Draft Protocol for Evidence Assessment and Analysis Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence

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1. Title of the project

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

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3. Plain English Summary

Pre-eclampsia is a condition that can affect women during pregnancy, most often in the second half of pregnancy. Some women are more at risk of developing pre-eclampsia than others. Pre-eclampsia can have serious consequences if not identified and treated and as such screening of women for potential signs of pre-eclampsia is routine in antenatal care in the NHS. In women who are suspected to be at risk of pre-eclampsia closer monitoring is undertaken. This aims to prevent the significant health risks to both mother and fetus that may occur if pre-eclampsia develops. For some women with suspected pre-eclampsia this monitoring involves admission to hospital for long periods of time. This can have an impact on a woman's quality of life.

Tests that enable an earlier and more accurate prediction of the risk of pre-eclampsia may enable those at low risk to remain in the community setting. Tests have been developed which measure the levels of two proteins in blood, each of which can be abnormal in women with pre-eclampsia. The first, placental growth factor (PlGF), promotes the development of new blood vessels (which is important for a healthy placenta) and is found in abnormally low levels in women with pre-eclampsia. The second, soluble FMS-like tyrosine kinase-1 (sFlt-1), blocks the effect of PlGF and occurs in abnormally high levels in women with pre-eclampsia. The tests measure the blood level either of PlGF or the ratio of sFlt-1 / PlGF and are intended for use in conjunction with clinical judgement and other existing diagnostic tests, to aid the diagnosis of pre-eclampsia. These tests may provide earlier and more accurate prediction of the risk of pre-eclampsia in pregnant women who have signs and symptoms suggestive of the condition.

This project will undertake a search in a number of medical databases to find any available studies that report on these tests. We will then review relevant studies using standard methods to ensure we minimise the risk of error. The costs of these tests will be identified and an economic model will be constructed to estimate the benefits to the patient and healthcare system, in terms of hospital admissions prevented in relation to how much they cost.

4. Background

General introduction into pre-eclampsia

Pre-eclampsia (PE) is a multisystem disorder affecting the mother and the unborn baby, which can have serious consequences if not identified and promptly treated.[1] In national guidelines, NICE defines pre-eclampsia as new hypertension presenting after 20 weeks of pregnancy with significant proteinuria (protein in the urine).[2] Rarely, PE can develop for the first time within the first few days postpartum, although effects of antenatal pre-eclampsia can last for up to 6 weeks postpartum. PE is considered severe when patients have severe hypertension and/or symptoms, and/or biochemical and/or haematological impairment,[2] and develops into eclampsia when the mother has seizures.[3]

About 1,000 babies die each year in the UK because of pre-eclampsia, mostly because of complications of early delivery, such as severe breathing difficulties.[4] Another consequence of PE is HELLP syndrome, when mothers develop haemolysis (breakdown of red blood cells), elevated liver enzymes and a low platelet count, and this is as potentially as dangerous as eclampsia.[4] Patients with PE also have a raised risk of stroke, disseminated intravascular coagulation or kidney dysfunction. The cause of PE is unknown, though it is thought to be related to failure to establish the normal blood supply to the placenta.[4] Pre-eclampsia is usually asymptomatic until well-advanced.[3]

Epidemiology

Women with pre-existing hypertension, hypertension in a previous pregnancy, gestational hypertension, diabetes, obesity, chronic kidney disease or autoimmune disease are at increased risk of developing pre-eclampsia.[1] Pre-eclampsia affects up to 5% of pregnancies, and severe cases develop in about 1-2% of pregnancies.[4] Maternal deaths due to PE have fallen, but hypertension in pregnancy remains a leading indirect cause of maternal death in the UK.[1] Nineteen deaths were caused directly by pre-eclampsia or eclampsia in the UK in 2006-8 (0.85 per 100,000).[5] The case fatality rate from eclampsia is estimated to be 3.1%.[5]

Hypertension is associated with 8–10% of preterm births and more than half of women with severe pre-eclampsia give birth preterm:[1] in a UK study, one in 250 women in their first pregnancy gave birth before 34 weeks as a consequence of pre-eclampsia, and in one region 5% of women with severe pre-eclampsia or eclampsia were admitted to intensive care.[2] Between 20 and 25% of preterm births and 14 to 19% of term births in women with pre-eclampsia result in small-for-gestational-age babies.[2] Delivery of an infant weighing less than the 10th customised[1] birthweight centile was an outcome in 48.3% of births in women with confirmed preeclampsia in a UK study.[7] About 5% of stillbirths without congenital abnormality occur in infants whose mothers have pre-eclampsia.[1]

The impact of the condition (maternal and fetal)

