

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Diagnostics Assessment Programme

Pre-eclampsia: The Triage PIGF test, Elecsys immunoassay sFlt-1/PIGF ratio, DELFIA Xpress PIGF 1-2-3 test and BRAHMS sFlt-1 Kryptor / PIGF plus Kryptor PE ratio to aid the assessment of suspected pre-eclampsia

Final scope

March 2015

1 Introduction

The Triage PIGF test is manufactured by Alere. The Medical Technologies Advisory Committee identified the Triage PIGF test as potentially suitable for evaluation by the Diagnostics Assessment Programme on the basis of a briefing note. The revised scope was informed by discussions at the scoping workshop held on 4 February 2015 and the assessment subgroup meeting held on 20 February 2015.

A glossary of terms is provided in appendix A.

2 Description of the technologies

This section describes the properties of the diagnostic technologies based on information provided to NICE from the companies and on information available in the public domain. NICE has not carried out an independent evaluation of this description.

2.1 Purpose of the medical technologies

Pre-eclampsia is a potentially serious complication of some pregnancies which, when identified, requires referral to a specialist and hospital admission for both maternal and fetal monitoring. Pre-eclampsia is characterised by high blood pressure (hypertension) and proteinuria which occurs when the kidneys leak protein into the urine. If pre-eclampsia is not diagnosed and closely monitored it can lead to potentially life-threatening complications including

eclampsia, HELLP syndrome, disseminated intravascular coagulation, stroke, or organ dysfunction.

The PIGF tests measure the amount of placental growth factor (PIGF) in blood plasma. PIGF is a protein involved in placental angiogenesis (the development of new blood vessels). In pre-eclampsia, a condition that is thought to be related to problems with the development of the placenta, levels of PIGF can be abnormally low. In normal pregnancy, PIGF levels rise and peak at 26 to 30 weeks gestation so the failure of PIGF levels to rise during pregnancy may be an indicator of placental dysfunction. In addition, some PIGF tests also measure soluble FMS-like tyrosine kinase-1 (sFlt-1), a protein which is thought to disable proteins, such as PIGF, which are associated with blood vessel formation. In women who develop pre-eclampsia, the levels of sFlt-1 are thought to be higher than those seen in normal pregnancy. The tests are intended for use in conjunction with clinical judgement and other existing diagnostic tests, to aid the diagnosis of pre-eclampsia.

Using the PIGF tests in addition to current clinical practice could result in faster and more accurate diagnosis of pre-eclampsia and better risk assessment of adverse outcomes for women with suspected pre-eclampsia. They could also allow women who have pre-eclampsia ruled out with the PIGF test to receive outpatient care instead of being admitted to hospital for observation.

2.2 Product properties

2.2.1 Triage PIGF

The Triage PIGF test (Alere) is a CE marked single use fluorescence immunoassay device which is used in conjunction with the Triage MeterPro point of care analyser for the quantitative determination of PIGF in blood plasma samples. The test is intended for use in conjunction with clinical judgement and other existing diagnostic tests, to aid the diagnosis of pre-eclampsia and to assess the level of risk for delivery arising from pre-eclampsia within 14 days of testing.

Each Triage PIGF test device contains mouse monoclonal antibodies against PIGF, fluorescent dye and stabilisers. Prior to use of the test device, the blood sample is centrifuged for around 3 minutes to obtain an EDTA anticoagulated plasma specimen. A 250 microlitre sample of plasma is then added to the Triage PIGF test device's sample port where it reacts with fluorescent antibody conjugates and flows through the test device, via capillary action, to a measurement zone where complexes of the fluorescent antibody conjugates

are captured. The test device is inserted into the Triage MeterPro analyser which measures levels of fluorescence from the antibody conjugate complexes. It is reported that the test has a limit of detection of 9 picograms/millilitre and a measurable range of 12 to 3000 picograms/millilitre. The test turnaround time is reported as approximately 15 minutes.

The Triage PIGF test is recommended for use in pregnant women with a gestational age of between 20 weeks and 34 weeks plus 6 days. The test cut-offs recommended by the company are shown in Table 1.

Table 1 Recommended cut-offs for the Triage PIGF test

Result	Classification	Interpretation
PIGF < 12pg/mL	Test positive – highly abnormal	Highly abnormal and suggestive of patients with severe placental dysfunction and at increased risk for preterm delivery
PIGF ≥12 pg/mL and <100pg/mL	Test positive – abnormal	Abnormal and suggestive of patients with placental dysfunction and at increased risk for preterm delivery
PIGF ≥100 pg/mL	Test negative – normal	Normal and suggestive of patients without placental dysfunction and unlikely to progress to delivery within 14 days of the test.

