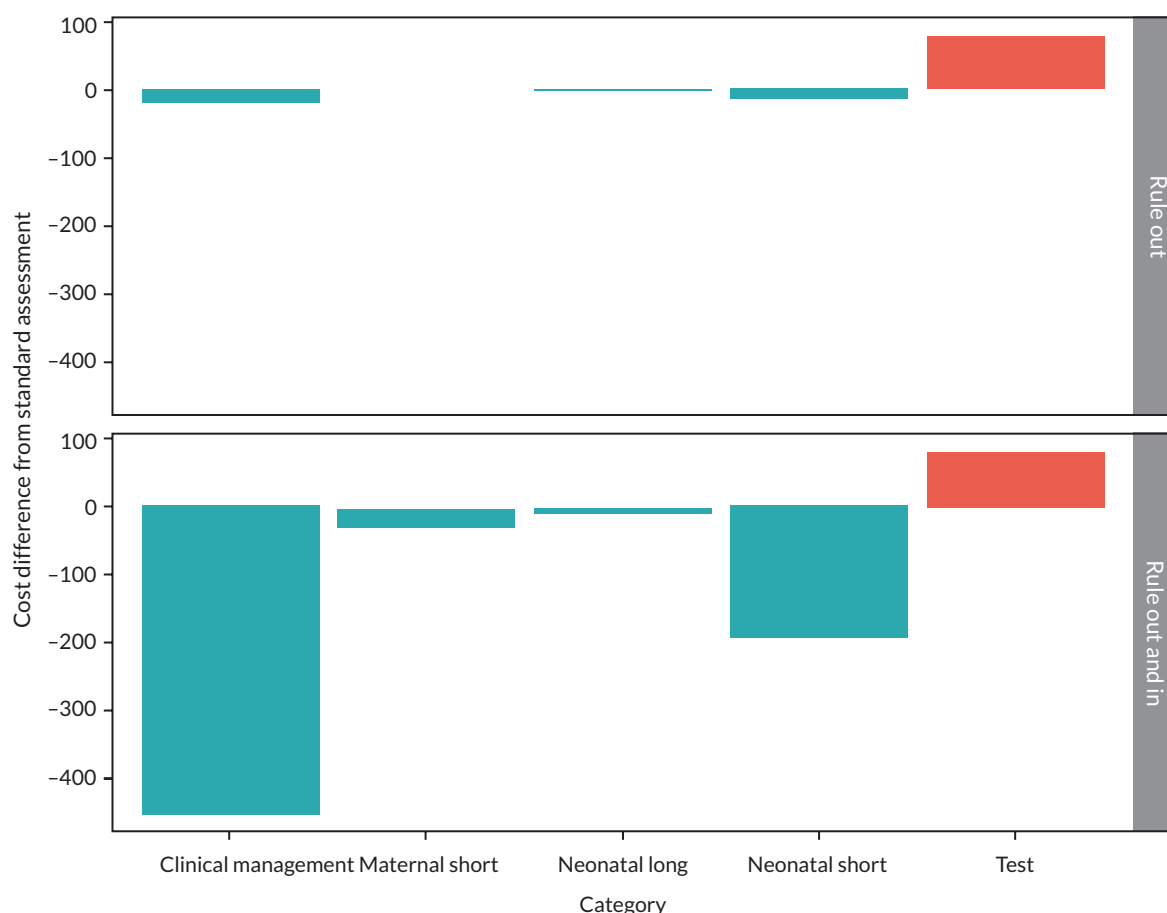


FIGURE 8 Breakdown of incremental costs for PLGF-based tests compared with standard clinical assessment.

When using PLGF-based testing to rule out pre-eclampsia, 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 baseline (and PLGF-based tests to rule out pre-eclampsia), use of the Elecsys test (stand-alone or add-on) had ICERs ranging from £10,572 to £1,044,065 against standard clinical assessment from INSPIRE. This may reflect that in INSPIRE the primary benefit of PLGF-based testing was to rule in pre-eclampsia (more women with pre-eclampsia were correctly identified).

Comparison with the results of other economic evaluations

Since we conducted our systematic review, additional evidence on use of the Triage test has been published from the PARROT Ireland trial.¹³⁸ In contrast to the PARROT trial,¹⁹ 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 pre-eclampsia. Comparative estimates of test performance were not available from either PARROT trial, but evidence on baseline hypertension was. When using hypertension evidence from PARROT Ireland, PLGF-based tests were found to have more favourable cost-effectiveness outcomes than when using hypertension evidence from PARROT.

The published cost-effectiveness analysis by Duhig *et al.*⁹² based on the PARROT-UK trial (reported in more detail in [Appendix 6](#)) did not include utility outcomes but found that PLGF-based testing was cost saving. Results provided for

TABLE 38 Sensitivity analyses comparing PLGF-based tests with standard clinical assessment from DG23

PLGF-based test	ICER vs. standard clinical assessment (£/QALY)	
	Testing to rule out PE	Testing to rule out and rule in PE
Base-case^a		
Triage test	£47,393	Dominates
Elecsys	£16,290	Dominates
Elecsys add-on	£10,099	Dominates
DELFI	£3874	Dominates
BRAHMS	£3508	Dominates
Scenario: INSPIRE trial for baseline test performance		
Triage test	£2836	Dominates
Elecsys	£19,353	Dominates
Elecsys add-on	£10,572	Dominates
DELFI	Dominates	Dominates
BRAHMS	£3027	Dominates
Scenario: True-positive test results cost more than false-negative results		
Triage test	£43,279	Dominates
Elecsys	£15,603	Dominates
Elecsys add-on	£9829	Dominates
DELFI	£3283	Dominates
BRAHMS	£3327	Dominates
Scenario: Hypertension distribution from PARROT Ireland study		
Triage test	£114,233	Dominates
Elecsys	£42,789	Dominates
Elecsys add-on	£28,897	Dominates
DELFI	£16,290	Dominates
BRAHMS	£15,015	Dominates
Scenario: Hypertension distribution from PELICAN study		
Triage test	£43,602	Dominates
Elecsys	£26,576	Dominates
Elecsys add-on	£18,729	Dominates
DELFI	Dominates	Dominates
BRAHMS	Dominates	Dominates

PE, pre-eclampsia.

^a Baseline treatment effects and hypertension distribution from PARROT, true-positive test results cost same as false negatives.

TABLE 39 Sensitivity analyses comparing PLGF-based tests with standard clinical assessment from INSPIRE

PLGF-based test	ICER vs. standard clinical assessment (£/QALY)	
	Testing to rule out PE (£)	Testing to rule out and rule in PE
Base-case^a		
Triage test	10,777	Dominates
Elecsys	8638	Dominates
Elecsys add-on	5834	Dominates
DELFIA	637	Dominates
BRAHMS	1183	Dominates
Scenario: INSPIRE trial for baseline test performance		
Triage test	13,169	£15,673
Elecsys	1,044,065	Dominates
Elecsys as add-on	37,382	Dominates
DELFIA	6713	£14,379
BRAHMS	14,726	Dominates
Scenario: True-positive test results cost more than false-negative results		
Triage test		£11,395
Elecsys		£9156
Elecsys as add-on		£6398
DELFIA		£1266
BRAHMS		£1801
Scenario: Hypertension distribution from PARROT Ireland trial		
Triage test		£30,555
Elecsys		£25,435
Elecsys as add-on		£19,182
DELFIA		£8316
BRAHMS		£9396
Scenario: Hypertension distribution from PELICAN study		
Triage test		£9655
Elecsys		£15,158
Elecsys as add-on		£11,962
DELFIA		Dominates
BRAHMS		Dominates
a Baseline treatment effects and hypertension distribution from PARROT, true-positive test results cost same as false negatives.		

the model were sensitive to how test results were incorporated into clinical decision-making, and it is unclear what approach was taken for the PARROT trial. This limits comparisons with the PARROT cost-effectiveness analysis. In addition, some of the cost savings observed in the PARROT 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 pre-eclampsia was generally found to be cost saving in the analyses of this report, while testing to rule out pre-eclampsia was not cost saving. Hence, either approach could be consistent with the results of the PARROT-UK cost-effectiveness analysis.

The UK-based cost-effectiveness analysis by Vatish *et al.*⁹⁹ found that use of the Elecsys test was likely to be cost saving. This study is reported in more detail in [Appendix 6](#). 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.

Chapter 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, for example if the laboratory uses 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.

Chapter 7 Discussion

Statement of principal findings

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 5-year intervening period. We included a total of 17 studies in this update review of test accuracy and clinical outcomes, compared to just 4 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 ongoing studies whose results, when available, are likely to have significant implications for clinical practice in England and the UK.

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, is based on 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 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%); lower odds of 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 preterm delivery (< 37 weeks), gestation at delivery and perinatal and neonatal outcomes.

There was no statistically significant difference between the trial arms in pre-eclampsia-related hospital admissions within 24 hours of the test, the primary outcome. However, 100% of participants in the revealed 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 correctly diagnosed 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 several potential explanations for the limited clinical effectiveness impact in the studies of these two tests, one of which is 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 sFit-1 Kryptor/BRAHMS PLGF plus Kryptor pre-eclampsia 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.

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 (DG23⁷). The current model, however, differs from the original⁶ 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.

For the model, a single 'baseline' trial was used, to which relative treatment effects are applied. Two baselines were considered: PARROT and INSPIRE. This approach ensures consistency in both the modelled population and the modelled assessment methods. 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 clinical assessment. Standard clinical assessment was included in two studies, both of which compared with the Elecsys test. Relative effects were very different between the two studies. Hence, two different estimates of standard clinical assessment were included in the model (one for each study).

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 pre-eclampsia or using tests to both rule out and rule in a suspicion of pre-eclampsia.

For the base-case cost-effectiveness analysis, PLGF-based tests were used to rule out pre-eclampsia, baseline test accuracy and hypertension severity were both taken from PARROT, 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 clinical assessment.

When used as rule-out tests (with neonatal outcomes included), all tests produced higher QALYs and higher costs than both types of standard clinical assessment. ICERs ranged from £637 (DELFI vs. standard clinical assessment from INSPIRE) to £47,393 (Triage vs. standard clinical 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 < 0.006. Excluding all neonatal outcomes led to all ICERs (compared with either standard clinical assessment) exceeding £20,000.

When used to both rule out and rule in pre-eclampsia, PLGF-based tests always dominated standard clinical assessment as used in DG23. This dominance remained when excluding all neonatal outcomes. When compared with standard clinical 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 pre-eclampsia dominated both types of standard clinical assessment. When used to just rule out pre-eclampsia, 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 clinical 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 pre-eclampsia, followed by short-term neonatal costs. The largest cost increases were always the cost of the test. Among the PLGF-based tests, cost-effectiveness results were generally the most favourable for the Elecsys test when used as an add-on to standard clinical assessment. For all 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 underestimate the value of PLGF-based tests when used alongside standard clinical assessment.

Strengths and limitations of the assessment

Strengths

Since the previous DAR, more data have been published on the maternal outcomes and neonatal outcomes from RCTs of the Triage and Elecsys PLGF-based 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 used in the base case 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 < 35 weeks.

The economic 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 pre-eclampsia.

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 clinical assessment is consistently defined, and that realistic clinical management decisions are included.

Limitations

A fully incremental cost-effectiveness analysis of the four PLGF-based tests relevant to the decision problem was not possible because of available clinical effectiveness data limitations for the DELFIA Xpress PLGF 1-2-3 test and the BRAHMS Kryptor sFlt-1/PLGF ratio test.

It was not possible to compare the performance of the Triage and Elecsys tests directly because the clinical effectiveness evidence for these tests came from different studies.

There was substantial heterogeneity in the evidence base, particularly with regards to the population studied and test outcome measure. This limits the usefulness of using relative treatment effects from different studies. It was therefore not possible to meta-analyse the test accuracy and clinical effectiveness studies due to the notable heterogeneity. However, we have provided a detailed exploration of the results of the studies in a narrative synthesis. There is heterogeneity in how PLGF-based tests are used in clinical practice, which makes it difficult to identify a single base case for this.

Two different approaches to standard clinical assessment were considered for this report. In general, PLGF-based tests performed better when compared with standard clinical assessment from DG23 than standard clinical assessment from INSPIRE. The latter was based on a single large teaching hospital, and so may be representative of how suspected pre-eclampsia is managed in these types of setting, but not in others. Conversely, evidence on standard clinical 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 the NHS is unclear.

A further limitation is that most of the evidence on treatment effects was for PLGF-based tests when used as stand-alone tests. In practice, PLGF-based tests would be used as add-ons to standard clinical 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 are likely to be underestimated.

Uncertainties

Comparisons of PLGF-based tests, both to each other and to standard clinical 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 clinical assessment for a representative cohort of women with suspected pre-eclampsia.

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.

Equality, diversity and inclusion

The risk of pre-eclampsia increases with the presence of linked factors such as advancing maternal age, excessive weight, Black and South Asian ethnicity, history of hypertension and diabetes and previous history of pre-eclampsia. Traditionally, however, reporting of these factors in clinical studies has been patchy, limited in detail and inconsistent. Furthermore, analysis and interpretation of clinical study data often lack a full consideration of these factors, resulting in missed opportunities to identify characteristics which are prognostic or predictive of health outcomes and any risk there may be for increasing health inequalities. Good data on participant characteristics are also essential for our understanding of the generalisability of study results to clinical practice, particularly across geographically diverse areas.

As reported earlier (see [Characteristics of participants in the add-on studies](#)), the add-on test studies included in the systematic review of test accuracy and clinical effectiveness provided baseline data on study participants' age, their weight, parity, ethnicity, smoking status and gestational age. The data illustrate, albeit to a limited degree, the sociodemographic profile of the study samples. Most participants were of White ethnic origin, varying from 66% to 90% of the patients across the studies. The proportion of participants whose ethnicity was classed as Black was much smaller, varying from 13% to 25%. Likewise, the proportion of participants classed as Asian varied from 2% to 26%. The average age of women was around 31 years old and median BMI was around 26–29 kg/m². While these data are informative, only a relatively small selection of characteristics are considered and the level of detail given is limited. The relatively low proportion of women from Black, Asian and Mixed ethnic backgrounds in the studies contrasts starkly to the disproportionately high incidence of pre-eclampsia and burden of disease among these population groups.