Hypertension in pregnancy carries risks for mother and baby, and can result in maternal death and increase women's lifetime risk of hypertension and cardiovascular disease.[2] Decisions about when to deliver the baby when mothers have pre-eclampsia involve a balance between the best outcomes for both the mother and baby.[3] Before 34 weeks, clinicians try to prolong the pregnancy so that the fetus has time to develop as much as possible before birth. Negative consequences of pre-eclampsia for the baby include fetal growth restriction and preterm birth,[7] which can lead to complications including intracranial haemorrhage, nutritional compromise, necrotising enterocolitis, and breathing difficulties

[1] Customised birthweight taking the mother's characteristics and birthweights from previous pregnancies into consideration. The adjusted birthweight range expected at 40 weeks' gestation is combined with a standard, longitudinal ultrasound-derived curve for intrauterine weight gain.[6]

(neonatal respiratory distress syndrome).[4] Some babies die because of complications related to early delivery, and a few are stillborn.[4] Babies born early, or small-for-gestational-age may have pre-school developmental delays,[8] or ongoing risk of adult disease.[9]

The economic burden of pre-eclampsia includes longer maternal inpatient stay (12.7 days versus 5.4 days for patients without pre-eclampsia) and increased frequency of neonatal unit admission (35% versus 12%).[7]

Current management

Pre-eclampsia may progress unpredictably, within hours or over weeks,[3] so NICE Clinical Guideline 107 recommends immediate hospital referral for assessment of mother and fetus, and conservative management in hospital until 34 weeks, unless there is clinical and test evidence of severe hypertension or potential harm to the baby.[2;10] NICE Guideline 107 recommends management according to blood pressure thresholds[2] (Table 1). Antihypertensive drugs (labetalol, methyldopa or nifedipine) are given, with a target systolic blood pressure of 150 mmHg.[5] Pre-eclampsia can only be cured by delivering the baby, so women are monitored until the optimum time for delivery for both mother and baby is reached. This is around 37-38 weeks of pregnancy, but may be earlier in more severe cases.[4] For women with pre-eclampsia with mild or moderate hypertension at 34 weeks to 36 weeks plus 6 days of gestation, birth is offered depending on maternal and fetal condition, risk factors and availability of neonatal intensive care.[2] Birth is recommended within 24 to 48 hours for women who have pre-eclampsia with mild or moderate hypertension after 37 weeks of gestation.[2]

During hospitalisation for pre-eclampsia, ultrasound scans are carried out to monitor fetal growth and wellbeing (by blood flow measurements in the umbilical cord).[4] Cardiotocography is used to measure the baby's heart rate to detect any signs of compromise.[4]

Specific recommendations for sub-groups

Women with one high risk factor, or more than one moderate risk factor for pre-eclampsia, are advised to take aspirin daily from 12 weeks of gestation until the birth of the baby.[3] NICE makes specific management recommendations for the following high risk factors for PE:

Chronic hypertension

Taking angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) in pregnancy increases the risk of congenital abnormalities, so other antihypertensive treatment is suggested, with the aim of keeping blood pressure below 150/100 mmHg.[2]

Chronic kidney disease

Renal disease may be a result of chronic hypertension. Treatment aims to keep blood pressure below 140/90 mmHg.[2] Women are referred to a specialist in hypertensive disorders.

Gestational diabetes

Women are screened for gestational diabetes at the antenatal booking appointment.[10] Risk factors include BMI >30kg/m^2, a previous baby weighing above 4.5 kg, previous gestational diabetes, a family history of diabetes, and South Asian, Black Caribbean or Middle Eastern origins.[10] Testing for gestational diabetes is recommended if any of these factors are present.[11]

Type 1 or type 2 diabetes

Women are recommended to plan their pregnancy, in order to establish good glycaemic control before conception and to maintain this throughout pregnancy (fasting blood glucose should be between 3.5 and 5.9 mmol/L and 1-hour postprandial blood glucose below 7.8 mmol/L).[11]

Autoimmune disease, including systemic lupus erythematosus (SLE)

Significant flares in disease activity may occur in pregnancy, particularly if lupus was active at the time of conception.[12] No specific guideline recommendations exist, but some experts advise against planning conception until the patient is symptom free for 6 months.[12] When hypertension and proteinuria develop after 20-weeks' gestation in an SLE patient, it is often difficult to distinguish between an SLE flare and pre-eclampsia.[12]

5. Decision problem

5.1 Purpose of the decision to be made

Pre-eclampsia can affect women during pregnancy, mostly in the second and third trimesters. Without diagnosis and monitoring it can lead to significant health risks to the mother and fetus. Pre-eclampsia is a heterogeneous and unpredictable condition, and diagnosis is made based on clinical signs and symptoms. Women with suspected pre-eclampsia can be admitted to acute maternity units for initial evaluation; however, tests that enable an earlier and more accurate diagnosis may enable those at low risk of developing pre-eclampsia to remain instead in the community setting. Tests that measure PlGF levels may provide this earlier and more accurate diagnosis of PE in pregnant women who have signs and symptoms of the condition.[13] Some of these tests may also function (or be developed in future to function) as screening tests to predict the risk of PE before it occurs – but it should be noted that this aspect of their design is outside the scope of the current assessment.