2.2.2 Elecsys immunoassay sFlt-1/PIGF ratio

The Elecsys immunoassay sFlt-1/PIGF ratio (Roche) measures the relative amounts of PIGF to soluble FMS-like tyrosine kinase-1 (sFlt-1; also known as VEGFR1) in serum samples from women with suspected pre-eclampsia. The ratio is formed by combining the results from 2 CE marked sandwich electrochemiluminescence immunoassays (the Elecsys PIGF and Elecsys sFlt-1 assays) which are compatible with both the Roche Elecsys and the Cobas e automated clinical chemistry analysers. The sFlt-1/PIGF ratio is calculated and reported to the user alongside the individual assay values by the laboratory information system. The Elecsys immunoassay sFlt-1/PIGF ratio is intended for use in aiding the diagnosis of pre-eclampsia in conjunction with clinical judgement and other diagnostic tests. In addition, the ratio may be used as an aid to predict pre-eclampsia, eclampsia and HELLP syndrome in the short term. The Elecsys sFlt-1 assay has a limit of detection of 10 picograms/millilitre (measuring range 10 to 85,000 picograms/millilitre) and a limit of quantitation of 15 picograms/millilitre. The Elecsys PIGF assay has a limit of detection of 3 picograms/millilitre (measuring range 3 to 10,000 picograms/millilitre) and a limit of quantitation of 10 picograms/millilitre.

The Elecsys immunoassay sFlt-1/PIGF ratio may be used for testing pregnant women with suspected pre-eclampsia from a gestational age of 20 weeks, up until the time of delivery. The test cut-offs recommended by the company are shown in Table 2.

Table 2 Recommended cut-offs for the Elecsys immunoassay sFlt-1/PIGF ratio

			sFlt-1/PIGF ratio
Aid in diagnosis of pre-eclampsia	Week 20 ⁺⁰ to week 33 ⁺⁶	Rule out cut-off	33
		Rule in cut-off	85
	Week 34 ⁺⁰ to delivery	Rule out cut-off	33
		Rule in cut-off	110
Short-term prediction of pre-eclampsia (week 24 ⁺⁰ to 36 ⁺⁶)		Rule out*	<38
		Rule in**	>38

* rule out pre-eclampsia for one week; ** rule-in pre-eclampsia within 4 weeks

2.2.3 DELFIA Xpress PIGF 1-2-3 test

The DELFIA Xpress PIGF 1-2-3 test (Perkin Elmer) is a CE marked solid-phase, two-site fluoroimmuno-metric sandwich assay for the quantitative determination of PIGF in serum samples. The test is intended as an aid to the diagnosis of pre-eclampsia during the second and third trimesters of pregnancy, and is used in conjunction with clinical assessment.

The assay includes both immobilized and europium labelled monoclonal antibodies which bind to PIGF molecules present in the sample to form PIGF-monoclonal antibody complexes. The resulting europium fluorescence from each sample is proportional to the concentration of PIGF. The assay has a limit of detection of 1.9 picograms/millilitre (measuring range 1.9 to 4000 picograms/millilitre) and a limit of quantitation of 3.3 picograms/millilitre. The assay is compatible with the 6000 DELFIA Xpress random access analyser.

The company advises that cut-off values for PIGF measurements obtained during the second trimester are highly dependent on gestational day and should be established by individual laboratories. In the third trimester the company advises that, in addition to laboratory calculated cut-off values based on gestational day, a fixed cut-off of 184 picograms/millilitre can be used. Levels of PIGF lower than 184 picograms/millilitre indicate an elevated probability of pre-eclampsia developing.

2.2.4 BRAHMS sFlt-1 Kryptor / BRAHMS PIGF plus Kryptor PE ratio

The BRAHMS sFlt-1 Kryptor / BRAHMS PIGF plus Kryptor PE ratio (Thermo Scientific) is formed by combining the results from 2 automated immunofluorescent sandwich assays, the BRAHMS sFlt-1 Kryptor and BRAHMS PIGF plus Kryptor assays. The assays are indicated for the quantitative determination of sFlt-1 and PIGF in serum samples and are compatible with the BRAHMS Kryptor compact plus analyser. The assays are intended to be run simultaneously, with the analyser reporting both the concentrations for each assay and the sFlt-1/PIGF ratio to the user. The BRAHMS sFlt-1 Kryptor / BRAHMS PIGF plus KRYPTOR PE ratio is intended to be used in conjunction with clinical assessment to aid the diagnosis of pre-eclampsia.