Concerningly, it has been shown that use of PLGF as a biomarker to diagnose pre-eclampsia can potentially increase health inequality. A large UK prospective observational study of 29,035 pregnant women attending a routine hospital visit found that, compared with White women, Black women, South Asian, East Asian and Mixed-race women had higher mean serum PLGF concentrations and lower sFlt-1/PLGF concentration ratios.¹⁵² Accordingly, the study demonstrated that use of fixed PLGF concentration cut-offs for detecting pre-eclampsia resulted in lower detection rates for Black women compared to White women. Wright *et al.*¹⁵² conclude that, in a multicultural society, applying a fixed pre-eclampsia diagnostic cut-off disadvantages Black and South Asian women. They propose a 'competing risks' model which combines the prior distribution of gestational age at delivery with pre-eclampsia with likelihoods

obtained by multiple of the median values of PLGF and sFlt-1 adjusted according to maternal characteristics (e.g. race, demographic characteristics, medical history) to estimate patient-specific risks for pre-eclampsia.

It should be acknowledged that the Wright *et al.*¹⁵² study investigated use of PLGF and sFlt-1 testing as a screening tool and not necessarily as a diagnostic test. Thus, in practice, patient-specific risks (e.g. ethnicity, medical history and demographic factors) should be taken into consideration by the clinician as part of standard clinical assessment, and the results of the biomarker tests interpreted accordingly. Irrespective of clinical context, greater consideration of patient characteristics, particularly ethnicity, is recommended, particularly to increase awareness of the limitations of PLGF-based testing using fixed cut-offs across the spectrum of women with suspected pre-eclampsia.

Chapter 8 Conclusions

Implications for service provision

Use of PLGF-based tests to rule out and rule in pre-eclampsia has the potential to provide improved outcomes at reduced cost when compared with standard clinical assessment. However, results are limited by heterogeneity in the evidence, particularly with regards to outcomes assessed by PLGF-based tests. In addition, any estimated QALY benefits associated with PLGF-based tests were very small. Furthermore, uncertainty remains for factors such as the impact of PLGF-based tests on improving neonatal outcomes, the accuracy of standard clinical 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.

Much of the evidence for the performance of PLGF-based tests comes from studies in which the tests were used stand-alone. In practice, the tests would be used as add-ons to standard clinical assessment. The results of this diagnostic assessment suggest that add-on test use leads to improved cost-effectiveness results compared with stand-alone use.

The evidence showing higher PLGF/lower sFlt-1 concentrations among women of Black, Asian or Mixed ethnicity, compared to women of White ethnicity, underlines the importance of patient-specific testing strategies accounting for factors such as ethnicity and other patient characteristics. The use of fixed cut-offs across the spectrum of women presenting with suspected pre-eclampsia may disadvantage women from these ethnic groups. Standard clinical assessment protocols should be reviewed and, where necessary, updated to emphasise the importance of considering patient-specific risks when interpreting PLGF-based test results.

Suggested research priorities

Despite an increase in the number of studies included in this update 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.
- Further evaluation of the diagnostic accuracy and analytical validity of the DELFIA Xpress PLGF 1-2-3 test and BRAHMS sFlt-1 Kryptor/BRAHMS PLGF plus Kryptor pre-eclampsia ratio tests is needed.
- Further primary research is needed into the diagnostic performance of initial PLGF-based testing alongside standard clinical assessment among minority ethnic groups. This is especially important given recent evidence demonstrating higher PLGF levels in Black and minority ethnic women,¹⁵² leading to artificially low pre-eclampsia detection rates. The research should explore alternatives to standard cut-offs, such as expressing PLGF levels as multiples of the mean for each gestational age.
- An overarching recommendation for all future research is that study sampling and recruitment should seek greater representation from non-White ethnicities and women with low income/socioeconomic status, than has been the case in the previous studies.

The lack of evidence in our study for the use of repeat PLGF-based testing for suspected pre-eclampsia suggested the need for further research in this area. However, since this report was completed, a large phase 3 multicentre RCT evaluating repeat PLGF-based testing (using a clinical management algorithm) in women with suspected pre-eclampsia has been published – the PARROT-2 study.¹⁵³ The trial was conducted in 22 maternity units across England, Scotland and Wales, and is believed to be the first major RCT to investigate the clinical benefits of repeat testing. The results demonstrated high test performance for repeat PLGF-based tests predicting need for delivery for pre-eclampsia within 14 days (similar to with the findings of the add-on studies of initial PLGF-based testing included in our systematic

review). However, the trial demonstrated that repeat testing had no impact on severe adverse perinatal and maternal outcomes and concluded that PLGF-based testing of all individuals with suspected pre-eclampsia is not recommended. The results reflect the use of repeat testing in a high-income setting with low prevalence of events and the authors suggest that further research could identify subgroups of people who might benefit from repeat testing. We echo this recommendation, and suggest investigation focuses on subgroups of women at disproportionately high risk of pre-eclampsia, for example women from minority ethnic backgrounds, and women of low socioeconomic status.

Additional information

CRedit contribution statement

Jonathan Shepherd (<https://orcid.org/0000-0003-1682-4330>): Conceptualisation (supporting), Formal analysis (supporting), Funding acquisition (supporting), Investigation (equal), Methodology (supporting), Project administration (equal), Supervision (equal), Visualisation (equal), Writing – original draft (lead), Writing – reviewing and editing (lead).

Geoff Frampton (<https://orcid.org/0000-0003-2005-0497>): Conceptualisation (supporting), Formal analysis (supporting), Funding acquisition (supporting), Investigation (equal), Methodology (supporting), Project administration (equal), Supervision (equal), Visualisation (equal), Writing – original draft (supporting), Writing – reviewing and editing (supporting).

Ben Kearns (<https://orcid.org/0000-0001-7730-668X>): Conceptualisation (equal), Formal analysis (lead), Investigation (equal), Methodology (equal), Project administration (supporting), Software (equal), Supervision (equal), Visualisation (supporting), Writing – original draft (supporting), Writing – reviewing and editing (supporting).

Karen Pickett (<https://orcid.org/0000-0002-8631-6465>): Formal analysis (supporting), Investigation (supporting), Methodology (supporting), Visualisation (supporting), Writing – original draft (supporting), Writing – reviewing and editing (supporting).

Ines Souto-Ribeiro (<https://orcid.org/0000-0001-8464-4513>): Formal analysis (supporting), Investigation (supporting), Methodology (supporting), Visualisation (supporting), Writing – original draft (supporting), Writing – reviewing and editing (supporting).

Allan J Wailoo (<https://orcid.org/0000-0002-9324-1617>): Conceptualisation (equal), Formal analysis (equal), Funding acquisition (supporting), Investigation (equal), Methodology (equal), Software (equal), Supervision (equal), Visualisation (supporting), Writing – original draft (supporting), Writing – reviewing and editing (supporting).

Lois Woods (<https://orcid.org/0000-0002-4587-9149>): Formal analysis (supporting), Investigation (supporting), Methodology (supporting), Visualisation (supporting), Writing – original draft (supporting), Writing – reviewing and editing (supporting).

Keith Cooper (<https://orcid.org/0000-0002-0318-7670>): Formal analysis (supporting), Investigation (supporting), Methodology (supporting), Visualisation (supporting), Writing – original draft (supporting), Writing – reviewing and editing (supporting).

Lorna Hazell (<https://orcid.org/0000-0002-5962-0648>): Formal analysis (supporting), Investigation (supporting), Methodology (supporting), Visualisation (supporting), Writing – original draft (supporting), Writing – reviewing and editing (supporting).

Abdullah Pandor (<https://orcid.org/0000-0003-2552-5260>): Formal analysis (equal), Investigation (supporting), Methodology (supporting), Visualisation (supporting), Writing – original draft (supporting), Writing – reviewing and editing (supporting).

David A Scott (<https://orcid.org/0000-0001-6475-8046>): Formal analysis (supporting), Investigation (supporting), Methodology (supporting), Visualisation (supporting), Writing – original draft (supporting), Writing – reviewing and editing (supporting).

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Data-sharing statement

Completed data extractions for all studies included in the systematic review of diagnostic test evaluation and clinical effectiveness can be provided on request to the authors.

Ethics statement

Ethical approval was not sought for this study as this is not a requirement for secondary research, including economic modelling.

Information governance statement

The University of Southampton is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation the University of Southampton is the Data Processor; the NIHR is the Data Controller and we process personal data in accordance with their instructions. You can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer here: www.southampton.ac.uk/about/governance/policies/privacy-policy.page.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at <https://doi.org/10.3310/HDST9104>.

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Appendix 1 Searching, study selection and study appraisal methods

Clinical and test accuracy 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 to 13 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 18 March 2021.

Searches of the Database of Abstracts of Reviews of Effects 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 ([Table 40](#)). Search strategies for test accuracy and health economic studies.^{97,154}

TABLE 40 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 and Other Non-Indexed Citations, Daily and Versions(R) 1946–10 November 2020 Search limited year 2015 Date searched: 11 November 2020 Update search: 18 March 2021	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/ 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	First search:1494 Update search: 82

continued

TABLE 40 Search strategies for test accuracy and health economic studies (continued)

Database, host, years searched, date searched	Literature search strategy	Results
EMBAE 1996–2020 Week 45 Limited 2015–current Searched: 13 November 2020 Update search: 18 March 2021	1 preeclampsia/ or "eclampsia and preeclampsia"/ 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 hypertensi*).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 ((Elecys 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 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"	First search: 377 Update search: 10

TABLE 40 Search strategies for test accuracy and health economic studies (continued)

Database, host, years searched, date searched	Literature search strategy	Results
Cochrane Library (CDSR and CENTRAL) Searched: 13 November 2020 Update search: 18 March 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 #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,kw 1 #23 ((("placental growth factor" and (triage or alere or quidel))):ti,ab,kw 3 #24 (((Elecys 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	Cochrane reviews: 5 Trials: 141 Update search: Reviews: 0 Trials: 6

continued

TABLE 40 Search strategies for test accuracy and health economic studies (continued)

Database, host, years searched, date searched	Literature search strategy	Results
Web of Science Indexes=SCI- EXPANDED, CPCI-S Timespan=2015–20 Searched: 13 November 2020 Update search: 18 March 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=((Elecys 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: 13 November 2020 Update search: 18 March 2021	((ELECTSYS 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 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 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-eclamp*" or "pre eclamp*")) OR ("Eclampsia"[mhe]))) FROM 2015 TO 2020	First search: 2 Update search: 0
Epistemonikos Title search only. 2015–20 Searched: 13 November 2020 Update search: 18 March 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 elecys 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

TABLE 40 Search strategies for test accuracy and health economic studies (continued)

Database, host, years searched, date searched	Literature search strategy	Results
PROSPERO Searched: 18 November 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 #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	27
ClinicalTrials.gov Searched: 13 November 2020 Update search: 18 March 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 Identification of studies) Searched: November 2020	Conferences from 2016 up to 2020 (where possible) were hand-searched. Keywords: pre-eclampsia, hypertension, 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 Identification of studies) Searched: November 2020	Keywords: pre-eclampsia, hypertension, toxemia, gestosis, placenta growth factor, PLGF, SFLT	0

Study selection worksheet for the systematic review of test accuracy and clinical effectiveness (add-on tests)

The inclusion and exclusion criteria worksheet which was applied to full-text publications is shown in [Table 41](#).

TABLE 41 Inclusion and exclusion criteria 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
<i>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.</i>			
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 • 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 • Fetal morbidity and mortality^c • Neonatal morbidity and mortality • HRQoL	Yes ↓ next question	Unclear ↓ next question	No → EXCLUDE
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	Fetal/neonatal		
Biochemical abnormalities	Breathing difficulties		
Disseminated intravascular coagulation/thrombosis	Chronic lung disease		
Eclampsia	Gestational age at delivery		
Emergency caesarean for compromised baby	Growth at delivery		
Haematological abnormalities	Intracranial haemorrhage		
HELLP syndrome	Late-onset infection		
Liver failure	Necrotising enterocolitis		
Renal failure	Neonatal length of stay		
Severe hypertension	Neonatal resuscitation		
Stroke	Preschool developmental delays		
Weight at delivery (very low = < 1500g).			

Risk-of-bias assessments for studies included in the systematic review of test accuracy and clinical effectiveness

Table 42 gives the results of the critical appraisal of add-on studies using the QUADAS-2 criteria for diagnostic test performance. The results are expressed as judgements of the risk of bias (high, low or unclear).

TABLE 42 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 Kryptor sFlt-1/PLGF ratio							
Andersen 2019	Unclear	Low	Low	Unclear	Low	Low	Low

a Accuracy was assessed in the concealed trial arm only, so the PLGF test was not used alongside standard clinical assessment.

Note

Of the seven identified add-on studies, no accuracy data were reported in the PreOS and MAPPLE study publications.

Risk-of-bias assessments for clinical and test accuracy randomised controlled trials (add-on studies)

Table 43 gives the results of the critical appraisal of add-on studies using the Cochrane risk of Bias instrument, version 1. The results are expressed as judgements of the risk of bias (high, low or unclear).

TABLE 43 Risk-of-bias assessments for add-on RCTs

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

Note

Risk-of-bias criteria version 1. Judgements: low, high or unclear.

Appendix 2 Excluded studies with rationale for exclusion

Systematic review of test accuracy and clinical effectiveness

[Table 44](#) lists publications excluded from the review based on inspection of the publication full text. For each publication, a reason for exclusion is provided (i.e. the first criterion of the study selection worksheet the study failed to meet – discussed in this section).