5.2 Objectives

The aim of this project is to assess the clinical effectiveness and cost-effectiveness of technologies that could 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 who have received blood pressure assessment and qualitative assessment of proteinuria. Specific objectives are to determine, through a systematic review and economic evaluation, the clinical and cost-effectiveness of the Triage PlGF test, Elecsys immunoassay sFlt-1 / PlGF ratio, DELFIA Xpress PlGF 1-2-3 test and BRAHMS sFlt-1 Kryptor / PlGF plus Kryptor PE ratio:

- in addition to clinical assessment for the diagnosis of pre-eclampsia in the second and third trimesters of pregnancy;
- as a replacement for quantitative proteinuria tests in the diagnosis of pre-eclampsia in the second and third trimesters of pregnancy.

The scope of these objectives is as defined by the eligibility criteria (population, intervention, comparators and outcomes) specified below in sections 6.1 to 6.4.

5.3 Clear definition of the intervention

A number of technologies measuring PlGF have been proposed to aid the clinical assessment of women suspected of having pre-eclampsia in the second and third trimesters of pregnancy. There are potentially four commercial tests of relevance to this diagnostic assessment.

The Triage PlGF test (Alere International Ltd) aims to quantify the presence of PlGF in plasma samples from women suspected of pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation. It is authorised as a point-of-care test with the company suggesting that the test can be undertaken by the midwife, clinician or laboratory assistant alongside routine maternity assessments.[13] The aim of the Alere Triage PlGF test is to aid the diagnosis of pre-eclampsia by identifying or excluding placental dysfunction, and assessing the level of risk for pre-term delivery. It is used in conjunction with clinical judgement and other existing tests.

The test requires a blood sample which is then centrifuged for approximately three minutes to obtain a plasma sample. The plasma sample is then anticoagulated and several drops are then used to obtain the concentration of PlGF. The assay uses fluorescently-labelled monoclonal antibodies against PlGF for PlGF quantification.[14] The range of the assay for the detection of PlGF is between 12–3000 pg/ml.[14;15] The results are available after approximately 15 minutes.

The Elecsys immunoassay sFlt-1 / PlGF ratio is an automated test (Roche Diagnostics Ltd) which can be used to aid the diagnosis of pre-eclampsia in women suspected of pre-eclampsia from a gestational age of 20 weeks up until the time of delivery. The Roche test measures relative amounts of PlGF and sFlt-1 (soluble FMS-like tyrosine kinase-1) using two immunoassays, one for each marker. The

concentrations from each of these assays are determined and then a ratio of sFlt-1 to PlGF is generated.[16;17] The tests are undertaken in the laboratory using electro-chemiluminescence.[13] The results can be obtained in approximately 18 minutes.[17] The Elecsys immunoassay sFlt-1 / PlGF ratio is intended for use in diagnosing pre-eclampsia in conjunction with clinical judgement and other diagnostic tests. The Elecsys sFlt-1 assay has a limit of detection of 10 pg/mL and a limit of quantification of 15 pg/mL. The Elecsys PlGF assay has a limit of detection of 3 pg/mL and a limit of quantification of 10 pg/mL.

The DELFIA Xpress PlGF 1-2-3 test (Perkin Elmer) is a CE marked solid-phase, two-site fluoroimmunometric sandwich assay for the quantitative determination of PlGF 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 PlGF molecules present in the sample to form PlGF-monoclonal antibody complexes. The resulting europium fluorescence from each sample is proportional to the concentration of PlGF. The assay has a limit of detection of 1.9 pg/mL (measuring range 1.9 to 4000 pg/mL) and a limit of quantitation of 3.3 pg/mL. The assay is compatible with the 6000 DELFIA Xpress random access analyser.

The BRAHMS sFlt-1 Kryptor / BRAHMS PlGF plus Kryptor PE ratio (Thermo Fisher Scientific)[18] is formed by combining the results from 2 automated immunofluorescent sandwich assays, the BRAHMS sFlt-1 Kryptor and BRAHMS PlGF plus Kryptor assays. The assays are indicated for the quantitative determination of sFlt-1 and PlGF in serum samples and are compatible with the BRAHMS Kryptor compact plus analyser. The assays are intended to be run simultaneously, with the analyser reporting both the concentrations for each assay and the sFlt-1 / PlGF ratio to the user. The BRAHMS sFlt-1Kryptor / BRAHMS PlGF 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 pg/mL and a limit of quantification of 34 pg/mL. The BRAHMS PlGF plus Kryptor assay has a limit of detection of 3.6 pg/mL and a limit of quantification of 6.9 pg/mL.