The BRAHMS sFlt-1 Kryptor assay has a limit of detection of 22 picograms/millilitre (measuring range 22 to 90,000 picograms/millilitre) and a limit of quantitation of 34 picograms/millilitre. The BRAHMS PIGF plus kryptor assay has a limit of detection of 3.6 picograms/millilitre (measuring range 3.6 to 7000 picograms/millilitre) and a limit of quantitation of 6.9 picograms/millilitre. Reference ranges for each of the assays and the sFlt-1/PIGF ratio are provided in the company instructions, and the company recommends that individual laboratories should validate these ranges or establish their own reference ranges prior to use.

3 Target conditions / indications

Gestational hypertension and pre-eclampsia

3.1 Background

Pre-eclampsia is a condition which can affect pregnant women and most frequently occurs during the second half of pregnancy. It is thought to be associated with placental dysfunction, whereby blood flow through the placenta is reduced. Pre-eclampsia is characterised by maternal hypertension and proteinuria, and may also cause restricted growth in the fetus. It is thought to affect up to 5% of pregnancies (Patient UK 2012), and if not detected and monitored, pre-eclampsia can develop into eclampsia, a potentially life-threatening convulsive condition, which affects around 1 in 2000 pregnancies in the UK (Patient UK 2012). Pre-eclampsia may also result in HELLP syndrome, disseminated intravascular coagulation, stroke or organ dysfunction. Women who have hypertension or pre-eclampsia during pregnancy may also have a higher risk of complications from placental

abruption. It is also thought that women who develop pre-eclampsia during pregnancy may be at greater risk of cardiovascular disease later in life.

In 2012-13 there were 12,356 admissions to hospital for pre-eclampsia and 294 for eclampsia (HSCIC Hospital Episode Statistics 2012-13). It is estimated that pre-eclampsia, and associated eclampsia, are the second leading cause of direct maternal deaths in the UK (Centre for Maternal and Child Enquiries 2011), and that half of women with severe pre-eclampsia give birth pre-term ([NICE clinical guideline 107](#)). Gestational hypertension and pre-eclampsia may also impact upon the fetus, placing them at increased risk of intrauterine growth restriction, prematurity and intrauterine death. It is estimated that around 1000 babies die each year because of pre-eclampsia and associated early delivery (NHS Choices 2013).

Pre-eclampsia is frequently asymptomatic and may only be detected through routine antenatal testing. Symptoms of pre-eclampsia include severe headache, problems with vision, severe pain just below the ribs, vomiting, and sudden swelling of the hands or face.

3.2 Care pathway

3.2.1 Identifying and managing the risk of developing pre-eclampsia

[Antenatal care](#) (NICE clinical guideline 62) recommends that blood pressure measurement and urinalysis for protein should be carried out at each antenatal visit to screen for pre-eclampsia. The guideline also recommends determining risk factors for pre-eclampsia at the booking appointment (by 10 weeks of pregnancy). As outlined in [Hypertension in pregnancy: the management of hypertensive disorders in pregnancy](#) (NICE clinical guideline 107), women who are classified as being at high risk for pre-eclampsia are those who have any of the following risk factors identified during the booking appointment:

- Hypertensive disease during a previous pregnancy
- Chronic kidney disease
- Autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome
- Type 1 or type 2 diabetes
- Chronic hypertension

Women who are classified as being at moderate risk for pre-eclampsia are those who have any of the following risk factors identified during the booking appointment:

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- First pregnancy
- Age 40 years old
- Pregnancy interval of more than 10 years
- Body mass index of 35 kg/m² or more at first visit
- Family history of pre-eclampsia
- Multiple pregnancy

It is advised that women with either one high risk factor, or more than one moderate risk factor for pre-eclampsia, take 75mg of aspirin daily from 12 weeks gestation until the birth of the baby.

Pregnant women who are considered to be at risk of developing pre-eclampsia should also be considered for more frequent blood pressure monitoring, and assessment for proteinuria. Women who have significant hypertension (diastolic pressure of 90-110mmHg) and/or a proteinuria result of 1+ on urinalysis reagent strips will need increased surveillance.

It is recommended that proteinuria should be assessed using an automated reagent-strip reading device or a spot urinary protein:creatinine ratio. Where a result of 1+ is obtained using an automated reagent-strip reading device, a spot urinary protein:creatinine ratio or 24 hour urine collection should be used to quantify the level of proteinuria present.