TABLE 44 References excluded from the test accuracy review at full-text screening

Reference	Exclusion reason: first reason identified
Adami 2020 ¹⁵⁵	(9) Insufficient information (no response received to author enquiries)
Adami 2020 ⁷⁷	(7) No relevant outcomes
Adami 2019 ¹⁵⁶	(9) Insufficient information (no response received to author enquiries)
Andersen 2015 ¹⁵⁷	(3) Ineligible population
Andersen 2016 ¹⁵⁸	(3) Ineligible population
Andrietti 2017 ¹⁵⁹	(3) Ineligible population
Andrietti 2016 ¹⁶⁰	(3) Ineligible population
Bahlmann 2016 ¹⁶¹	(7) No relevant outcomes
Bednarek-Jedrzejek 2019 ¹⁶²	(6) Ineligible comparator/reference standard
Birdir 2018 ¹⁶³	(3) Ineligible population
Black 2019 ¹⁶⁴	(3) Ineligible population
Black 2019 ¹⁶⁵	(3) Ineligible population
Black 2020 ¹⁶⁶	(3) Ineligible population
Caillon 2018 ¹⁶⁷	(3) Ineligible population
Cetin 2017 ¹⁶⁸	(3) Ineligible population
Chaiworapongsa 2016 ¹⁶⁹	(3) Ineligible population
Chang 2017 ¹⁷⁰	(3) Ineligible population
Cheng 2018 ¹⁷¹	(6) Ineligible comparator/reference standard
Cheng 2018 ¹⁷²	(3) Ineligible population
Choi 2020 ¹⁷³	(3) Ineligible population
Ciobanu 2019 ¹⁷⁴	(3) Ineligible population
Contino 2018 ¹⁷⁵	(8) Conference abstract with insufficient information
Dröge 2015 ⁶⁷	(3) Ineligible population
Dröge 2021 ¹⁷⁶	(9) Insufficient information (no response received to author enquiries)
Duhig 2020 ¹⁷⁷	(1) Not primary diagnostic research
Enengl 2020 ¹⁷⁸	(3) Ineligible population
Evers 2018 ¹⁷⁹	(3) Ineligible population
Frenna 2017 ¹⁸⁰	(3) Ineligible population
Gaccioli 2018 ¹⁸¹	(3) Ineligible population
Giardini 2019 ⁹⁵	(6) Ineligible comparator/reference standard
Giardini 2020 ¹⁸²	(3) Ineligible population

TABLE 44 References excluded from the test accuracy review at full-text screening (*continued*)

Reference	Exclusion reason: first reason identified
Giblin 2020 ⁷²	(1) Not primary diagnostic research
Gomez-Roig 2015 ¹⁸³	(3) Ineligible population
Graupner 2018 ¹⁸⁴	(3) Ineligible population
Griffin 2018 ¹⁸⁵	(1) Not primary diagnostic research
Heimberger 2020 ¹⁸⁶	(3) Ineligible population
Herraiz 2018 ¹⁸⁷	(3) Ineligible population
Herraiz 2018 ¹⁸⁸	(3) Ineligible population
Hirashima 2018 ¹⁸⁹	(5) Ineligible test (i.e. not listed in protocol)
Hoffmann 2017 ¹⁹⁰	(7) No relevant outcomes
Honigberg 2016 ¹⁹¹	(3) Ineligible population
Huhn 2018 ¹⁹²	(3) Ineligible population
Jadli 2019 ¹⁹³	(3) Ineligible population
Karge 2020 ¹⁹⁴	(3) Ineligible population
Karge 2021 ¹⁹⁵	(3) Ineligible population
Lind Malte 2018 ¹⁹⁶	(6) Ineligible comparator/reference standard
Lou 2019 ¹⁹⁷	(3) Ineligible population
Lubis 2020 ¹⁹⁸	(3) Ineligible population
Lubis 2019 ¹⁹⁹	(3) Ineligible population
MacDonald 2018 ²⁰⁰	(3) Ineligible population
Mathur 2016 ²⁰¹	(3) Ineligible population
Menke 2016 ²⁰²	(2) Non-English language
Mihalceanu 2015 ²⁰³	(3) Ineligible population
Mueller 2020 ²⁰⁴	(9) Insufficient information (no response received to author enquiries)
Nagalla 2018 ²⁰⁵	(8) Conference abstract with insufficient information
Nagalla 2020 ²⁰⁶	(3) Ineligible population
Navaratnam 2019 ²⁰⁷	(3) Ineligible population
Navaratnam 2019 ²⁰⁸	(3) Ineligible population
Neuman 2020 ²⁰⁹	(3) Ineligible population
Neuman 2021 ²¹⁰	(3) Ineligible population
Nguyen 2018 ²¹¹	(3) Ineligible population
Niemczyk 2016 ²¹²	(1) Not primary diagnostic research
Palmer 2017 ²¹³	(3) Ineligible population
Palmer 2019 ²¹⁴	(9) Insufficient information (no response received to author enquiries)
Parchem 2019 ²¹⁵	(6) Ineligible comparator/reference standard
Parchem 2020 ²¹⁶	(6) Ineligible comparator/reference standard
Perales 2017 ²¹⁷	(3) Ineligible population
Perdigao 2019 ²¹⁸	(6) Ineligible comparator/reference standard
Perry 2020 ⁷³	(3) Ineligible population
Pluddemann 2020 ²¹⁹	(1) Not primary diagnostic research
Raia-Barjat 2019 ²²⁰	(3) Ineligible population

continued

TABLE 44 References excluded from the test accuracy review at full-text screening (*continued*)

Reference	Exclusion reason: first reason identified
Rana 2017 ²²¹	(1) Not primary diagnostic research
Ratnik 2020 ²²²	(3) Ineligible population
Ratnik 2016 ²²³	(3) Ineligible population
Roche 2019 ²²⁴	(9) Insufficient information (no response received to author enquiries)
Rodriguez-Almarez 2018 ²²⁵	(3) Ineligible population
Rolfo 2015 ²²⁶	(3) Ineligible population
Rowson 2019 ²²⁷	(4) Ineligible biomarker(s) (i.e. not PLGF, sFlt-1 or ratio)
Sa 2020 ²²⁸	(7) No relevant outcomes
Sabria 2018 ²²⁹	(3) Ineligible population
Sabria 2018 ²³⁰	(7) No relevant outcomes
Saleh 2020 ²³¹	(3) Ineligible population
Saleh 2018 ⁶⁸	(3) Ineligible population
Saleh 2018 ²³²	(6) Ineligible comparator/reference standard
Saleh 2017 ²³³	(6) Ineligible comparator/reference standard
Saleh 2015 ²³⁴	(6) Ineligible comparator/reference standard
Saleh 2016 ²³⁵	(6) Ineligible comparator/reference standard
Saleh 2016 ²³⁶	(6) Ineligible comparator/reference standard
Saleh 2017 ²³⁷	(3) Ineligible population
Saleh 2016 ²³⁸	(6) Ineligible comparator/reference standard
Sarween 2017 ²³⁹	(3) Ineligible population
Sebastian 2019 ²⁴⁰	(3) Ineligible population
Simon 2020 ¹⁴¹	(3) Ineligible population
Simon 2020 ²⁴¹	(3) Ineligible population
Slomski 2019 ²⁴²	(1) Not primary diagnostic research
Smith 2016 ²⁴³	(3) Ineligible population
Sovio 2017 ²⁴⁴	(3) Ineligible population
Stepan 2016 ²⁴⁵	(3) Ineligible population
Stolz 2018 ²⁴⁶	(3) Ineligible population
Suresh 2020 ²⁴⁷	(1) Not primary diagnostic research
Tan 2017 ²⁴⁸	(3) Ineligible population
Tardif 2018 ²⁴⁹	(3) Ineligible population
ThermoFisher 2020 ²⁵⁰	(3) Ineligible population
ThermoFisher 2020 ²⁵¹	(3) Ineligible population
Torchin 2019 ²⁵²	(3) Ineligible population
Tsiakkas 2016 ²⁵³	(3) Ineligible population
Tsiakkas 2016 ²⁵⁴	(3) Ineligible population
Tsiakkas 2016 ²⁵⁵	(3) Ineligible population
Valino 2016 ²⁵⁶	(3) Ineligible population
Valino 2016 ²⁵⁷	(3) Ineligible population
Van Helden 2015 ²⁵⁸	(3) Ineligible population
Vatish 2017 ²⁵⁹	(1) Not primary diagnostic research

TABLE 44 References excluded from the test accuracy review at full-text screening (*continued*)

Reference	Exclusion reason: first reason identified
Verlohren 2018 ²⁶⁰	(1) Not primary diagnostic research
Verlohren 2017 ²⁶¹	(9) Insufficient information (no response received to author enquiries)
Villalain 2020 ²⁶²	(6) Ineligible comparator/reference standard
Widmer 2015 ²⁶³	(3) Ineligible population
Wiles 2021 ²⁶⁴	(3) Ineligible population
Zeisler 2016 ²⁶⁵	(1) Not primary diagnostic research
Zeisler 2016 ³⁹	(6) Ineligible comparator/reference standard

Systematic review of cost-effectiveness evidence

[Table 45](#) lists publications excluded from the systematic review of cost-effectiveness studies. For each publication, a reason for exclusion is provided (see [Methods for the systematic review of economic studies](#) for details of the inclusion/exclusion criteria).

TABLE 45 References excluded from the systematic review of cost-effectiveness evidence

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

Review of health-related quality-of-life studies

[Table 46](#) lists publications excluded from the review of HRQoL studies. For each publication, a reason for exclusion is provided (see [Methods for review and data extraction of health-related quality-of-life studies](#) for details of the inclusion/exclusion criteria).

TABLE 46 References excluded from the review HRQoL studies

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

Appendix 3 Predictive concordance studies of placental growth factor-based tests

Table 47 lists studies reporting predictive concordance between PLGF-based tests relevant to this diagnostic assessment.

TABLE 47 Predictive concordance studies

Study	Tests compared				Comments
	Triage PLGF	Elecsys ratio	BRAHMS Kryptor ratio	Delfia Xpress	
Black 2019 ¹⁶⁵ 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 ¹⁶⁴ 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 ¹⁶⁶ PLGF, sFlt-1		✓ ^a	✓	✓	Screening at 19 ⁺⁰ –24 ⁺⁵ 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 ²⁶⁶ 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 ⁷¹ PLGF, sFlt-1, sFlt-1 ratio		✓	✓	✓	Normal pregnancies, 20–39 weeks GA, Chinese population. There were notable intertest 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 ⁷² PLGF	✓	✓		✓	Women with suspected PE before 35 weeks GA
McCarthy 2019 ²⁹ 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 three 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 ⁴⁵		✓	✓		
Simon 2020 ¹⁴¹		✓	✓		
Stepan 2016 ²⁴⁵	✓	✓			
Stepan 2019 ²⁶⁷		✓	✓		

GA, gestational age; PE, pre-eclampsia.
a Used Roche cobas e-411; not specified as Elecsys test.

Note
✓ Test included in the study.

Appendix 4 Narrative summary of the INSPIRE and PARROT studies

Of the seven add-on studies included in the systematic review of test accuracy and clinical effectiveness, 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 (see *Independent economic evaluation*).

In this subsection, 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 earlier [see [Assessment of test accuracy \(add-on studies\)](#)].

The PARROT trial

The PARROT trial^{14,19} 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 SGA. 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 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 48](#).

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 vs. 4.1 days). The authors stated this corresponded to a 64% reduction in time to diagnosis.

Use of the Triage placental growth factor Test to rule in pre-eclampsia

In DG23, NICE recommended research on the use of a positive Triage PLGF test result (< 12 pg/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

TABLE 48 Summary of the PARROT trial key findings

PARROT trial outcome	Revealed PLGF test result, <i>n</i> = 573	Concealed PLGF test result, <i>n</i> = 446	Difference
Trial 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; <i>p</i> = 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 to 1.24)
Preterm deliveries < 37 weeks, <i>n/N</i> (%)	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, <i>n/N</i> (%)	22/573 (4)	24/446 (5)	Adjusted OR 0.32, 95% CI 0.11 to 0.96, <i>p</i> = 0.043
Perinatal and neonatal outcomes			
Perinatal adverse outcomes, <i>n/N</i> (%) (post hoc)	86*/573 (15)	63/446 (14)	aOR 1.45, 95% CI 0.73 to 2.90
Perinatal deaths, <i>n/N</i> (%) ^b	6/573 (1)	4/446 (1)	aOR 1.00, 95% CI 0.61 to 1.63
Late neonatal deaths (8–27 complete days of life), <i>n/N</i> (%) ^b	3/573 (1)	1/446 (< 1)	Not reported
Any grade of intraventricular haemorrhage (perinatal), <i>n/N</i> (%)	7/573 (1)	11/446 (3)	Not reported
Respiratory distress syndrome (perinatal), <i>n/N</i> (%)	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)
aOR, adjusted odds ratio; SE, standard error.			
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.			
Note			
Underlining denotes outcomes used in our economic model base case.			

decisions on time to delivery and the outcomes associated with this' (NICE DG23).⁷ The PARROT trial reported a Triage PLGF test result of < 12 pg/ml, when used alone and not in conjunction with standard clinical assessment (i.e. 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 (see [Table 47](#)). The authors stated there were no differences in the rates of preterm 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)⁴ 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 revealed arm and one in the concealed arm (< 1%) (statistical significance not reported).
- Data from PARROT on neonatal unit admissions (stratified by pre-eclampsia 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 vs. 33% in the concealed testing arm). The mean number of inpatient nights in the neonatal unit and SCBU appeared to be similar between groups. 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 CI 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 [Onset of labour](#) and [Mode of delivery](#) for results).

The INSPIRE trial

The INSPIRE trial³² 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 7 days and of > 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 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 49](#).

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 soluble fms-like tyrosine kinase-1/placental growth factor 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⁺⁰–37⁺⁰ weeks, the INSPIRE study

TABLE 49 Summary of the INSPIRE trial key findings

INSPIRE trial outcome	Revealed PLGF test result, n = 186	Concealed PLGF test result, n = 184	Difference
Primary outcome			
Admission for suspected pre-eclampsia 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			
<u>Pulmonary oedema, n/N (%)</u>	1/186 (0.54)	1/184 (0.54)	p = 0.994
<u>Abruption, n/N (%)</u>	2/186 (1.1)	5/184 (2.7)	p = 0.246
<u>Eclampsia</u>	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
Note			
Underlining shows the trial outcomes that are used in our economic model base case.			

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 to 0.550) for ruling in the development of pre-eclampsia within 1 week of testing, when it was used alone (i.e. 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 49](#), but available in [Maternal admissions](#)).

Our base-case economic model uses data from the INSPIRE trial to estimate severe/major maternal complications. As [Table 49](#) 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 49](#); see [Severe maternal adverse outcomes](#) for results).

Regarding fetal and neonatal outcomes, the trial found no statistically significant difference in gestational age at delivery between the trial arms (see [Table 49](#)), nor in the other four outcomes assessed: birthweight, APGAR score, SCBU admissions and SGA.

Appendix 5 Outcomes from add-on studies not used in the economic analysis

[Table 50](#) lists the various prognostic/diagnostic accuracy measures reported by the add-on studies.

TABLE 50 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.