5.4 Populations and relevant subgroups

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

There are four potential subgroups of women for this decision problem: those with chronic hypertension; those with pre-existing or gestational diabetes; those with renal conditions; and those with an autoimmune condition.

5.5 Place of the intervention in the treatment pathway(s)

Two NICE clinical guidelines outline recommendations for care in relation to pre-eclampsia: Clinical Guideline 62, on antenatal care which was last modified in December 2014;[10] and Clinical Guideline 107, which outlines the recommended assessment and treatment of women with PE.[2] NICE has also produced a Quality Standard on hypertension in pregnancy.[1] NICE Guideline NG3 outlines recommendations for the management of diabetes, including gestational diabetes, in pregnancy.[11]

Current pathways of care for screening and diagnosis

Screening in primary and secondary care

NICE Guideline 62 was updated in December 2014 to recommend that pregnant women's blood pressure and urine samples are checked at every antenatal appointment for signs of hypertension and proteinuria.[10] The update recommends noting women's risk factors for PE, specifically nulliparity, pregnancy interval of over 10 years, age over 40 years, body mass index of 30kg/m^2 or more, a previous PE, family history of PE, multiple pregnancy, or pre-existing vascular or renal disease.[10] Increased surveillance is recommended if diastolic blood pressure is greater than 110 mmHg, or there are two consecutive readings of 90 mmHg at least 4 hours apart and/or significant proteinuria.[10] If the systolic blood pressure is above 160 mmHg on two consecutive readings at least 4 hours apart, antihypertensive drug treatment is considered.[10] Patients are also advised to seek immediate advice if they experience swollen feet, ankles, face, hands, severe headaches, vision problems, pain below the ribs, vomiting, excessive weight gain, or feel very unwell.[4]

Pregnant women with chronic hypertension may be suspected of having pre-eclampsia if significant proteinuria develops after 20 weeks gestation. 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.

Women may have new hypertension after 20 weeks of pregnancy without proteinuria. This is called gestational hypertension and may develop into PE, so NICE recommends assessment in secondary care, including blood tests at the first visit, testing for proteinuria at each visit, or admission to hospital and daily proteinuria testing and weekly blood tests if hypertension is severe (>160/110 mmHg).

Screening and diagnosis of PE in secondary care

If pre-eclampsia is suspected, patients are normally referred to hospital for more frequent and additional tests as it can take several days for test results to reach primary care.[3] Blood pressure thresholds for admitting women with pre-eclampsia to hospital are given in NICE Clinical Guideline 107 (Table 1).[2] Assessments recommended in hospital include regular blood pressure measurement, and blood tests for kidney function, electrolytes, full blood count, transaminases and bilirubin. The frequency of repeating these tests depends on blood pressure thresholds.[2]

Blood pressure monitoring, blood tests and biochemical monitoring continue during labour.[2] NICE also recommends postnatal monitoring of women with pre-eclampsia or severe gestational hypertension, as maternal hypertension usually recovers within two to three weeks of delivery but can take up to three months to resolve.[3] Monitoring includes measurement of maternal blood pressure, platelet count, transaminases and serum creatinine 48 to 72 hours after birth.[2] If these measures improve but remain abnormal they may be repeated as clinically indicated, and at the postnatal review (6 to 8 weeks after the birth). If measures do not improve, platelet count, transaminases and serum creatinine measures are repeated as clinically indicated. A urinary reagent-strip test is recommended at the postnatal review. If women still have proteinuria at the postnatal review, a further review is recommended 3 months after the birth to assess kidney function and referral for specialist kidney assessment may be suggested.[2]

Table 1 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	Do not repeat quantification of	Do not repeat quantification of

	proteinuria	proteinuria	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

From: NICE Clinical Guideline 107, Section 1.5, Table 2.[2]

Tests for PlGF may assist the assessment of women suspected of pre-eclampsia from gestation week 20 to gestation week 36 + 6 days. The tests would be used after a positive result from an initial screen of the woman's blood pressure and/or qualitative assessment of urine for protein, and taking into account any symptoms or previous risk factors. Results of such tests may more accurately predict those women who are at low risk of pre-eclampsia, with the aim of reducing the need for hospital admissions for monitoring.

5.6 Relevant comparators

The relevant comparator for the decision problem is usual clinical assessment, which includes a combination of the presence and degree of maternal hypertension, levels of protein in urine, clinical symptoms and signs of biochemical or haematological impairment, and ultrasound fetal growth assessments.