In addition to antenatal surveillance for hypertension and proteinuria, [NICE clinical guideline 62](#) and [NICE clinical guideline 107](#) recommend that all pregnant women should be made aware of the symptoms of pre-eclampsia, which include severe headache, problems with vision such as blurring or flashing before the eyes, severe pain just below the ribs, vomiting and sudden swelling of the face, hands or feet. Pregnant women experiencing any of these symptoms should seek immediate advice from a healthcare professional.

3.2.2 Management of pregnancy with gestational hypertension

The management of pregnancy with gestational hypertension, that is new hypertension presenting after 20 weeks without significant proteinuria, is outlined in [NICE clinical guideline 107](#). Increased surveillance is required to confirm a diagnosis of gestational hypertension, as some women may present with transient hypertension. Women with gestational hypertension are recommended to be assessed for proteinuria at each visit, in order to detect the onset of suspected pre-eclampsia. The recommended management of pregnancy with gestational hypertension is outlined below in Table 3.

Table 3 Management of pregnancy with gestational hypertension

Degree of hypertension	Mild hypertension (140/90 to 149/99 mmHg)	Moderate hypertension (150/100 to 159/109 mmHg)	Severe hypertension (160/110 mmHg or higher)
Admit to hospital	No	No	Yes (until blood pressure is 159/109 mmHg or lower)
Treat	No	With oral labetalol as first-line treatment to keep: - diastolic blood pressure between 80–100 mmHg - systolic blood pressure less than 150 mmHg	With oral labetalol as first-line treatment to keep: - diastolic blood pressure between 80–100 mmHg - systolic blood pressure less than 150 mmHg
Measure blood pressure	Not more than once a week	At least twice a week	At least four times a day
Test for proteinuria	At each visit using automated reagent strip reading device or urinary protein:creatinine ratio	At each visit using automated reagent strip reading device or urinary protein:creatinine ratio	Daily using automated reagent strip reading device or urinary protein:creatinine ratio
Blood tests	Only those for routine antenatal care	Test kidney function, electrolytes, full blood count, transaminases, bilirubin Do not carry out further blood tests if no proteinuria at subsequent visits	Test at presentation and then monitor weekly: kidney function, electrolytes, full blood count, transaminases, bilirubin
Birth before 37 weeks should not be offered to women with gestational hypertension whose blood pressure is lower than 160/110 mmHg with or without antihypertensive treatment.			

Pregnant women who have gestational hypertension may be subsequently suspected of having pre-eclampsia if proteinuria is detected.

3.2.3 Suspected pre-eclampsia

[NICE clinical guideline 107](#) defines pre-eclampsia as new hypertension with significant proteinuria after 20 weeks gestation. Significant proteinuria should be diagnosed if the urinary protein:creatinine ratio is greater than 30 milligrams/millimol or if a validated 24 hour urine collection result shows greater than 300 milligrams protein. Pre-eclampsia may also arise in pregnant women with chronic hypertension, that is, women in whom pre-existing or previously undiagnosed hypertension was identified during the 10 week antenatal booking appointment. Pregnant women with chronic hypertension may be suspected of having pre-eclampsia if significant proteinuria develops after 20 weeks gestation.

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Pregnant women presenting with suspected pre-eclampsia often have one or more clinical signs or symptoms which may be caused by other underlying health conditions and which may not be directly attributable to pre-eclampsia. The assessment of suspected pre-eclampsia, therefore, represents a significant diagnostic challenge and often requires a large degree of clinical judgement to determine whether a definitive diagnosis of pre-eclampsia is appropriate. Pregnant women who present with suspected pre-eclampsia include, but are not limited to women with borderline hypertension, women with borderline proteinuria measurements, and women presenting with clinical symptoms such as headache, oedema or visual disturbances. In current practice these women may be admitted to hospital for clinical assessment to determine whether pre-eclampsia is an appropriate diagnosis.

Expert opinion suggests that the majority of pregnant women with suspected pre-eclampsia present with gestational hypertension, while a minority present with other signs and symptoms; the most common of which is proteinuria. It is thought that around 20% of pregnant women presenting with new gestational hypertension and 30% to 50% of pregnant women presenting with proteinuria (quantitatively measured) will have pre-eclampsia.

3.2.4 Management of pregnancy with pre-eclampsia

The management of pregnancy with pre-eclampsia, that is where hypertension and significant proteinuria are present, is outlined in [NICE clinical guideline 107](#) and summarised below in table 4. It is recommended that women diagnosed with pre-eclampsia should be assessed at each consultation by a suitably trained healthcare professional and offered an integrated package of care which includes admission, testing and treatment relating to the severity of hypertension.