Prediction of preterm delivery (< 37 weeks) by test-birth interval (Triage placental growth factor test)

Triage placental growth factor test

Ormesher *et al.*³¹ provide test accuracy data for the prediction of preterm delivery by test-birth interval in women at < 37 weeks gestation ([Table 51](#)). 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 51 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
<i>Ormesher et al.,²¹ Triage PLGF; test concealed < 37 weeks gestation</i>							
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

NR, not reported.

a 95% CIs not reported.

b Calculated by reviewer.

Prediction of pre-eclampsia requiring delivery by time point (Triage test and Elecsys ratio test)

Data from the concealed arm only of the PARROT¹⁷ study provided high NPV values (> 0.95) for prediction of pre-eclampsia requiring delivery within 2 weeks (in women < 35 weeks gestation) at test cut-offs of < 12 pg/ml and < 100 pg/ml (Table 52), while PPVs were 0.446 and 0.257, respectively.

TABLE 52 Prediction of pre-eclampsia requiring delivery by time point (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)
<i>PARROT,¹⁹ Triage test, result concealed, 20⁺⁰–35⁺⁰ weeks</i>							
Within 2 weeks	< 100 pg/ml	265	0.949 (0.827 to 0.994)	52.7 (0.459 to 0.593)	0.257 ^a (0.228 to 0.288)	0.983 ^a (0.939 to 99.6)	14.72 (10.68 to 19.57) ^b
	< 12 pg/ml	265	0.744 (0.579 to 0.870)	0.841 (0.786 to 0.886)	0.446 ^a (0.362 to 0.534)	0.950 ^a (0.917 to 0.970)	14.72 (10.68 to 19.57) ^b
<i>Binder et al.,⁴⁷ Elecsys ratio, result revealed, median GA at assessment 33.6 weeks</i>							
Within 1 week (rule out) ^c	< 38 ^{d,e}	164	0.965 (0.822 to 0.999)	0.711 (0.627 to 0.786)	0.418 (0.353 to 0.485)	0.990 (0.933 to 0.999)	NR
	< 38 (adj) ^{d,f}	164	0.862 (0.683 to 0.961)	0.763 (0.682 to 0.832)	0.439 (0.358 to 0.522)	0.963 (0.912 to 0.985)	NR
Within 2 weeks (rule out) ^c	< 38 ^{d,e}	164	0.881 (0.744 to 0.960)	0.770 (0.686 to 0.842)	0.569 (0.494 to 0.651)	0.949 (0.891 to 0.977)	NR
	< 38 (adj) ^{d,f}	164	0.982 (0.838 to 0.994)	0.713 (0.624 to 0.791)	0.533 (0.461 to 0.604)	0.977 (0.918 to 0.994)	NR

NR, not reported.

a CI 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.⁷³

Elecsys soluble fms-like tyrosine kinase-1/placental growth factor ratio test

Binder *et al.*⁴⁷ reported high NPVs for the use of this test as part of routine care in ruling out pre-eclampsia 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 (see [Table 51](#)). 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.

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

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 100 pg/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 53](#)).

Two stand-alone studies (PETRA, PELICAN),^{22,24–26,215} 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. NPVs ranged from 0.864 to 0.975 when a cut-off of 100 pg/ml was used. In contrast, this test had lower NPVs (0.440 to 0.619) and higher PPVs (0.942 to 0.989) for the prediction of any preterm delivery when the lower test cut-off of 12 pg/ml was used (see [Report Supplementary Material 1](#)). Another stand-alone study, 'COMPARE',²⁹ also reported high NPVs (> 0.872) for the Triage test for a variety of different delivery outcomes (see [Report Supplementary Material 1](#)).

Additional prognostic accuracy data for the Elecsys sFlt-1/PLGF ratio test for prediction of delivery outcomes are reported by the following stand-alone studies: ROPE, Baltajian and PROGNOSIS Asia in (see [Report Supplementary Material 1](#)). While the results from the PROGNOSIS Asia⁴¹ study support the use of the test for ruling out pre-eclampsia requiring delivery within 1 week (NPV:1.00), Baltajian *et al.*⁴⁴ reported a relatively high PPV (0.91) for the prediction of indicated delivery within 2 weeks. Results from the ROPE study⁴³ 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 study²⁹ also reported high NPVs (> 0.866) for the Elecsys ratio test for a variety of different delivery outcomes (see [Report Supplementary Material 1](#)).

BRAHMS Kryptor soluble fms-like tyrosine kinase-1/placental growth factor ratio test

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

DELFIA Xpress placental growth factor test

No data were available from add-on studies; however, one stand-alone study, COMPARE,²⁹ reported NPVs > 0.912 for a range of delivery-related outcomes.

TABLE 53 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,¹⁹ Triage test, result concealed, 35⁺0–36⁺6 weeks							
Before 37 weeks gestation	< 100 pg/ml	170	0.962 ^a (0.804 to 0.999)	0.236 ^a (0.169 to 0.314)	0.185 ^a (0.168 to 0.204)	0.971 ^a (0.830 to 0.996)	15.29 (10.24% to 21.60%) ^b
	< 12 pg/ml	170	0.370 (0.194 to 0.576)	0.783 (0.707 to 0.848)	0.244 ^c (0.153 to 0.366)	0.868 ^c (0.830 to 0.899)	15.88 (10.74 to 22.26%) ^b

NR, not reported.

^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 CI for sensitivity, specificity and PPV; and to CI for NPV.

^b Calculated by reviewer.

^c CI as calculated by reviewer; differs slightly from reported value.

Prediction of severe maternal morbidity

Binder *et al.*⁴⁷ 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 54). No further test accuracy data were provided from the add-on studies for the other three tests.

Two stand-alone studies^{45,56} provide additional accuracy data for the Elecsys sFit-1/PLGF ratio test for the prediction of adverse outcomes (see Report Supplementary Material 1).

TABLE 54 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)
<i>Binder et al.,⁴⁷ Elecsys ratio, result revealed, median GA at assessment 33.6 weeks</i>							
Severe maternal mortality (rule out)	< 38 ^{a,b}	164	0.857 (0.637 to 0.970)	0.531 (0.446 to 0.615)	0.212 (0.174 to 0.256)	0.962 (0.898 to 0.987)	NR
	< 38 (adj) ^{a,c}	164	0.952 (0.762 to 0.999)	0.489 (0.405 to 0.574)	0.215 (0.185 to 0.248)	0.986 (0.911 to 0.998)	NR

NR, not reported.

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.*⁷³

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

Table 55 gives the results for the time to diagnosis of pre-eclampsia based on the Triage PLGF test and the Elecsys sFit-1/PLGF ratio test.

TABLE 55 Time to diagnosis of pre-eclampsia, test result revealed vs. concealed

Study	Outcome	Group	Revealed	Concealed	Difference (as reported in study)
Triage PLGF test					
PARROT ^{14,19}	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, <i>p</i> = 0.027)
		PLGF < 12	1.0 (0.3–4.5); <i>n</i> = 130	2.0 (0.3–9.0); <i>n</i> = 106	Adjusted time ratio = 0.17 (95% CI 0.03 to 1.06)
		PLGF 12–100	2.0 (0.9–8.70); <i>n</i> = 212	4.6 (1.0–14.5); <i>n</i> = 173	Adjusted time ratio = 0.66 (95% CI 0.09 to 4.95)
		PLGF > 100	22.8 (8.4–39.2); <i>n</i> = 229	30.3 (5.9–65.1); <i>n</i> = 156	Adjusted time ratio = 0.13 (95% CI 0.16 to 1.07)
Elecsys sFit-1/PLGF ratio test					
INSPIRE ³²	Time (days) to pre-eclampsia diagnosis within 7 days, median (IQR); N	Total	0 (0–2); N = 186	0 (0–3); N = 184	0 days; ^a <i>p</i> = 0.7777
	Time (days) to pre-eclampsia diagnosis within 28 days, median (IQR); N	Total	2 (0–9); N = 186	4 (0–10.5); N = 184	2 days; ^a <i>p</i> = 0.5641
	Time (days) to pre-eclampsia diagnosis at any time, median (IQR); N	Total	7 (0–29); N = 186	9.5 (0–32); N = 184	2.5 days; ^a <i>p</i> = 0.6387

a Absolute difference as calculated by reviewer.

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

Table 56 compares the number of pre-eclampsia diagnoses made by the revealed and concealed arms of the studies, for the Triage PLGF test and the Elecsys sFlt-1/PLGF ratio test.

TABLE 56 Pre-eclampsia diagnosis by time point, test result revealed vs. concealed

Study	Outcome	Group	Revealed	Concealed	Difference (as reported in study)
Triage PLGF test					
PARROT ^{14,19}	PE diagnosis by clinician at any time, % (n/N)	Total	36 (205/573)	35 (155/446)	1.0 ^a
		PLGF < 12 ^b	73.8 (96/130)	66.0 (70/106)	7.0 ^a
		PLGF 12-100 ^b	39.6 (84/212)	37.0 (64/173)	4.5 ^a
		PLGF > 100 ^b	10.0 (23/229)	12.2 (19/156)	0.4 ^a
cMAPPLE ³⁰	PE diagnosis at any time, % (n/N)	Total	52.9 (193/397)	61.3 (176/287)	8.4; ^a risk ratio (95% CI) 0.86 (0.75 to 0.99)
		PLGF < 12 ^b	48.6 (51/116)	97.1 (67/69)	48.5 ^a
		PLGF 12-100 ^b	53.1 (69/137)	74.2 (72/97)	21.1 ^a
		PLGF > 100 ^b	56.2 (73/143)	30.6 (37/121)	25.6 ^a
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; ^a <i>p</i> = 0.344
	PE within 28 days, % (n/N)	Total	18.8 (35/186)	15.2 (28/184)	3.6; ^a <i>p</i> = 0.357
	PE at any time, % (n/N)	Total	25.2 (47/186)	20.6 (38/184)	4.6; ^a <i>p</i> = 0.291

PE, pre-eclampsia.

a Absolute % difference as calculated by reviewer.

b pg/ml.

c Unadjusted indirect comparison.

Severe pre-eclampsia, test result revealed versus concealed

Table 57 compares the number of severe pre-eclampsia diagnoses made by the revealed and concealed arms of the studies, for the Triage PLGF test and the Elecsys sFlt-1/PLGF ratio test.

TABLE 57 Severe pre-eclampsia, test result revealed vs. concealed

Study	Outcome	Group	Revealed	Concealed	Difference (as reported in study)
Triage PLGF test					
PARROT ^{14,19}	Severe PE (ACOG definition), n/N (%)	Total	27 (155/573)	24 (106/446)	3.0; ^a aOR 1.22 (95% CI 0.71–2.12)
		PLGF < 12 ^b	56.2 (73/130)	46.2 (49/106)	10.0 ^a
		PLGF 12-100 ^b	30.2 (64/212)	28.3 (49/173)	1.9 ^a
		PLGF > 100 ^b	7.9 (18/229)	4.5 (7/156)	3.4 ^a
Elecsys sFlt-1/PLGF ratio test					
INSPIRE ³²	Severe PE (ACOG criteria), % ^c (n/N)	Total	72.3 (34/47)	63.3 (24/38)	9.0; ^a <i>p</i> = 0.366
	Severe PE with 2 or more criteria for severity, % ^c (n/N)	Total	12.7 (6/47)	18.4 (7/38)	5.7; ^a <i>p</i> = 0.471

aOR, adjusted odds ratio; PE, pre-eclampsia.

a Absolute % difference as calculated by reviewer.

b pg/ml.

c As a proportion of those diagnosed with PE.

Severe pre-eclampsia, test result revealed versus concealed

Table 58 compares the gestational age at delivery between the revealed and concealed arms of the studies, for the Triage PLGF test and the Elecsys sFlt-1/PLGF ratio test.

TABLE 58 Gestational age at delivery, test result revealed vs. concealed

Study	Outcome	Group	Revealed	Concealed	Difference (as reported in study)
Triage PLGF test					
PARROT ^{14,19}	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)
		PLGF < 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 ³⁰	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
PE, pre-eclampsia. a pg/ml. b Number of infants. c Absolute % difference as calculated by reviewer.					

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

Table 59 compares the number of perinatal deaths between the revealed and concealed arms of the studies, for the Triage PLGF test.

TABLE 59 Perinatal mortality of fetus/neonate, test result revealed vs. concealed

Study	Outcome	Group	Revealed	Concealed	Difference (as reported in study)
Triage PLGF test					
PARROT ¹⁹	Perinatal deaths ^a % (n/N)	Total ^b	1.0 (6/573)	1.0 (4/446)	0; ^c aOR 1.00, 95% CI 0.61 to 1.63
^d MAPPLE ³⁰	Perinatal deaths ^e % (n/N ^f)	Total ^b	0.5 (2/433)	3.0 (9/299)	2.5; ^c risk ratio (95% CI) 0.16 (0.03 to 0.74)

aOR, adjusted odds ratio.

a Defined as deaths from 24 weeks of gestation, including those defined as stillbirths, until 7 completed days after birth.

b Data not stratified by PLGF level for these outcomes.

c Absolute % difference as calculated by reviewer.

d Unadjusted indirect comparison.

e Definition not reported; assumed by EAG to be the same as for PARROT study.

f N = number of infants.

Early and late neonatal mortality, test result revealed versus concealed

Table 60 compares the number of early/late perinatal deaths between the revealed and concealed arms of the studies, for the Triage PLGF test.

TABLE 60 Early and late neonatal mortality, test result revealed vs. concealed

Study	Outcome	Group	Revealed	Concealed	Difference (as reported in study)
Triage PLGF test					
PARROT ^{14,19}	Early neonatal death; n/N ^a	Total	0.0 (9/573)	0.0 (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 ^b
		PLGF < 12 ^b	0.8 (1/130)	1.0 (1/106)	Not reported
		PLGF 12–100 ^b	0.9 (2/212)	0.0 (0/173)	Not reported
		PLGF > 100 ^b	0.0 (0/229)	0.0 (0/156)	Not reported
^c MAPPLE ³⁰	Early neonatal death; n/N ^a	Total	0.2 (1/433)	0.7 (2/299)	0.5 ^d

a Assumed to be within 7 days of birth; N = number of infants.

b pg/ml.

c Unadjusted indirect comparison.

d Absolute % difference as calculated by reviewer.

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

Table 61 compares the number of perinatal and neonatal adverse outcomes between the revealed and concealed arms of the studies, for the Triage PLGF test.