5.7 Key factors to be addressed

Assessment of the effectiveness of testing may be measured using a number of intermediate and clinical outcomes. A key outcome of testing for pre-eclampsia is the diagnostic accuracy of the test to predict pre-eclampsia, and to predict pre-eclampsia requiring pre-term delivery indicated for the mother or the baby (e.g. within 14 days of testing). Time to delivery may be different depending on whether PIGF values are very low, low, or normal, and therefore appropriate clinical management can be decided accordingly.[15] Management decisions may also be informed by the timeliness of the diagnosis, thus measuring time to the test result and time to diagnosis are relevant outcomes. Accurate testing may also result in heath service savings, by reducing unnecessary hospital admissions and investigations for women in whom pre-eclampsia is ruled out, or by reducing the length of in-patient stays among diagnosed women.

Given that pre-eclampsia is a leading cause of direct maternal deaths in the UK, and that half of women with severe pre-eclampsia give birth pre-term, an important clinical outcome is pre-eclampsia related mortality and morbidity, for both the mother and the baby (e.g. including small for gestational age fetus, very preterm birth, and potential need for caesarean section). Another important consideration for assessment is whether an improvement in health related quality of life (HRQoL)

(e.g. reduced anxiety, or reduced post-natal depression) is achieved as a result of accurate diagnosis and appropriate clinical management. This is a key consideration in determining the cost-effectiveness of testing.

6. Report methods for assessing the outcomes arising from the use of the interventions

6.1 Population

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 (dipstick or automated regent-strip reading device[2]) assessment of proteinuria. Potential sub-groups (if data are available) would include:

- Women with chronic hypertension
- Women with pre-existing or gestational diabetes
- Women with renal disease
- Women with autoimmune disease

6.2 Interventions (index tests)

Clinical assessment (including or excluding quantitative determination of proteinuria) in conjunction with one or more of the following tests:

- Triage PlGF test
- Elecsys immunoassay sFlt-1 / PlGF ratio
- DELFIA Xpress PlGF 1-2-3 test
- BRAHMS sFlt-1 Kryptor / PlGF plus Kryptor PE ratio

To evaluate the index test as an adjunct to usual clinical assessment, the clinical assessment will be as defined for the comparator and will include quantitative determination of proteinuria. To evaluate the index test as a replacement for the quantitative proteinuria assessment, the clinical assessment will exclude quantitative determination of proteinuria, but in all other respects will be as defined for the comparator.

Comparisons of the index tests against one another will be made where the availability of evidence permits. The relevant setting for initiation of testing is antenatal clinics in secondary care.

6.3 Comparator (reference standard)

The relevant comparator is clinical assessment guided by the following clinical information:

- Maternal hypertension (based on 3 blood pressure measurements)
- Proteinuria (qualitative and quantitative)

- Clinical symptoms suggestive of pre-eclampsia
- Ultrasound fetal growth measurements

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.

6.4 Outcomes

Studies will be included if they report one or more of the following outcomes:

Intermediate outcomes

- Diagnostic accuracy (e.g. sensitivity and specificity)
- 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

Clinical outcomes

- Maternal morbidity and mortality
- Fetal and neonatal morbidity and mortality
- Emergency admission for hypertensive disease
- HRQoL (including anxiety)

Data on these indirect outcomes will be used to estimate quality-adjusted life years (QALYs) as final health outcomes.

6.5 Study design

Relevant study designs for the assessment of diagnostic accuracy of tests for pre-eclampsia may be randomised trials, prospective or retrospective longitudinal cohort studies or cross-sectional studies. Given the range of potentially eligible study designs that could include diagnostic assessments, the systematic review will not be limited to particular study designs. Instead, issues of study quality that may relate to the study design (specifically, influencing risk of bias and applicability of the study findings) will be evaluated at the formal quality assessment step (Section 6.8).

6.6 Search strategy

A comprehensive search strategy will be developed, tested and refined by an experienced information scientist (see Appendix 1 for a draft Medline search strategy). The search strategy will aim to identify studies on the diagnosis of pre-eclampsia and studies providing relevant clinical outcomes (morbidity, mortality, HRQoL) using the intervention and relevant comparators as specified above.

The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of included studies

Electronic resources to be searched will include:

- General health and biomedical databases – MEDLINE (Ovid); PreMedline In-Process & Other Non-Indexed Citations; EMBASE; the Cochrane Library; Web of Science; Database of Abstracts of Reviews of Effectiveness (DARE); Health Technology Assessment database; MEDION database of diagnostic accuracy studies.
- Relevant conferences – including those of the American Society of Hypertension; British Hypertension Society; British Maternal and Fetal Medicine Society; European Society of Hypertension; International Society for the Study of Hypertension in Pregnancy; ISPD International Conference on Prenatal Diagnosis and Therapy.
- Internet pages of relevant institutions and other organisations – including those of the Royal College of Obstetricians and Gynaecologists; American College of Obstetricians and Gynaecologists; International Society of Perinatal Obstetricians; Society for Maternal Fetal Medicine; Action on Pre-Eclampsia; Pre-Eclampsia Foundation; National Childbirth Trust; Cochrane Pregnancy and Childbirth Group; Tommy's (funds research into pregnancy problems and provides information to parents).
- Grey literature and research in progress – UK Clinical Research Network Portfolio Database; World Health Organization International Clinical Trials Registry Platform (WHO ICTRP); ISRCTN (controlled and other trials); Clinical Trials.gov; NIHR Clinical Research Network Portfolio; UK Clinical Trials Gateway (UKCTG).