Table 4 Management of pregnancy with pre-eclampsia

Degree of hypertension	Mild hypertension (140/90 to 149/99 mmHg)	Moderate hypertension (150/100 to 159/109 mmHg)	Severe hypertension (160/110 mmHg or higher)
Admit to hospital	Yes	Yes	Yes
Treat	No	With oral labetalol as first-line treatment to keep: - diastolic blood pressure between 80–100 mmHg - systolic blood pressure less than 150 mmHg	With oral labetalol as first-line treatment to keep: - diastolic blood pressure between 80–100 mmHg - systolic blood pressure less than 150 mmHg
Measure blood pressure	At least four times a day	At least four times a day	More than four times a day, depending on clinical circumstances
Test for proteinuria	Do not repeat quantification of proteinuria	Do not repeat quantification of proteinuria	Do not repeat quantification of proteinuria
Blood tests	Monitor using the following tests twice a week: kidney function, electrolytes, full blood count, transaminases, bilirubin	Monitor using the following tests three times a week: kidney function, electrolytes, full blood count, transaminases, bilirubin	Monitor using the following tests three times a week: kidney function, electrolytes, full blood count, transaminases, bilirubin

[NICE clinical guideline 107](#) recommends that pre-eclampsia should be managed conservatively until 34 weeks, that is same-day delivery of the baby should not be planned. The timing of birth should be determined by maternal (biochemical, haematological and clinical) and fetal thresholds, which are documented in a care plan developed by consultant obstetric staff. Birth can be offered to women before 34 weeks of pregnancy if severe hypertension develops despite treatment or, if any of the maternal or fetal indications for birth which are documented in woman's care plan develop after a course of corticosteroids has been completed. Maternal and fetal indications for birth could include vascular complications, abnormal umbilical artery doppler studies, or intrauterine growth restriction.

Fetal cardiotocography should be carried out at the time of diagnosis of pre-eclampsia, along with ultrasound fetal growth and amniotic fluid volume assessment and umbilical artery doppler velocimetry if conservative management is planned. The frequency of subsequent cardiotocography assessments is dependent on the initial cardiotocography findings, any reported changes in fetal movement, vaginal bleeding, abdominal pain or maternal condition.

The guideline states that birth should be recommended for women who have pre-eclampsia with severe hypertension after 34 weeks when their blood pressure has been controlled and, if appropriate, a course of corticosteroids has been completed. For women who have pre-eclampsia with mild or moderate hypertension at 34 weeks to 36 weeks plus 6 days, birth should be offered depending on maternal and fetal condition, risk factors and the availability of neonatal intensive care. Birth within 24 to 48 hours should be recommended for women who have pre-eclampsia with mild or moderate hypertension after 37 weeks.

3.3 Patient issues and preferences

Pre-eclampsia may be associated with significant maternal and fetal morbidity. Babies of women with pre-eclampsia are at risk of stillbirth or complications arising from premature birth. The quality of life of pregnant women with pre-eclampsia may be substantially impacted by anxiety arising from having a condition which can deteriorate rapidly, and which could require them to decide whether to prolong their pregnancy or opt for a premature birth. Women who have had pre-eclampsia during pregnancy may also have reduced quality of life in the longer-term. Previous adverse pregnancy outcomes may lead to increased anxiety in subsequent pregnancies, and in some cases a decision to not complete their family. The risk and experience of pre-eclampsia can also lead to substantial anxiety for the family of pregnant women.

Use of tests which are intended to aid the diagnosis of suspected pre-eclampsia may identify women who are at low risk of developing pre-eclampsia, who may therefore be managed more conservatively, preventing inpatient hospital stays and increased anxiety. Use of the test may also provide additional information to permit planning for a pre-term birth and reduce anxiety in women who have borderline results from blood pressure and proteinuria monitoring.