TABLE 61 Perinatal and neonatal adverse outcomes: composite, test result revealed vs. concealed

Study	Outcome	Group	Revealed	Concealed	Difference (as reported in study)
<i>Triage PLGF test</i>					
PARROT ^{14,19}	Perinatal adverse outcomes, ^a % (n/N)	Total	15 (86/573)	14 (63/446)	1.0; ^b aOR 1.45, 95% CI 0.73 to 2.90
		PLGF < 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)
^a MAPPLE ³⁰	Perinatal adverse outcomes, ^d % (n/N)	Total	30.4 (131/433)	20.1 (60/299)	10.3; ^b risk ratio (95% CI) 1.51 (1.15 to 1.98)
	Perinatal adverse outcomes, ^d % (n/N)	Singleton pregnancies only	28.4 (101/356)	18.9 (52/275)	9.5; ^b unadjusted odds ratio 1.74 (1.20 to 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; ^b risk ratio (95% CI) 1.78 (1.32 to 2.41)
		PLGF < 12 ^c	60.7 (74/124)	39.1 (27/69)	21.6 ^b
		PLGF 12–100 ^c	23.4 (37/158)	13.3 (14/105)	10.1 ^b
		PLGF > 100 ^c	13.3 (20/151)	7.2 (9/125)	6.1 ^b

aOR, adjusted odds ratio.

a Unadjusted indirect comparison.

b Absolute % difference as calculated by reviewer.

c pg/ml.

d N = number of infants; perinatal death or neonatal adverse outcome.

e EAG assumes this excludes perinatal death but notes minor inconsistencies in numbers reported between text and tables within MAPPLE publication.

Antenatal corticosteroids, test result revealed versus concealed

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 62](#)).^{14,19,30}

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.⁴⁶

TABLE 62 Antenatal corticosteroids, test result revealed vs. concealed

Study	Outcome	Group	Revealed	Concealed	Difference (as reported in study)
Triage PLGF test					
PARROT ^{14,19}	Use of antenatal corticosteroids for fetal lung maturity, % (n/N)	Total	34.9 (200/573)	29.6 (132/446)	5.3; ^a OR 1.26 (CI 0.75 to 2.11)
		PLGF < 12 ^b	75.4 (98/130)	50.9 (54/106)	24.5 ^a
		PLGF 12–100 ^b	31.6 (67/212)	29.5 (51/173)	2.1 ^a
		PLGF > 100 ^b	15.3 (35/229)	14.1 (22/156)	1.2 ^a
cMAPPLE ³⁰	Use of antenatal corticosteroids for fetal lung maturity, % (n/N)	Total	59.9 (236/397)	30.7 (88/287)	29.2; ^b risk ratio (95% CI) 1.95 (1.61 to 2.37)
		PLGF < 12 ^b	89.6 (103/116)	59.4 (41/69)	30.2 ^a
		PLGF 12–100 ^b	59.6 (81/137)	35.1 (34/97)	24.5 ^a
		PLGF > 100 ^b	36.4 (52/143)	10.7 (13/121)	25.7 ^a

a Absolute % difference as calculated by reviewer.

b pg/ml.

c Unadjusted indirect comparison.

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

[Table 63](#) compares the number of preterm/early preterm deliveries between the revealed and concealed arms of the studies, for the Triage PLGF test.

TABLE 63 Preterm delivery and early preterm delivery, test result revealed vs. concealed

Study	Outcome	Revealed	Concealed	Difference
Triage PLGF test				
PARROT ^{14,19}	Preterm delivery < 37 weeks, % (n/N)	41 (234/573)	37 (167/446)	4.0 ^a
bMAPPLE ³⁰	Preterm delivery < 37 weeks, % (n/N) ^c	70.2 (304/433)	52.8 (158/299)	17.4 ^a
	Early preterm delivery < 34 weeks, % (n/N) ^c	38.6 (167/433)	27.8 (83/299)	10.8 ^a

a Absolute difference as calculated by reviewer.

b Unadjusted indirect comparison.

c Paper reports frequencies by PLGF level subgroup only; frequencies summed by reviewer for whole study population.

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

Table 64 compares the number of maternal admissions at different times between the revealed and concealed arms of the studies, for the Elecsys sFlt-1/PLGF ratio test.

TABLE 64 Maternal admissions at different times, test result revealed vs. 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)
PE, pre-eclampsia.					

Assessment of test on clinical decision-making and monitoring intensity

Klein *et al.*⁴⁶ (the 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 65). Decisions to change monitoring within 1 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 most 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 65 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 1 week, % (n/N)	65.8 (75/114)	52.6 (60/114)

Appendix 6 Systematic review of economic evaluations of placental growth factor-based tests

The flow chart for the identification of economic evaluations is shown in [Figure 9](#).

The characteristics of the included economic studies are shown in [Tables 66](#) and [67](#).

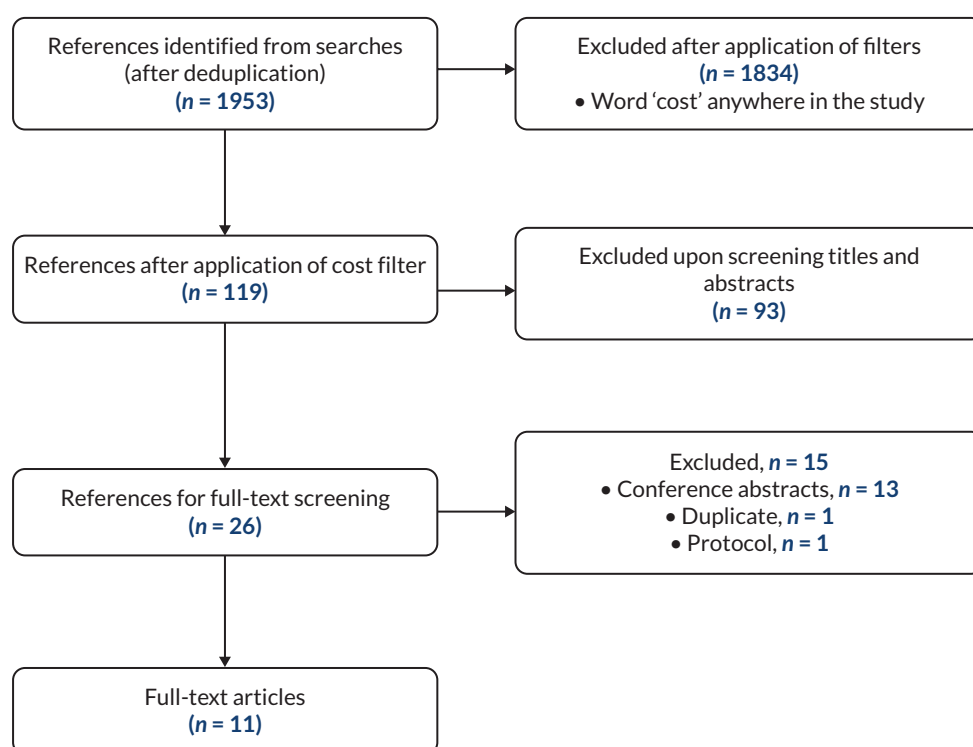


FIGURE 9 Flow chart for the identification of economic studies.

TABLE 66 Characteristics of included economic studies

Study	Duckworth <i>et al.</i> ⁹¹	Duhig <i>et al.</i> ⁹²	Figueira <i>et al.</i> ⁹³	Frampton <i>et al.</i> ⁶	Frusca <i>et al.</i> ⁹⁴
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 sFit-1/PLGF ratio test ^b + usual care Comparator: usual care	Interventions: PLGF tests (Triage PLGF test, Elecsys sFit-1/PLGF ratio test) + usual care Comparator: usual care	Intervention: Elecsys sFit-1/PLGF ratio test ^b + usual care Comparator: usual care

TABLE 66 Characteristics of included economic studies (continued)

Study	Duckworth <i>et al.</i> ⁹¹	Duhig <i>et al.</i> ⁹²	Figueira <i>et al.</i> ⁹³	Frampton <i>et al.</i> ⁶	Frusca <i>et al.</i> ⁹⁴
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 negative initial test (ratio < 38) if the woman had not been hospitalised and had presented continuing symptoms of pre-eclampsia]	No	Yes, included in the base case [2 weeks after a negative initial test (ratio < 38) if the woman had not developed pre-eclampsia, had not been hospitalised 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	2013–4	2016–7, except for the cost of test (2017–8)	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	PLGF 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 weeks 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

continued

TABLE 66 Characteristics of included economic studies (continued)

Study	Duckworth <i>et al.</i> ⁹¹	Duhig <i>et al.</i> ⁹²	Figueira <i>et al.</i> ⁹³	Frampton <i>et al.</i> ⁶	Frusca <i>et al.</i> ⁹⁴
Base-case results ^c	Cost saving of £635 per woman tested ^d	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 No retest scenario: Cost saving in M'Boi Mirim of £94 per woman and £183 in Einstein	For women presenting before 35 weeks, cost saving of £2896 (Triage PLGF test vs. current standard care), £2489 (Elecsys sFlt-1/PLGF ratio test vs. current standard care) and £408 (Triage PLGF test vs. Elecsys sFlt-1/PLGF ratio test) For women presenting between 35 weeks and 37 weeks, cost saving of £365 (Triage PLGF test vs. current standard care), £174 (Elecsys sFlt-1/PLGF ratio test vs. current standard care) and £191 (Triage PLGF test vs. Elecsys sFlt-1/PLGF ratio test)	Over 5 years, net cost saving per woman is equal to £607
Funding source	Tommy's Charity and Alere (San Diego, CA)	NIHR, Research for Patient Benefit Programme and NIHR Professorship	Roche Diagnostics	Health Technology Assessment programme of the NIHR.	Roche Diagnostics

CE, cost-effectiveness.

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 Figueira *et al.*: converted from Brazilian real at an exchange rate of 1 Brazilian real = £0.14 December 2020; Frusca *et al.*, Giardini *et al.*, Hodel *et al.*; Schlembach *et al.*: converted from Euro at an exchange rate of 1 Euro = £0.91 December 2020; Myrhaug *et al.*: converted from Norwegian Krone at an exchange rate of 1 Norwegian Krone = £0.086 December 2020.

d 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.

TABLE 67 Characteristics of included economic studies (continued)

Study	Giardini <i>et al.</i> ⁹⁵	Hodel <i>et al.</i> ⁹⁶	Myrhaug <i>et al.</i> ⁹⁷	Ohkuchi <i>et al.</i> ¹⁰	Schlembach <i>et al.</i> ⁹⁸	Vatish <i>et al.</i> ⁹⁹
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

TABLE 67 Characteristics of included economic studies (continued)

Study	Giardini <i>et al.</i> ⁹⁵	Hodel <i>et al.</i> ⁹⁶	Myrhaug <i>et al.</i> ⁹⁷	Ohkuchi <i>et al.</i> ¹⁰	Schlembach <i>et al.</i> ⁹⁸	Vatish <i>et al.</i> ⁹⁹
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 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	Intervention: Elecsys sFlt-1/PLGF ratio test ^a + usual care 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 pre-eclampsia, > 38 high risk of pre-eclampsia	≤ 38, > 38 and < 85 (for gestational weeks 20–33) OR > 38 and < 110 (gestational week 34 onwards), ≥ 85 (gestational weeks 20–33) 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 ^b 2. Inclusion of a 100% retest rate for all women 3. Inclusion of 4 times retesting for all women in intermediate follow up setting	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 hospitalised]	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]
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 hospitalisations, 35% of hospitalisations for blood pressure increase, 43% of outpatient referrals, and 13% of emergency room accesses.	Hospitalisation rates were reduced in the test vs. the no-test scenario, with 822 (14%) vs. 1160 (19%) women hospitalised, 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 hospitalisation rate compared with the rate in the no-test scenario (14.4% vs. 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

continued

TABLE 67 Characteristics of included economic studies (continued)

Study	Giardini <i>et al.</i> ⁹⁵	Hodel <i>et al.</i> ⁹⁶	Myrhaug <i>et al.</i> ⁹⁷	Ohkuchi <i>et al.</i> ¹⁰	Schlembach <i>et al.</i> ⁹⁸	Vatish <i>et al.</i> ⁹⁹
Base-case results ^d	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 3. cost saving of £97 per woman	Cost per additional correctly identified case of pre-eclampsia of £3710	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
Funding source	No funding ^c	Roche Diagnostics	Norwegian Institute of Public Health	Roche Diagnostics	Roche Diagnostics	Roche Diagnostics

CE, cost-effectiveness.

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

b There is an inconsistency within the publication, chapter 2.7. Sensitivity Analyses report that this rate was applied to women in low follow-up settings and [Figure 3](#) reports that this rate was applied to women in both low and intermediate follow-up settings.

c Clarification provided after contact from EAG.

d Figueira *et al.*: converted from Brazilian Real at an exchange rate of 1 Brazilian Real = £0.14, December 2020; Frusca *et al.*, Giardini *et al.*, Hodel *et al.*; Schlembach *et al.*: converted from Euro at an exchange rate of 1 Euro = £0.91, December 2020; Myrhaug *et al.*: converted from Norwegian Krone at an exchange rate of 1 Norwegian Krone = £0.086, December 2020; Ohkuchi *et al.* converted from Japanese Yen at an exchange rate of 1 Japanese Yen = £0.0065, May 2021.

Triage placental growth factor test

Duckworth *et al.*

Duckworth *et al.*⁹¹ 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 [Quantity and quality of research available](#)).¹³⁹ All women were managed according to the 2010 NICE guideline on the Management of Hypertension in Pregnancy,⁵⁸ 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 (1) the number of women who would be tested for pre-eclampsia using PLGF; (2) the number of women who fall into each of the three PLGF categories; (3) the number of women who would eventually have a diagnosis of pre-eclampsia or not in each of the resulting branches; and (4) 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 68](#). 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.

Healthcare resource use was based on the treatment algorithm used at that time and the 2010 NICE Hypertension in Pregnancy Guideline.⁵⁸ Cost parameters (cost year 2013–4) 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 2 weeks of costs. Plasma samples were tested for PLGF by trained laboratory staff at the point of care.