All databases will be searched from 2000 (clinical experts advised this is an appropriate start date, given that the technologies under comparison are relatively new) to the present and searches will be limited to the English language. Systematic reviews will only be retrieved in order to check their reference lists for potentially relevant primary research studies.

Studies published as abstracts or conference proceedings will be included only if sufficient details are presented to allow appraisal of the methodology and the assessment of results to be undertaken.

For the cost-effectiveness assessment, searches for other evidence to inform cost-effectiveness modelling will be conducted as required (see Section 7.3) and may include a wider range of study types.

6.7 Data extraction strategy

Studies will be selected for inclusion through a two-stage process using the predefined and explicit criteria specified above (Sections 6.1-6.4). The titles and abstracts of bibliographic records identified by the search strategy will be assessed by two reviewers independently for potential eligibility. Full papers of studies which appear potentially relevant will be requested for further assessment. These will be screened by one reviewer and checked by a second, and a final decision regarding inclusion will be agreed. At both stages any disagreements will be resolved by discussion, with involvement of a third reviewer where necessary.

Relevant data will be extracted on the study and population characteristics, methodological details of the technologies under comparison and diagnostic outcomes. Where reported, data on morbidity, mortality and HRQoL will also be extracted. Data extraction and quality assessment will be undertaken by one reviewer and checked by a second reviewer using a pre-designed and piloted data extraction form (see Appendix 2 for sample data extraction form) to avoid any errors. Any disagreements between reviewers at the study selection and data extraction stages will be resolved by consensus or if necessary by arbitration by a third reviewer. Papers that refer to the same primary study will be assessed together, to avoid double-counting of information.

6.8 Quality assessment strategy

The methodological rigour of studies will be assessed by one reviewer and checked by a second reviewer, with any disagreements resolved by consensus or if necessary by arbitration by a third reviewer. The quality of studies reporting diagnostic accuracy will be assessed using the Cochrane Collaboration adaptation[19] of the QUADAS tool[20]

6.9 Methods of analysis/synthesis

Studies will be synthesized through a structured narrative review with tabulation of results of included studies. Where appropriate and where suitable data are available, meta-analysis will be employed to synthesise data on test sensitivity and specificity. The appropriateness of meta-analysis will be determined by assessing the clinical and statistical heterogeneity of the primary studies and will be informed by critical appraisal of the primary studies during the quality assessment step (section 6.8)

(e.g. sensitivity analyses may be conducted to assess the effect of study quality on diagnostic outcomes). To account for correlation between sensitivity and specificity, and their dependence on the prevalence of pre-eclampsia, any pooling of sensitivity and specificity outcomes will be based on appropriate hierarchical random effects models (using statistical software such as Winbugs or R). Synthesis of the findings may include summary receiver operating characteristic (sROC) curves to illustrate the trade-off between test sensitivity and specificity for different diagnostic thresholds. Consideration will be given to the presentation of likelihood ratios and diagnostic odds ratios which can usefully inform interpretation of diagnostic test accuracy but also have some limitations. Heterogeneity among studies and analyses of relevant subgroups will be explored and presented (e.g. using sensitivity and specificity paired forest plots). Where possible, the analysis and synthesis will follow good practice approaches as recommended by the Centre for Reviews and Dissemination (CRD) (Chapter 2: Systematic reviews of Clinical Tests),[21] the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy,[22;23] and the NICE Diagnostics Assessment Programme Manual.[24]

7. Report methods for synthesising evidence of cost effectiveness

7.1 Identifying and systematically reviewing published cost-effectiveness studies

The methods detailed in section 6 will be used to systematically review the cost-effectiveness literature. The population, interventions and comparators to be included will be the same as for the systematic review of clinical effectiveness (as described in sections 6.1, 6.2 and 6.3), with the exception of study design and outcomes. Studies will be included if they are full economic evaluations, assessing both costs and consequences, of the specified technologies. Outcomes to be included are those consistent with full economic evaluations and are likely to include intermediate outcomes (such as budget impact, cost per patient, cost per case of pre-eclampsia correctly managed) as well as final outcomes (life years or QALYs gained). The data will be extracted from these studies using standardised forms and will be tabulated and discussed in a narrative review.

Where presented, HRQoL data will be extracted from studies included in both the systematic review of clinical effectiveness and the systematic review of cost-effectiveness. In addition, a targeted literature search will be conducted specifically for publications reporting HRQoL or health state utility for women undergoing medical management for suspected pre-eclampsia.