4 Scope of the evaluation

Table 5: Scope of the evaluation

<p>Decision question</p>	<ol style="list-style-type: none"> 1. What is the clinical and cost-effectiveness of the Triage PIGF test, Elecsys immunoassay sFlt-1/PIGF ratio, DELFIA Xpress PIGF 1-2-3 test and BRAHMS sFlt-1 Kryptor / PIGF plus Kryptor PE ratio in addition to clinical assessment for the diagnosis of pre-eclampsia in the second and third trimesters of pregnancy? 2. What is the clinical and cost-effectiveness of the Triage PIGF test, Elecsys immunoassay sFlt-1/PIGF ratio, DELFIA Xpress PIGF 1-2-3 test and BRAHMS sFlt-1 Kryptor / PIGF plus Kryptor PE ratio as a replacement for quantitative proteinuria tests in the diagnosis of pre-eclampsia in the second and third trimesters of pregnancy?
<p>Populations</p>	<p>Women presenting with suspected pre-eclampsia between 20 weeks and 36 weeks and 6 days of pregnancy who have received blood pressure assessment and qualitative assessment of proteinuria.</p> <p>Potential subgroups include:</p> <ul style="list-style-type: none"> • Women with chronic hypertension • Women with pre-existing or gestational diabetes • Women with renal disease • Women with an autoimmune disease
<p>Interventions</p>	<ol style="list-style-type: none"> 1. Clinical assessment (as defined for the comparator) in conjunction with: <ul style="list-style-type: none"> • Triage PIGF test • Elecsys immunoassay sFlt-1/PIGF ratio • DELFIA Xpress PIGF 1-2-3 test • BRAHMS sFlt-1 Kryptor / PIGF plus Kryptor PE ratio 2. Clinical assessment (as defined for the comparator but without quantitative proteinuria testing) in conjunction with the PIGF tests listed above in 1.
<p>Comparator</p>	<p>Clinical assessment guided by a combination of the following clinical information:</p> <ul style="list-style-type: none"> • maternal hypertension (based on 3 blood pressure measurements) • proteinuria test (qualitative and quantitative) • clinical symptoms suggestive of pre-eclampsia

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	<ul style="list-style-type: none"> ultrasound fetal growth measurements <p>Maternal hypertension, proteinuria or clinical symptoms alone may be sufficient to diagnose pre-eclampsia, or they may also occur in combination with fetal growth restriction and/or signs of biochemical or haematological impairment.</p>
Healthcare setting	Secondary care
Outcomes	<p>Intermediate measures for consideration may include:</p> <ul style="list-style-type: none"> Diagnostic accuracy Prognostic accuracy Time to test result Test failure rate Time to diagnosis Proportion of women diagnosed with pre-eclampsia Time to onset of pre-eclampsia and/or eclampsia Proportion of women returned to less intensive follow-up Length of in-patient hospital stay Time to delivery
	<p>Clinical outcomes for consideration may include:</p> <ul style="list-style-type: none"> Maternal morbidity and mortality Fetal morbidity and mortality Emergency admission for hypertensive disease Health related quality of life including anxiety
	<p>Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include:</p> <ul style="list-style-type: none"> Costs of equipment, reagents and consumables Cost of staff and associated training Medical costs arising from testing and care such as hospital stay Medical costs arising from adverse events including those associated with false test results and inappropriate treatment
	<p>The cost-effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life years (QALYs).</p>
Time horizon	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

5 Modelling approach

5.1 Existing models

During scoping searches, two economic evaluations using the sFlt-1/PIGF ratio were identified. Hadker et al. (2010) report the results of a decision analytic model which was developed to investigate the economic impact of introducing the Elecsys immunoassay sFlt-1/PIGF ratio into the NHS. The analysis assumed that the test would be used in addition to current clinical practice, from 20 weeks gestation. The authors conclude that use of the test could result in cost savings of £945 per patient which are driven by the consequences associated with a reduction in both false positive and false negative diagnoses.

Schnettler et al. (2013) report the results of a retrospective cost analysis from a prospective cohort study of 176 women (at less than 34 weeks gestation presenting to an American hospital with possible pre-eclampsia) who received additional testing using sFlt-1 and PIGF immunoassays. The results of the sFlt-1 and PIGF immunoassays were combined into a ratio. The authors conclude that the use of a sFlt-1/PIGF ratio could reduce average per patient costs by \$1215. This cost saving is driven by a decrease in false positive results and an increase in true negative results, and a subsequent reduction in antenatal admissions and fetal monitoring. The authors also conclude that the use of the ratio could have avoided iatrogenic pre-term deliveries in some women.

In addition, Meads et al. (2008) report the results of a systematic review and health economic evaluation which aimed to identify combinations of tests and treatments that may be able to predict and prevent pre-eclampsia. Although the evaluation did not include PIGF, the authors constructed a decision tree model which assumed an NHS perspective and incorporated parameters for test accuracy, effectiveness, intervention costs, cost of pre-eclampsia outcomes and prevalence of pre-eclampsia.