TABLE 68 Population parameters reported in Duckworth *et al.*

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 <i>et al.</i> (2010) ²⁶⁸
Percentage with severe hypertension in women diagnosed with pre-eclampsia	8	Anumba <i>et al.</i> (2010) ²⁶⁸
Percentage with moderate hypertension in women not diagnosed with pre-eclampsia	55	Anumba <i>et al.</i> (2010) ²⁶⁸
Percentage with severe hypertension in women not diagnosed with pre-eclampsia	4	Anumba <i>et al.</i> (2010) ²⁶⁸
PLGF test characteristics (< 35 weeks predictive for the next 2 weeks)		
Sensitivity PLGF > 100 pg/ml	96	Chappell <i>et al.</i> (2013) ¹³⁹
Specificity PLGF > 100 pg/ml	55	Chappell <i>et al.</i> (2013) ¹³⁹
Sensitivity PLGF < 12 pg/ml	63	Chappell <i>et al.</i> (2013) ¹³⁹
Specificity PLGF < 12 pg/ml	90	Chappell <i>et al.</i> (2013) ¹³⁹
Source: Duckworth <i>et al.</i> ⁹¹		

Of 1000 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 > 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, healthcare resource use and the cost of PLGF test. Results were most sensitive to changes to cost of admission to the inpatient ward.

Duhig *et al.*

Duhig *et al.*⁹² 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.¹⁹ 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.⁵⁸ 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 2016–7.²⁶⁹ The cost of each PLGF test was estimated at £70 (prices from 2017 to 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, HDU and ICU). Resource use was taken from the PARROT trial.¹⁹

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 soluble fms-like tyrosine kinase-1/placental growth factor ratio test

Vatish et al.

Vatish *et al.*⁹⁹ 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 *et al.*⁹⁹ 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, IUGR, or abnormal uterine perfusion) will receive a second sFlt-1/PLGF ratio test 2 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 statement²⁷⁰ and the 2010 NICE guideline,⁵⁸ 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 study³⁷ and are reported in [Table 69](#). It was assumed that women with a ratio < 38 were hospitalised if their blood pressure was higher than 160/110 mmHg, as recommended by NICE guidelines.⁵⁸

TABLE 69 Hospitalisation rates and distribution of women by test threshold

	Distribution by test threshold	Hospitalisation rate (%)
Usual care alone	N/A	36
<i>Elecsys sFlt-1/PLGF ratio test in addition to usual care</i>		
≤ 38	76.1%	1.7
> 38 and < 85	10.7%	55.4
≥ 85	13.2%	64.8
NA, not applicable.		
Source Vatish <i>et al.</i> ⁹⁹		

Resource use assumptions were informed by the 2010 NICE guidelines for the management of women with hypertension in pregnancy⁵⁸ 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.

Briefer descriptions of the studies by Figueira *et al.*,⁹³ Frusca *et al.*,⁹⁴ Hodel *et al.*,⁹⁶ Ohkuchi *et al.*¹⁰ and Schlembach *et al.*⁹⁸ are given here as they used the same model structure as Vatish *et al.*⁹⁹ described above. The study population, clinical inputs and the interventions in comparison were also the same as in Vatish *et al.*,⁹⁹ except for the study by Schlembach *et al.* in which the clinical inputs were based on data for the subgroup of German women in the PROGNOSIS study³⁷ and the study by Ohkuchi *et al.*¹⁰ in which the clinical inputs were based on data from a subgroup of Japanese women in the PROGNOSIS study. None of these five economic studies reported any details of what was included in the PLGF testing costs.

Figueira *et al.*⁹³ 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, antihypertensive 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 were 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\$1287.26 (£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 24 hours 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 *et al.*⁹⁴ 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 *et al.*,⁹⁹ although this proportion was not reported by Vatish *et al.*⁹⁹ The resource use assumptions were informed by national and international guidelines for the management of women with hypertension in pregnancy^{58,271–273} and validated by Italian clinical experts. The cost data were derived from Italian sources. Hospitalisation costs, emergency admission costs and NICU costs were reported, while the costs for lab and diagnostic tests, outpatient appointments and antihypertensive 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 5 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 5 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 *et al.*⁹⁶ 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,³⁷ 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 *et al.*⁹⁶ 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 study⁴⁶ (there is an inconsistency within the publication, because [Figure 3](#) reports that this rate was applied to women in both low and intermediate settings⁹⁶); (2) retest rate of 100%, that is all women 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 hospitalisation 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 *et al.*⁹⁸ 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) from the PreOS study.⁴⁶ The Schlembach *et al.* study uses clinical data for the subgroup of German women in the PROGNOSIS study, so the clinical inputs differ from those in [Table 69](#) for Vatis *et al.* ([Table 70](#)). Schlembach *et al.*⁹⁸ derived unit costs for hospitalisations, outpatient appointments, antihypertensive 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 hospitalised or not. The cost of hospitalisation was based

TABLE 70 Hospitalisation rates and distribution of women by test threshold

	Distribution by test threshold	Hospitalisation rate (%)
Usual care alone	N/A	44.6
Elecsys sFlt-1/PLGF ratio test in addition to usual care		
$\leq 38^a$	64.2%	1.5
> 38 and < 85 OR > 38 and $< 110^a$	16.2%	57.6
≥ 85 OR $\geq 110^a$	19.6%	70.0

N/A, not applicable.

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).

Source

Schlembach *et al.*⁹⁸

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 hospitalisation cost by 20% resulted in the greatest saving [€449 (£407)] and introducing a retest for all women resulted in the lowest saving [€257 (£233)].

Ohkuchi *et al.*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 pre-eclampsia 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. The introduction of the sFlt-1/PLGF ratio test using a cut-off value of 38 resulted in a reduced hospitalisation rate compared with the rate in the no-test scenario (14.4% vs. 8.7%). The reduction in the rate of hospitalisations 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 hospitalisation rate for women with sFlt-1/PLGF ratio ≤ 38 to 4% [cost saving per woman 6782 JPY (£45)] and an increase in the hospitalisation rate in the no-test scenario to the overall hospitalisation rate in PROGNOSIS Asia [cost saving per woman 69,482 JPY (£457)].

Other placental growth factor tests

Frampton et al.

The study by Frampton *et al.*⁶ is the previous DAR produced for NICE for PLGF-based 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⁺ 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 study¹³⁹ 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,⁵⁸ the PELICAN study¹³⁹ 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 £2896 (Triage PLGF test) and £2489 (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-based tests were processed and analysed and the use of a PLGF-based test as a replacement for quantitative proteinuria testing. The length of NICU stay was the

most influential parameter. Women with multiple pregnancies were not excluded from the study; however, there were limited data to assume that the results are relevant to multiple pregnancies.

Giardini et al.

Giardini *et al.*⁹⁵ 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, 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, that is women who had not developed clinical complications, and (2) women with significant blood pressure increase, that is followed by clinical complication such as pre-eclampsia and/or FGR. 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 71). 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).

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 1000 iterations.

The total cost of managing women with increased blood pressure was €2634 (£2385) per patient. The introduction of a PLGF test provided an estimated cost saving of €401 (£363) per patient versus usual care. Giardini *et al.*⁹⁵ did not report any sensitivity or scenario analyses.

TABLE 71 Avoidable percentage of healthcare services due to PLGF test

Healthcare services	Avoidable percentage (%)
<i>Emergency room access</i>	
Not significant blood pressure increase	18
Significant blood pressure increase	4
All	13
<i>Hospital admission</i>	
Not significant blood pressure increase	19
Significant blood pressure increase	15
All	18
<i>Obstetric day service access</i>	
Not significant blood pressure increase	68
Significant blood pressure increase	22
All	43
Source	
Giardini <i>et al.</i> ⁹⁵	

Myrhaug et al.

Myrhaug et al.⁹⁷ 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 second or third trimester [week 20–36 (+ 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 pre-eclampsia rates were derived from the INSPIRE study by Cerdeira et al.³² (Table 72). 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 1252 NOK (£108; at an exchange rate of 1 Norwegian Krone =£0.086, December 2020), ranging from 4 NOK (£85) to 1510 NOK (£129). We note that there is an inconsistency within the publication because a different test cost is reported in Table 11 – 1247 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.

For an initial cohort of 6000 women, 777 receiving PLGF test plus usual care versus 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 (£3710). The cost of the test was varied in sensitivity analyses.

TABLE 72 Transition probabilities by Myrhaug et al.

	Usual care alone (%)	PLGF-based 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

SourceMyrhaug et al.⁹⁷

Appendix 7 Systematic review of health-related quality-of-life studies in pre-eclampsia

The inclusion and exclusion criteria for the review of HRQoL studies are shown in [Table 73](#).

TABLE 73 Inclusion and exclusion criteria for the review of HRQoL studies

Inclusion criteria
<i>Research type</i>
Primary research studies
<i>Population</i>
Women with pre-eclampsia or gestational hypertension;
General pregnancy/postpartum 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.
<i>Outcomes</i>
SF-36, SF-12, SF-6D, EQ-5D, HUI-1, HUI-2 and HUI-3 and 15D
Exclusion criteria
<i>Research type</i>
Cost-effectiveness studies
<i>Population</i>
Conditions not specifically relevant to pre-eclampsia or gestational hypertension (e.g. thyroid disease, human immunodeficiency virus)
<i>Reference type</i>
Conference abstracts, letters, protocols, case reports
<i>Language</i>
Studies not in English language

The flow chart for the identification of HRQoL studies is shown in [Figure 10](#).

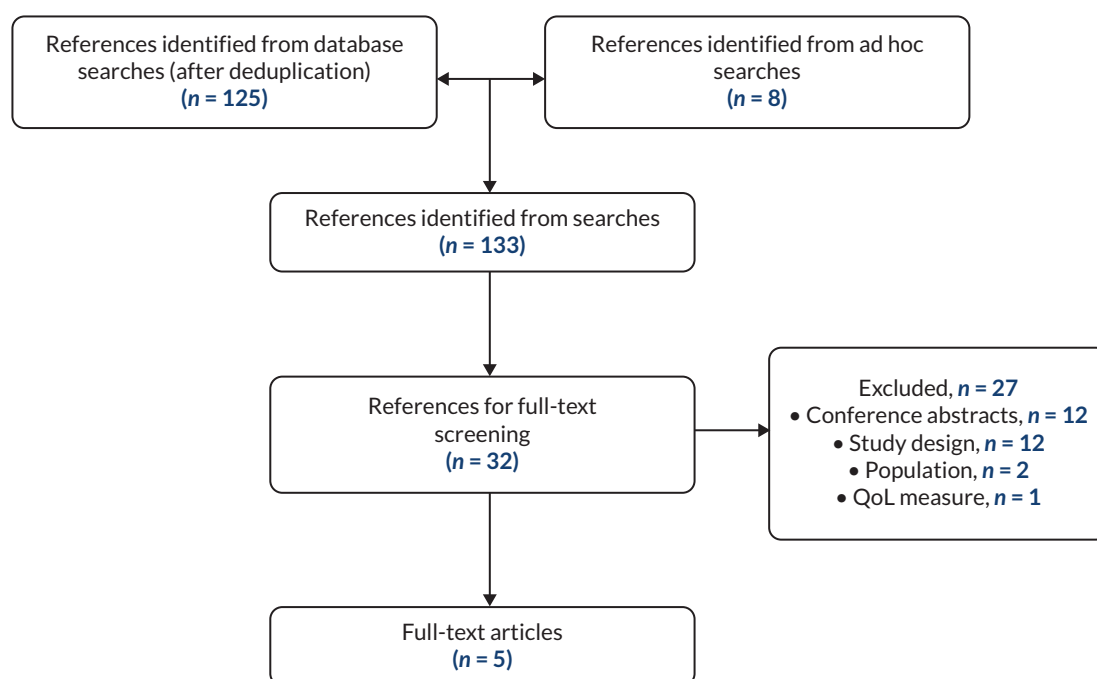


FIGURE 10 Flow chart for the identification of HRQoL studies.

The characteristics of the included HRQoL studies are shown in [Table 74](#).

The five HRQoL studies identified in the systematic review are described in more detail below.

TABLE 74 Characteristics of included HRQoL studies

First author, year	N (total analysed)	Country	Instrument	Health state(s) described
Brusse <i>et al.</i> , 2016 ¹⁰¹	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 <i>et al.</i> , 2016 ¹⁰²	60	China	SF-36	Pregnancy with hypertension with or without music therapy treatment (between about 26 weeks and 30 weeks of pregnancy)
Morin <i>et al.</i> , 2018 ¹⁰³	332	France	EQ-5D-3L	Pregnant women between third and ninth month of gestation with no complications, some complications (simple pathological) and multiple complications (complex pathological).
Prick <i>et al.</i> , 2015 ¹⁰⁴	1391	The Netherlands	SF-36	Induction of labour and expectant management in women with 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 <i>et al.</i> , 2017 ¹⁰⁰	229	Finland	EQ-5D-3L	Pregnant women before acute hospitalisation; 6 months postpartum/post discharge from ICU

EuroQol-5 Dimensions studies

Morin et al.

Morin *et al.*¹⁰³ 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 hospitalisation), or complex pathological pregnancies (occurrence of one or more conditions that did require home monitoring and/or hospitalisation). 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 75](#).

Morin *et al.*¹⁰³ 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 third 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 *et al.*¹⁰⁰ the HRQoL was 0.907 for women admitted to the ICU (i.e. at a more severe stage). Furthermore, other studies that evaluated HRQoL during pregnancy also reported higher utility values than Morin *et al.*;^{274–276} for example a cross-sectional study from the UK reported a utility of 0.81 around the third month of gestation.²⁷⁵

Seppänen et al.

Seppänen *et al.*¹⁰⁰ conducted a retrospective register-based study to examine HRQoL in pregnant women admitted to the ICU in Finland. Hypertensive complications (pre-eclampsia, eclampsia, hypertension) were the most common cause of admission to ICUs. Other admission causes included haemorrhage, pregnancy- or delivery-related complications and non-obstetric causes. Both EQ-5D-3L (Finnish tariff) and EuroQol visual analogue scale (EQ-VAS) were used to measure HRQoL at baseline (refers to the time preceding the acute hospitalisation) and 6 months after discharge from the ICU. 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 76](#).