7.2 Evaluation of costs and cost effectiveness

Data extraction will be undertaken by one reviewer and checked by a second health economist reviewer using a pre-designed and piloted data extraction form (see Appendix 3 for a sample data extraction form). The quality of the included economic evaluations will be assessed using a critical

appraisal checklist based upon that proposed by Drummond et al.[25] and Philips et al.[26] (see Appendix 4.

7.3 Development of a health economic model

A comparison of the costs and consequences of alternative approaches to diagnosing pre-eclampsia will be made using decision analytic models. The structure of the models will be informed by the systematic review of cost-effectiveness and other systematic searches of the literature and, where necessary, using guidelines and expert opinion. The model used in the assessment will be constructed according to standard modelling guidelines and a full explanation of our methods for formulating model structure and deriving parameter values will be given in the assessment report. The perspective will be that of the NHS and Personal Social Services (PSS). The outcome will be reported as cost per patient and cost per QALY gained, where possible.

The decision model will include the current costs of identifying and managing women with suspected pre-eclampsia (including on-going management of hypertension, stratified by severity), additional costs for new approaches to diagnosing pre-eclampsia (in terms of capital costs and consumables required for the diagnostic test, as well as any additional staff and laboratory resources involved in acquiring or analysing test specimens) and will identify any potential savings that may be associated with more appropriate management of women with suspected pre-eclampsia. Targeted searches will be conducted for publications reporting HRQoL or health state utility for women undergoing medical management for suspected pre-eclampsia to populate the model. If insufficient published HRQoL data are available it will be necessary to elicit HRQoL values from clinical experts or to conduct threshold analyses using a range of estimates.

Preliminary searches have identified three economic evaluations of diagnostic tests that are within the scope of this assessment, i.e. diagnostic tests for pre-eclampsia administered to women between 20 weeks and 36 weeks plus 6 days gestation. Two of these are evaluations of the Roche sFlt-1 / PlGF ratio test[27 28] and one is an unpublished evaluation of the Triage PlGF test.[29] All three studies describe themselves as budget impact analyses and use short-term decision trees to model the cost of managing women with suspected pre-eclampsia according to current practice (based on degree of hypertension and proteinuria) compared with diagnosis based on a specific diagnostic test combined with current practice. The models reported in these evaluations do not consider maternal or neonatal outcomes (in terms of morbidity, mortality or quality of life), but concentrate on potential savings through more appropriate management. In particular, they suggest that including diagnostic tests alongside clinical signs has the potential to reduce false-positive diagnoses of pre-eclampsia made using clinical symptoms and signs alone – thereby avoiding over- or inappropriate treatment.

We will review the models used in these evaluations, and any that may be identified during the full systematic review, to assess whether they would be appropriate (with or without modification) in the current assessment. Prior to deciding whether to adapt an existing model or to develop a de novo model, the existing models will be formally assessed for the appropriateness of their structural assumptions (for example whether it is acceptable to exclude maternal or neonatal outcomes from the model), and for their included parameters and associated values.

Parameter values will be obtained from the relevant research literature, including our own systematic review of clinical and cost-effectiveness. Sources for parameters will be stated clearly. Resource use will be specified and valued from the perspective of the NHS and PSS. Costs will be derived from primary data from previous studies, and national and local NHS unit costs. If insufficient data are retrieved from published sources, costs may be obtained from individual NHS Trusts or groups of Trusts.

Uncertainty will be explored through both one-way sensitivity analyses and scenario analyses (for variables such as gestational age, time to return of test results and the impact this may have on patient management, and different approaches to patient follow up based on test results). Where appropriate (for the Triage PlGF test only), the influence of the location of PlGF test analysis (i.e. in near-patient or centralised laboratory settings) will be explored. A probabilistic sensitivity analysis (PSA) will be undertaken if both the data and modelling approach permit this. The outputs of any PSA will be presented using plots of the cost–effectiveness plane and cost-effectiveness acceptability curves.

The model will be validated by checking the model structure, calculations and data inputs for technical correctness. The structure will be reviewed by clinical experts for appropriateness of the clinical and diagnostic pathways. The robustness of the model to changes in input values will be tested using sensitivity analyses.

8. Handling information from the companies

Any 'commercial in confidence' data provided by a manufacturer and specified as such will be highlighted in blue and underlined in the assessment report (followed by an indication of the relevant company name e.g. in brackets). Any academic-in-confidence data provided will be highlighted in yellow and underlined.