5.2 Modelling possibilities

The model may need to take into account the turnaround time for each of the tests used in the diagnostic work-up of pre-eclampsia and consider scenarios where the Triage PIGF test is run in a near patient setting or in a centralised hospital laboratory. Specifically, the impact of same day assessment and assessment which requires an overnight stay should be investigated. The utility of different follow up recommendations for women with indeterminate results should also be explored.

6 Equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Pregnancy and maternity are protected characteristics in the Equality Act (2010). Pregnant women who have pre-existing conditions such as autoimmune disease, chronic kidney disease or diabetes may be at a higher risk of developing pre-eclampsia. Women of African-Caribbean origin may be at increased risk of severe adverse pregnancy outcomes.

Levels of PIGF may differ according to ethnicity and maternal weight.

7 Implementation issues

Use of the Triage PIGF test in a near patient setting may require changes to the existing infrastructure in antenatal clinics and maternity units. The feasibility of centrifuging blood in a near patient setting will also need to be considered.

Where PIGF tests are used in a laboratory setting, changes to laboratory infrastructure may be required to ensure that test turnaround times facilitate same day assessment of women presenting with suspected pre-eclampsia. Use of PIGF tests in either a near patient or laboratory setting would also require the development of both internal and external quality assurance processes.

Antenatal services will need to develop local protocols to facilitate the introduction of PIGF testing into the care pathway for women presenting with suspected pre-eclampsia.

Appendix A Glossary of terms

Automated reagent-strip reading device

A point of care device for assessing proteinuria. Results obtained from an automated strip reading device need to be confirmed by spot urinary protein:creatinine ratio or 24 hour urine collection. The results from an automated strip reading device provide a crude estimation of protein concentration, where 1+ is equal to 30 milligrams/decilitre.

Cardiotocography

Fetal heart rate monitoring.

Eclampsia

A convulsive condition arising in pregnancy, associated with pre-eclampsia.

HELLP syndrome ('H' – haemolysis, 'EL' – elevated liver enzymes, 'LP' – low platelet count)

A rare liver and blood clotting disorder that can develop as a complication of pre-eclampsia. It is most likely to occur immediately after the delivery, but can appear any time after 20 weeks of pregnancy, and in rare cases before 20 weeks.

Placental growth factor (PlGF)

A biomarker from the vascular endothelial growth factor (VEGF) family of proteins. It is emitted by the placenta and is involved in the development of new placental blood vessels (placental angiogenesis).

Pre-eclampsia

A hypertensive condition arising in pregnancy, which is defined by new hypertension presenting after 20 weeks of pregnancy and proteinuria.

Proteinuria

The presence of a detectable level of protein in the urine. Initially, this is determined by an automated reagent-strip reading device and confirmed, and quantified, by either a spot urinary protein:creatinine ratio or 24 hour urine collection. A significant level of proteinuria is considered to be more than 300 milligrams per day or a protein:creatinine ratio of 30 milligrams/millimole.

Soluble FMS-like tyrosine kinase-1 (sFlt-1)

A protein which is thought to disable proteins that aid the development of new blood vessels. It is produced by variety of tissues and binds to circulating vascular endothelial growth factor and PlGF, reducing the effects of these proteins on the developing placenta.

Umbilical artery doppler velocimetry

A measure of blood flow in the umbilical artery via ultrasound.

Appendix B Related NICE guidance and pathways

Related NICE guidance

[Antenatal and postnatal mental health: clinical management and service guidance](#) (2014) NICE clinical guideline CG192

[Intrapartum care: care of healthy women and their babies during childbirth](#) (2014) NICE clinical guideline CG190

[Postnatal care](#) (2014) NICE clinical guideline CG37

[Fertility: assessment and treatment for people with fertility problems](#) (2013) NICE clinical guideline CG156

[Hypertension in pregnancy](#) (2013) NICE quality standard QS35

[Caesarean section](#) (2011) NICE clinical guideline CG132

[Multiple pregnancy: The management of twin and triplet pregnancies in the antenatal period](#) (2011) NICE clinical guideline CG129

[Hypertension in pregnancy: The management of hypertensive disorders during pregnancy](#) (2010) NICE clinical guideline CG107

[Pregnancy and complex social factors: A model for service provision for pregnant women with complex social factors](#) (2010) NICE clinical guideline CG110

[Weight management before, during and after pregnancy](#) (2010) NICE public health guidance PH27

[Antenatal care: routine care for the healthy pregnant woman](#) (2008) NICE clinical guideline CG62

[Diabetes in pregnancy: management of diabetes and its complications from pre-conception to the postnatal period](#) (2008) NICE clinical guideline CG63

[Induction of labour](#) (2008) NICE clinical guideline CG70

[Stroke: Diagnosis and initial management of acute stroke and transient ischaemic attack \(TIA\)](#) (2008) NICE clinical guideline CG68

Guidance in development

[Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period](#). NICE clinical guideline. Publication expected February 2015

[Intrapartum care for high risk women](#). NICE clinical guideline. Publication expected TBC.