The utility score of the study population upon admission to an ICU 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

TABLE 75 EuroQol-5 Dimensions scores reported in Morin *et al.*

Type of pregnancy		Third month	Fourth month	Fifth month	Sixth month	Seventh month	Eighth month	Ninth 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)
Complex pathological	N	47	44	50	44	49	46	26
	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.*¹⁰³

TABLE 76 EuroQol-5 Dimensions questionnaire scores reported in Seppänen *et al.*

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 ^a
25–34 years				
N	213	126	73	
Score	0.95	0.912	0.954	< 0.01 ^a
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 ^a
NS, non-significant. a Versus baseline. Source Seppänen <i>et al.</i> ¹⁰⁰				

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 DAR.⁶

The study by Bijlenga *et al.*²⁷⁷ used in the previous DAR⁶ followed up a cohort of women with hypertensive disorders and measured their HRQoL scores at the final weeks of gestation (between 36 weeks and 41 weeks), at 6 weeks postpartum and at 6 months postpartum. Therefore, we consider the utility values reported by Bijlenga *et al.* preferable to those from Seppänen *et al.* since the utility values from Bijlenga *et al.* can be used for different time points and, thus, for different health states of the model.²⁷⁷ However, none of the HRQoL studies of the previous DAR⁶ reported HRQoL scores related with admission to hospital and ICUs.

Short Form questionnaire-36 items studies

Brusse et al.

Brusse *et al.*¹⁰¹ 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 6–8 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 77](#). We mapped these scores to EQ-5D-3L utility values using the method developed by Ara and Brazier.²⁷⁸

Each population subgroup has a small sample size ($n \leq 25$). 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 6–8 weeks postpartum. Although previous studies^{6,135,277,279,280} 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 et al.

Cao et al.¹⁰² 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 4 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 78](#). We mapped these scores into EQ-5D-3L using the method developed by Ara and Brazier.²⁷⁸

TABLE 77 Short-form 36-dimension questionnaire scores reported in Brusse et al.

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 ^a	0.86	0.94	0.84	0.93	0.85

a Using Ara and Brazier algorithm.²⁷⁸

Source

Brusse et al.¹⁰¹

TABLE 78 Short-form 36-dimension questionnaire scores reported in Cao et al.

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 ^a	0.84	0.72	N/A

a Using Ara and Brazier algorithm.²⁷⁸

Source

Cao et al.¹⁰²

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 health care is likely to be not generalisable to the UK. Therefore, we do not use these results in our economic model.

Prick *et al.*

Prick *et al.*¹⁰⁴ used data from three RCTs 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 IUGR and hypertensive disorders. The WOMB trial randomised 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 6 weeks postpartum and its values, along with their mapping into EQ-5D-3L,²⁷⁸ are shown in [Table 79](#).

The HYPITAT trial reports utility values for women with hypertensive disorders 6 weeks postpartum (0.80). The utility values are lower than the general Dutch population and postpartum reference scores (0.89). We note that the study by Bijlenga *et al.*,²⁷⁷ used in the previous DAR,⁶ evaluated HRQoL in the same population of pregnant women with hypertensive disorders (from the HYPITAT trial). We consider the study by Bijlenga *et al.*,²⁷⁷ to be preferable to the study by Prick *et al.*¹⁰⁴ as Bijlenga reported the HRQoL scores for different time points (from the final stage of pregnancy to 6 weeks and 6 months postpartum). Furthermore, the study by Bijlenga *et al.*²⁷⁷ reported the HRQoL scores for the two groups of women in the HYPITAT trial (induction of labour group and expectant management group), while Prick *et al.*¹⁰⁴ study reports the results for the whole population of the trial.

TABLE 79 Postpartum SF-36 scores reported in three RCTs

SF-36	DIGITAT		HYPITAT		WOMB		Total all studies		Dutch population	Postpartum 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 ^a	N/A	0.87	NA	0.80	NA	0.88	NA	0.83	0.89	0.89

N/A, not applicable.

a Using Ara and Brazier algorithm.²⁷⁸

Source

Prick *et al.*¹⁰⁴

Appendix 8 Economic analysis input parameters

Resource use for managing women with suspected pre-eclampsia (base case)

The tables below present the resource use considered in the model for the base case for women with high risk ([Table 80](#)), intermediate risk and low risk of pre-eclampsia ([Table 81](#)). The resource use is based on the management of pre-eclampsia and gestational hypertension recommended in NICE CG107.⁵⁸

List of economic base-case model inputs

Below are listed all the model inputs used in the base case – clinical parameters ([Table 82](#)), healthcare resource parameters ([Table 83](#)), HRQoL parameters ([Table 84](#)) and cost estimates ([Table 85](#)).

Cost breakdown of placental growth factor-based 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

TABLE 80 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	8 days	Hospitalisation	< 35 weeks	8 days
	> 35 weeks	3 days		> 35 weeks	4 days
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 ^a		1x	Fetal assessment ^a		1x
Oral labetalol		–	Oral labetalol		Until delivery ^b
Corticosteroids		1x ^c	Corticosteroids		1x ^c
2 – Immediate delivery (if women > 35 weeks of gestation and severe hypertension)					
Resource		Frequency	Resource		Frequency
Hospitalisation		2 days ^d	Hospitalisation		2 days ^d
Other resources are the same as for expectant management			Other resources are the same as for expectant management		

^a Includes ultrasound fetal growth; amniotic fluid volume assessment, umbilical artery Doppler velocimetry and fetal cardiotocography.

^b At a dose of 200 mg twice daily.

^c Two doses of 12 mg intramuscularly.

^d 48 hours until delivery, based on CG107.⁵⁸

Source

Based on the management of pre-eclampsia recommended in CG107⁵⁸ and clinical expert opinion.

TABLE 81 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	–

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.

Source

Based on the management of gestational hypertension recommended in CG107⁵⁸ and clinical expert opinion.

TABLE 82 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 ¹⁹
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 ⁹¹
Severe hypertension	46.88		
Moderate hypertension	34.76		
Mild hypertension	20.18		
Test sensitivity			
Triage < 100	94.87	Beta (37, 39)	PARROT ¹⁹
Triage < 12	74.36	Beta (29, 39)	PARROT ¹⁹
Triage < 100	80.77	Beta (21, 26)	COMPARE ²⁹
Triage < 12	53.85	Beta (14, 26)	COMPARE ²⁹
Elecsys > 38	73.08	Beta (19, 26)	COMPARE ²⁹

continued

TABLE 82 Estimates of test sensitivity and specificity used in the model (*continued*)

Parameter	Mean (%)	Distribution	Source
Elecsys > 85	65.38	Beta (17, 26)	COMPARE ²⁹
DELFA > 150	84.62	Beta (22, 26)	COMPARE ²⁹
DELFA > 50	53.85	Beta (14, 26)	COMPARE ²⁹
Elecsys > 38	88.89	Beta (8, 9)	Simon 2020 ¹⁴¹
BRAHMS > 38	95.00	Beta (9.5, 10) ^a	Simon 2020 ¹⁴¹
Elecsys > 85	88.89	Beta (8, 9)	Simon 2020 ¹⁴¹
BRAHMS > 85	95.00	Beta (9.5, 10) ^a	Simon 2020 ¹⁴¹
Elecsys > 38 (no clinical judgement)	95.83	Beta (23, 24)	INSPIRE ³²
Elecsys > 38 (with no clinical judgement)	98.00	Beta (24.5, 25)	INSPIRE ³²
Clinical judgement	83.33	Beta (15, 18)	INSPIRE ³²
Elecsys > 38	90.48	Beta (57, 63)	INSPIRE (ruleout) ⁶⁹
Elecsys > 85	60.32	Beta (38, 63)	INSPIRE (rule- in) ¹⁴²
Test specificity			
Triage < 100	52.65	Beta (119, 226)	PARROT ¹⁹
Triage < 12	84.07	Beta (190, 226)	PARROT ¹⁹
Triage < 100	79.57	Beta (222, 279)	COMPARE ²⁹
Triage < 12	95.34	Beta (266, 279)	COMPARE ²⁹
Elecsys > 38	93.19	Beta (260, 279)	COMPARE ²⁹
Elecsys > 85	95.34	Beta (266, 279)	COMPARE ²⁹
DELFA > 150	79.93	Beta (223, 279)	COMPARE ²⁹
DELFA > 50	94.98	Beta (222, 279)	COMPARE ²⁹
Elecsys > 38	90.91	Beta (30, 33)	Simon 2020 ¹⁴¹
BRAHMS > 38	87.88	Beta (29, 33)	Simon 2020 ¹⁴¹
Elecsys > 85	96.97	Beta (32, 33)	Simon 2020 ¹⁴¹
BRAHMS > 85	93.94	Beta (31, 33)	Simon 2020 ¹⁴¹
Elecsys > 38 (no clinical judgement)	79.63	Beta (129, 162)	INSPIRE ³²
Elecsys > 38 (with no clinical judgement)	77.78	Beta (126, 162)	INSPIRE ³²
Clinical judgement	80.12	Beta (133, 166)	INSPIRE ³²
Elecsys > 38	81.76	Beta (251, 307)	INSPIRE (ruleout) ⁶⁹
Elecsys > 85	95.11	Beta (292, 307)	INSPIRE (rule- in) ¹⁴²
^a Denotes a continuity correction was applied.			

TABLE 83 Evidence on resource use used in the model

Parameter	Mean	Distribution	Source
<i>Time to delivery (days)</i>			
Gestational age < 35 weeks, no pre-eclampsia	44.86	Normal (10% of mean)	Derived from PELICAN ⁹¹
Gestational age < 35 weeks, pre-eclampsia	19.00	Normal (10% of mean)	Derived from PELICAN ⁹¹
Gestational age ≥ 35 weeks, no pre-eclampsia	7.98	Normal (10% of mean)	Derived from PELICAN ⁹¹
Gestational age ≥ 35 weeks, pre-eclampsia (not hospitalised)	4.91	Normal (10% of mean)	Derived from PELICAN ⁹¹
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 ⁹¹
Onset of delivery		Dirichlet (N = 1018)	PARROT ¹⁹
Spontaneous	15.42%		
Induced	46.46%		
Planned caesarean section	38.11%		
Mode of delivery			PARROT ¹⁴
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 ¹⁴
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 ¹⁴
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)	

continued

TABLE 83 Evidence on resource use used in the model (*continued*)

Parameter	Mean	Distribution	Source
Child deaths (excluding stillbirths)			PARROT ¹⁴
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 ¹⁴
High risk	4.66%	Beta (11, 236)	
Intermediate risk	1.56%	Beta (6, 385)	
Low risk	0.52%	Beta (2, 385)	
Neonatal admissions			PARROT ¹⁴
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 ¹⁹
Nights in ICU or HDU (with testing)	15.2	Gamma (SE = 0.12)	
Nights in ICU or HDU (without testing)	24.2	Gamma (SE = 0.31)	
Nights in a SBCU (with testing)	14.7	Gamma (SE = 1.03)	
Nights in a SBCU (without testing)	13.09	Gamma (SE = 1.02)	
Child deaths (excluding stillbirths)			PARROT ¹⁴
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 ¹⁴
High risk	5.08%	Beta (12, 236)	
Intermediate risk	0.78%	Beta (3, 385)	
Low risk	0.52%	Beta (2, 385)	

SE, standard error.

TABLE 84 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 ¹³³
Birth to 3 weeks postpartum (vaginal delivery)	0.6766	Beta (48.04, 71)	Jansen 2007 ¹³⁴
Birth to 3 weeks post-partum (caesarean section)	0.5895	Beta (21.22, 36)	Jansen 2007 ¹³⁴
Birth to 3 weeks postpartum (emergency C section)	0.5167	Beta (17.57, 34)	Jansen 2007 ¹³⁴
3–12 weeks postpartum	0.8676	Beta (195.21, 225)	Bijlenga 2011 ¹³⁵

TABLE 84 Utility and disutility values used in the model (*continued*)

Parameter	Mean	Distribution	Source
12 weeks to 6 months postpartum	0.8683	Beta (166.71, 192)	Bijlenga 2011 ¹³⁵
Decrement for women admitted to an ICU	0.039	See text for details	Seppänen 2018 ¹⁰⁰
Decrement for babies and parents of babies admitted to critical care units	0.039	See text for details	Seppänen 2018 ¹⁰⁰
Mothers whose child had no/minor complications	17.42	Normal (10% of mean)	Varley-Campbell 2019 ¹³⁶
Mothers whose child died	13.45	Normal (10% of mean)	Varley-Campbell 2019 ¹³⁶
Mothers whose child had complications (respiratory distress syndrome and intraventricular haemorrhage)	17.05	Normal (10% of mean)	Varley-Campbell 2019 ¹³⁶
Decrement for babies with complications (respiratory distress syndrome)	0.41	Normal (10% of mean)	Varley-Campbell 2019 ¹³⁶
Decrement for babies with complications (intraventricular haemorrhage)	0.91	Normal (10% of mean)	Varley-Campbell 2019 ¹³⁶
Decrement for child's death	24.70	See text for details	Ara and Brazier ¹³⁷

TABLE 85 Cost inputs: base case

Cost parameters	Input		Source	Notes
	Intervention (£)	Comparator (£)		
Cost per test				
Triage PLGF test	50	0	Quidel/expert opinion	
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 2020–1 ¹⁴⁴	N01A (maternity prices)
Proteinuria test (dipstick)				
Standard blood tests	2.79		NHS Reference Costs 2018/19 ¹⁴³	Standard blood tests
Kidney function + electrolytes + full blood count + transaminases + bilirubin	5.49		NHS Reference Costs 2018–9 ¹⁴³	DAPS04
Fetal assessment	134		NHS Reference Costs 2018–9 ¹⁴³	NZ22Z (OPROC, service code 501)
Oral labetalol	5.25		eMIT 2020 ¹⁴⁵	56 × 200mg tablets
Corticosteroids	46.26		BNF 2021 ¹⁴⁶	6 × 4 mg/1 ml ampoules
Antenatal hospitalisation cost (3 days)	661.67		NHS Payment by Results Tariffs 2020–1 ¹⁴⁴	NZ18B–NZ20B, NZ26B
Antenatal hospitalisation cost (< 35 weeks of gestation) • 8 days	1465		NHS Payment by Results Tariffs 2020–1 ¹⁴⁴	NZ18A (maternity prices); £1465 (8 days antenatal)

continued

TABLE 85 Cost inputs: base case (continued)