[Preterm labour and birth](#). NICE clinical guideline. Publication expected June 2016.

NICE pathways

The PIGF guidance will be included in several NICE pathways, for example: hypertension in pregnancy and antenatal care.

In some of these pathways, it may be appropriate to include the full recommendations of the guidance, in others it will only be necessary to give a link to the guidance.

Relevant guidance from other organisations

Action on Pre-eclampsia (2012) [The pre-eclampsia community guideline](#)

Action on Pre-eclampsia (2009) [Pre-eclampsia day assessment unit guideline for midwives](#)

Association of Anaesthetists of Great Britain & Ireland Obstetric Anaesthetists' Association (2013) [Guidelines for the obstetric anaesthetic services 2013](#)

Association of Anaesthetists of Great Britain & Ireland, The Obstetric Anaesthetists' Association, Regional Anaesthesia UK (2013) [Regional anaesthesia and patients with abnormalities of coagulation](#)

British HIV Association (2012) [British HIV Association guidelines for the management of HIV infection in pregnant women](#)

Clinical Knowledge Summaries (2012) [Pre-conception – advice and management summary](#)

Clinical Knowledge Summaries (2011) [Antenatal care - uncomplicated pregnancy](#)

Clinical Knowledge Summaries (2010) [Hypertension in pregnancy](#)

Pre-eclampsia: The Triage PIGF test, Elecsys immunoassay sFlt-1/PIGF ratio, DELFIA Xpress PIGF 1-2-3 test and BRAHMS sFlt-1 Kryptor / PIGF plus Kryptor PE ratio to aid the assessment of suspected pre-eclampsia
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Guidelines and Audit Implementation Network (GAIN) (2012) [Management of severe pre-eclampsia and eclampsia](#)

Joint Royal Colleges Ambulance Liaison Committee (2006) [Pregnancy induced hypertension \(including eclampsia\)](#)

Royal College of Obstetricians and Gynaecologists (2013) [The investigation and management of the small-for-gestational-age fetus](#)

Royal College of Obstetricians and Gynaecologists (2013) [Induction of labour at term in older mothers](#)

Royal College of Obstetricians and Gynaecologists (2011) [Providing equity of critical and maternity care for the critically ill pregnant or recently pregnant woman](#)

Royal College of Obstetricians and Gynaecologists (2011) [The investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage](#)

Royal College of Obstetricians and Gynaecologists (2011) [Diagnosis and treatment of gestational diabetes](#)

Royal College of Obstetricians and Gynaecologists (2010) [Late intrauterine fetal death and stillbirth](#)

Royal College of Obstetricians and Gynaecologists and Centre for Maternal and Child Enquiries (2010) [Management of women with obesity in pregnancy](#)

Royal College of Obstetricians and Gynaecologists (2007) [Birth after previous caesarean birth](#)

SIGN (2010) [Management of diabetes](#)

SIGN (2010) [Management of obesity](#)

Appendix C References

Centre for Maternal and Child Enquiries (CMACE) (2011) Saving Mothers' Lives: reviewing maternal deaths to make motherhood safer: 2006–08. The Eighth Report on Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG* 118(Suppl. 1):1–203.

Hadker N, Garg S, Costanzo C et al. (2010) Financial impact of a novel pre-eclampsia diagnostic test versus standard practice: a decision-analytic modeling analysis from a UK healthcare payer perspective. *J Med Econ.* 13(4):728-37.

Health and Social Care Information Centre (2013) Hospital Episode Statistics 2012-13 – admitted patient care, England 2012-13.

Meads CA, Crossen JS and Meher S et al. (2008) Methods of prediction and prevention of pre-eclampsia; systematic reviews of accuracy and effectiveness literature with economic modelling. *Health Technol Assess* 12 (6): 1-285.

Patient UK (2012) Pre-eclampsia and eclampsia (professional reference).

Schnettler WT, Dukhovny D, Wenger J, et al. (2013) Cost and resource implications with serum angiogenic factor estimation in the triage of pre-eclampsia *BJOG* 120 (10):1224-32.