Cost parameters				Input		Source	Notes
				Intervention (£)	Comparator (£)		
Management pathway costs							
Severe hypertension	PE	High-risk test result	< 35 weeks	1717.95	1717.95	See Table 24 in report <i>Resource use and costs associated with the management of patients with suspected pre-eclampsia</i>	
			35–37 weeks	895.61	895.61		
		Intermediate	< 35 weeks	1089.40	1089.40		
			35–37 weeks	875.40	875.40		
		Low-risk test result	< 35 weeks	1089.40	1089.40		
			35–37 weeks	875.40	875.40		
	No PE	High-risk test result	< 35 weeks	1814.97	1814.97		
			35–37 weeks	895.61	895.61		
		Intermediate	< 35 weeks	1487.22	1487.22		
			35–37 weeks	922.02	922.02		
		Low-risk test result	< 35 weeks	1487.22	1487.22		
			35–37 weeks	922.02	922.02		
Intermediate hypertension	PE	High-risk test result	< 35 weeks	1717.95	1717.95		
			35–37 weeks	895.61	895.61		
		Intermediate	< 35 weeks	1089.40	1089.40		
			35–37 weeks	875.40	875.40		
		Low-risk test result	< 35 weeks	1089.40	1089.40		
			35–37 weeks	875.40	875.40		
	No PE	High-risk test result	< 35 weeks	1814.97	1814.97		
			35–37 weeks	1665.13	1664.13		
		Intermediate	< 35 weeks	825.55	825.55		
			35–37 weeks	260.35	260.35		
		Low-risk test result	< 35 weeks	465.85	465.85		
			35–37 weeks	193.01	193.01		
Mild hypertension	PE	High-risk test result	< 35 weeks	1717.95	1717.95		
			35–37 weeks	895.61	895.61		
		Intermediate	< 35 weeks	1089.40	1089.40		
			35–37 weeks	875.40	875.40		
		Low-risk test result	< 35 weeks	1089.40	1089.40		
			35–37 weeks	875.40	875.40		
	No PE	High-risk test result	< 35 weeks	1814.97	1814.97		
			35–37 weeks	1665.13	1664.13		
		Intermediate	< 35 weeks	825.55	825.55		
			35–37 weeks	260.35	260.35		
		Low-risk test result	< 35 weeks	465.85	465.85		
			35–37 weeks	193.01	193.01		

TABLE 85 Cost inputs: base case (continued)

Cost parameters		Input		Source	Notes
		Intervention (£)	Comparator (£)		
Delivery costs					
Spontaneous delivery	Unassisted	2009		NHS Reference Costs 2018–9 ¹⁴³	NZ30A-NZ30C
	Assisted	2591		NHS Reference Costs 2018–9 ¹⁴³	NZ40A-NZ40C
Induced delivery	Unassisted	2946		NHS Reference Costs 2018–9 ¹⁴³	NZ31A-NZ32C
	Assisted	4053		NHS Reference Costs 2018–9 ¹⁴³	NZ41A-NZ44C
Caesarean section	Planned	3948		NHS Reference Costs 2018–9 ¹⁴³	NZ50A-NZ50C
	Emergency	5368		NHS Reference Costs 2018–9 ¹⁴³	NZ51A-NZ51C
Magnesium sulphate		8.31		BNF 2021 ¹⁴⁶	1 dose of 4 g injection and then 1 g/hour infusion for at least 24 hours – costed as 1 vial of 100 ml of magnesium sulphate 50% solution for infusion - 500 mg per 1 ml (10 vials = £83.10)
Maternal costs					
Maternal care, standard postnatal phase		252		NHS Payment by Results Tariffs 2020–1 ¹⁴⁴	Non-delivery phases 2b (maternity prices)
Maternal critical care, ICU		1697		NHS Reference Costs 2018–9 ¹⁴³	XC04Z
Neonatal costs					
Neonatal critical care, ICU and HDU		1241		NHS Reference Costs 2018–9 ¹⁴³	XA01Z-XA02Z
Neonatal critical care, special care unit		614		NHS Reference Costs 2018–9 ¹⁴³	XA03-XA04Z
Long-term costs					
Babies with IVH		93,251		Kurse <i>et al.</i> ¹⁵⁰	Assumed as the cost of babies with cerebral palsy, as done by Varley-Campbell <i>et al.</i> ¹³⁶
Babies with RDS		1037		Khan <i>et al.</i> ¹⁴⁸	Assumed as the cost of babies born between 32 and 37 weeks of gestation
Other babies		0		Khan <i>et al.</i> ¹⁴⁸	For those babies born > 37 weeks, all costs were incurred during the initial hospitalisation
BNF, <i>British National Formulary</i> ; IVH, intraventricular haemorrhage; PE, pre-eclampsia; RDS, respiratory distress syndrome.					

sFit-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 we 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 sFit-1/PLGF ratio test provided capital costs which have been annuitised by the authors and also maintenance and equipment costs as described below. However, the manufacturer of Elecsys sFit-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 sFit-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 component costs included in the base case are summarised in [Table 86](#) and explained in further detail below. Full calculations are provided below.

Cost per test kit

- Triage PLGF test: cost of £1000 (provided by the manufacturer), with each kit containing 25 tests – resulting in a cost per test of £40.
- BRAHMS Kryptor sFit-1/PLGF ratio test: cost of £825 for sFit-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 sFit-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 sFit-1/PLGF ratio test. A reportable test consists of those that give 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 syndrome but was not currently. One of our experts suggested that around 73% of NHS laboratories use multipurpose e602 or e811 machines compared to 27% using the e411 based on UKNEQAS data; however, it is not known whether hospitals using these larger multipurpose machines may face similar or different charges.
- Typically, bigger hospitals generating a large volume of tests may be able to negotiate more favourable contracts.

TABLE 86 Components of testing costs (base case)

Cost component	Triage PLGF test	Elecsys sFit-1/PLGF ratio	BRAHMS Kryptor sFit-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

To calculate the following costs (machine, maintenance, laboratory material, training, staff time and phone calls), we assumed that 365 PLGF-based tests were run per machine per year (based on expert advice). However, some laboratories would run these tests only weekly while 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 annuitised, these have been applied as per NICE Diagnostic Guideline 31²⁸¹ and NICE Diagnostic Guideline 39,²⁸² assuming a lifetime of 10 years discounted at 3.5%.

Machine costs

- Triage PLGF test: cost of £1400 (provided by the manufacturer). This cost was annuitised 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 annuitised 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 £4208 for Kryptor Compact Plus and £5892 for Kryptor Gold. Based on commercial in confidence data from the manufacturer (62.5% 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 apportionment of the ratio test to be 1 in 4000 tests (0.025%) as informed by one of our experts for the apportionment 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 £5000 after the second year of contract (provided by the manufacturer) – resulting in a cost per test of £0.003.

Cost of laboratory material (including 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 clinical 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 our clinical 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 for the Triage PLGF test. 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 Diagnostics Guidance DG36.²⁸³
- 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 pre-eclampsia 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.

The Triage PLGF test costs amounted to £50 ([Table 87](#)), Elecsys sFlt-1/PLGF ratio test to £79 ([Table 88](#)) and BRAHMS Kryptor sFlt-1/PLGF ratio test to £52 ([Table 89](#)). 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 *et al.*⁹⁹ reported a cost of £65, although it is unclear what this figure includes. Another clinical expert 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 *et al.*⁹² and Duckworth *et al.*⁹¹ 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. These figures are somewhat higher than our estimate (see [Table 87](#)); therefore, we include them in a scenario analysis.

TABLE 87 Cost breakdown of Triage PLGF test

Cost component	Price (£)	Cost per test (£)	Rationale/formula
Test kit	1000	40	Price/number of tests in kit ($n = 25$)
Machine			
Quidel Triage Meter Pro	1400	0.46	Lifetime = 10 years; 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)
Quidel Triage PLGF Control L2	50		Proportion of labs with monthly QC: 50%
			Price $\times$ number of units per year/number of tests per year ($n = 365$)
Annual service charge			
Year 1	0	0.64	Lifetime= 10 years
Year 2 +	259		$[(\text{price year } 1 \times 1/10) + (\text{price year } 2 \times 9/10)]/\text{number of tests per year}$ ($n = 365$)
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: 3 hours $\times$ 3 persons= 9 hours Cost of training per year (£17.43 $\times$ 9 hours)/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 (0.08 hour)
Staff who perform device QC	17.43	1.97	Time spent per device QC per year: 41 hours Cost of device QC per year (£17.43 $\times$ 41 hours)/number of tests per year ($n = 365$)
Other costs			
Phone calls	3.47	3.47	Proportion of tests processed in labs: 100% ($100\% \times 365 = 365$ tests) Cost per year (£3.47 $\times$ 365)/number of tests per year ($n = 365$)
Total		49.58	
QC, quality control.			

TABLE 88 Cost breakdown of the Elecsys sFlt-1/PLGF ratio test

Cost component	Price (£)	Cost per test (£)	Rationale/formula
Cost per reportable test	N/A	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: 3 hours × 3 persons = 9 hours Cost of training per year (£17.43 × 9 hours)/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 (0.08 hour)
Staff who perform device QC	17.43	£3.94	Time spent per device QC per year: 82 hour Cost of device QC per year (£17.43 × 82 hours)/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	
N/A, not applicable; QC, quality control.			

TABLE 89 Cost breakdown of 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 = 10 years; discount rate = 3.5% Cost per year (£4208)/number of tests per year (n = 365) Apportion of pre-eclampsia share = 0.025%
Annual service charge			
Year 1	0	0.003	Lifetime = 10 years
Year 2 +	5000		[(Price year 1 × 1/10) + (price year 2 × apportion of pre-eclampsia share × 9/10)]/number of tests per year (n = 365)
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)

TABLE 89 Cost breakdown of BRAHMS sFlt-1 Kryptor/BRAHMS PLGF plus Kryptor PE ratio test (*continued*)

Cost component	Price (£)	Cost per test (£)	Rationale/formula
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: 3 hours × 3 persons = 9 hours Cost of training per year (£17.43 × 9 hours)/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 (0.08 hour)
Staff who perform device QC	17.43	3.94	Time spent per device QC per year: 82 hours Cost of device QC per year (£17.43 × 82 hours)/number of tests per year ($n = 365$)
Other costs			
Phone calls	3.47	3.47	Proportion of tests processed in labs: 100% ($100\% \times 365 = 365$ tests) Cost per year (£3.47 × 365)/number of tests per year ($n = 365$)
Total		52.28	
QC, quality control.			

Appendix 9 Additional cost-effectiveness results

Deterministic base-case results (costs and QALYs) are presented below, based assumptions from our survey responses ([Table 90](#)) and from the PreOS study⁴⁶ ([Table 91](#)), respectively.

Additional results for the DELFIA ratio and BRAHMS tests

Since completion of the systematic review of test accuracy and clinical effectiveness, a (stand-alone) study has been published comparing the diagnostic accuracy of the DELFIA Xpress PLGF 1-2-3 test with the DELFIA sFlt1/PLGF ratio test⁴⁹ ([Table 92](#)).

Deterministic results (costs and QALYs) for the base case (i.e. using population from PARROT) for PLGF-based tests used to rule out pre-eclampsia are shown in [Tables 93](#) and [94](#).

TABLE 90 Deterministic base-case results, PLGF-based tests to rule out and rule in pre-eclampsia (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 costs (£)	10,724	10,239	10,203	10,117	10,111	10,150	10,133
Test (£)	0	0	50	79	79	37	52
Clinical management (£)	1238	844	813	761	776	816	814
Delivery (£)	3781	3781	3781	3781	3781	3781	3781
Maternal short term (£)	361	349	345	339	337	341	339
Neonatal short term (£)	4357	4257	4219	4172	4159	4190	4170
Neonatal long term (£)	987	£1007	£995	£984	£977	£984	£976
Total QALYs	17.6217	17.6461	17.6569	17.6699	17.6737	17.6652	17.6710
Clinical management	0.0	0.0	0.0	0.0	0.0	0.0	0.0
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 91 Deterministic base-case results, PLGF-based tests to rule out and rule in pre-eclampsia (based on PreOS evidence)

Rule-out and rule-in testing based on PreOS study ⁴⁶	SA: DG23	SA: INSPIRE	Triage test	Elecsys	Elecsys add-on	DELFI A	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 (£)	3781	3781	3781	3781	3781	3781	3781
Maternal short term (£)	364	362	360	360	359	360	359
Neonatal short term (£)	4374	4359	4344	4337	4334	4339	4336
Neonatal long term (£)	1062	1068	1063	1062	1060	1061	1060
Total QALYs	17.6118	17.6152	17.6195	17.6215	17.6225	17.6211	17.6220
Clinical management	0.0	0.0	0.0	0.0	0.0	0.0	0.0
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

TABLE 92 Sensitivity and specificity values used in the economic model for the DELFIA ratio test

Baseline = PARROT	Sensitivity	Specificity	Notes
DELFI A ratio < 50	0.84	0.67	Relative to DELFI A 1-2-3 from Bremner <i>et al.</i> ⁴⁹
DELFI A ratio ≥ 70	0.84	0.82	Relative to DELFI A 1-2-3 from Bremner <i>et al.</i> ⁴⁹
Baseline = INSPIRE	Sensitivity	Specificity	Notes
DELFI A ratio < 50	0.91	0.75	Relative to DELFI A 1-2-3 from Bremner <i>et al.</i> ⁴⁹
DELFI A ratio ≥ 70	0.90	0.78	Relative to DELFI A 1-2-3 from Bremner <i>et al.</i> ⁴⁹

TABLE 93 Deterministic results, PLGF-based tests to rule out pre-eclampsia

	DELFLA ratio	BRAHMS (updated)
Total costs (£)	10,261	10,227
Test (£)	71	52
Clinical management (£)	600	598
Delivery (£)	3781	3781
Maternal short term (£)	363	362
Neonatal short term (£)	4365	4357
Neonatal long term (£)	1080	1077
Total QALYs	17.6127	17.6151
Clinical management	0.0	0.0
Delivery	0.035	0.035
Maternal short term	0.384	0.384
Neonatal short term	-0.001	-0.001
Maternal long term	17.364	17.364
Neonatal long term	-0.170	-0.168
True positives (%)	8.7	9.2
True negatives (%)	66.2	66.2
False positives (%)	5.7	5.7
False negatives (%)	19.5	19.0

TABLE 94 Incremental base-case results, PLGF-based tests to rule out pre-eclampsia

	Total costs		Total QALYs		ICER	
	DG23	INSPIRE	DG23	INSPIRE		
Standard clinical assessment	£10,215	£10,223	17.6110	17.6093		
	Incremental costs vs. standard clinical assessment		Incremental QALYs vs. standard clinical assessment			
	DG23	INSPIRE	DG23	INSPIRE	DG23	INSPIRE
DELFLA ratio	£46.4	£38.7	0.0017	0.0034	£26,604	£11,342
BRAHMS (updated)	£12.3	£4.6	0.0042	0.0058	£2963	£794

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