9. Competing interests of authors

None

10. Timetable/milestones

Milestone	Date to be completed
Final protocol	9th March 2015
Progress report to NETSCC, HTA	9th June 2015
Draft report submitted to NICE	4th August 2015
Submission of final report to NETSCC, HTA; NICE	2nd September 2015

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Appendices

Appendix 1: Scoping searches for Medline

1 Pre-Eclampsia/ (23752)
2 (preeclamp* or pre eclamp*).tw. (19166)
3 (tox?emi* adj5 pregnan*).tw. (3132)
4 gestosis.tw. (1187)
5 (pregnan* adj3 hypertensi*).tw. (7866)
6 (gestation* adj3 hypertensi*).tw. (1865)
7 Hypertension, Pregnancy-Induced/ (1687)
8 or/1-7 (35060)
9 (alere and triage and PlGF).tw. (3)
10 (alere and triage and "placental growth factor").tw. (3)
11 (PlGF and (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 detect* or positive or negative)).tw. (783)
12 ("Placenta* growth factor" and (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 detect* or positive or negative)).tw. (1033)
13 Vascular Endothelial Growth Factor Receptor-1/bl [Blood] (546)
14 Early Diagnosis/ or Diagnosis/ (30642)
15 Maternal Serum Screening Tests/ (89)
16 Serologic Tests/ (16463)
17 Pregnancy Proteins/an, du [Analysis, Diagnostic Use] (895)
18 Membrane Proteins/bl, du [Blood, Diagnostic Use] (2505)
19 Biological Markers/bl, du [Blood, Diagnostic Use] (71520)
20 "soluble fms-like tyrosine kinase".tw. (477)
21 (("FLT 1" or "sFLT 1") and (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 detect* or positive or negative)).tw. (1490)
22 ("soluble fms-like tyrosine kinase" and (test* or assay* or immunoassay* or diagnos* or detect* or measur* or analys* or determin* or sensitiv* or specific* or accurac*)).tw. (388)
23 elecsys.af. (517)
24 roche.af. (18837)
25 alere.af. (84)
26 delfia.af. (347)
27 or/9-26 (142180)
28 8 and 27 (1598)
29 (comment or editorial of letter).pt. (561133)
30 28 not 29 (1565)
31 limit 30 to english language (1443)
32 limit 31 to yr="2000 -Current" (1339)

Appendix 2: Draft data extraction form for systematic review of diagnostic studies

Reference and design	**Diagnostic tests**	**Participants**	**Outcome measures**
Condition being diagnosed / detected: **First author:** **Publication year:** **Country:** **Study design:** **Number of centres:** **Funding:** **Competing interests:**	**Index test:** **Reference standard:** **Comparator:** **Intervention:**	**Number of participants:** **Sample attrition/dropout:** **Selection of participants:** **Inclusion criteria for study entry:** **Exclusion criteria for study entry:**	**Primary outcome of study:** **Other relevant outcomes:** **Diagnostic threshold:** **Recruitment dates:**
Participant characteristics			
Age, years, mean (SD)			
Other key characteristics (list)			
Results			
	Population with [disease] on [reference standard] name the condition and ref standard	**Population without [disease] on [reference standard]** name the condition and ref standard	**Total**
Index test positive	a	b	a+b
Index test negative	c	d	c+d
Total	a+c	b+d	a+b+c+d
Calculate clinical sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) if possible and note whether these agree with any values that may be reported in the paper			
Diagnosis			**95% CI**
Clinical sensitivity a / (a + c)			
Clinical specificity d / (b + d)			
PPV a / (a + b)			
NPV d / (c + d)			
Positive likelihood ratio [sensitivity/(1-specicifcity)]			
Negative likelihood ratio [(1-sensitivity)/specificty]			
Diagnostic odds ratio (a x d)/(b x c)			
Comments: e.g. Calculations agree with values reported in paper. Note if any cases where 0.5 added to values to avoid division by zero when calculating diagnostic odds ratio			
Repeat for other tests/thresholds as appropriate or delete if not required			
Interpretability of test			

Inter-observer agreement		
Intra-observer agreement		
Test acceptability (patients / clinicians)		
Adverse events		

Appendix 3: Draft data extraction form for full economic evaluations

Characteristics

Reference (Lead author, year, refid)

Health technology

Interventions and comparators
What interventions/ strategies were included?

Was a no treatment/ supportive care strategy included?

Describe interventions/ strategies

Research question
What are the stated objectives of the evaluation?

Study type Cost-effectiveness/ cost-utility/ cost-benefit analysis?

Study population
What definition was used for [condition]? What are the characteristics of the baseline cohort for the evaluation?

Institutional setting Where is/are the intervention(s) being evaluated usually provided?

Country/ currency
Has a country setting been provided for the evaluation? What currency are costs expressed in and does the publication give the base year to which those costs relate?

Funding source

Analytical perspective
What is the perspective adopted for the evaluation (health service, health and personal social services, third party payer, societal (i.e. including costs borne by individuals and lost productivity)?

Effectiveness

Were the effectiveness data derived from: a single study, a review/ synthesis of previous studies or expert opinion? Give the definition of treatment effect used in the evaluation. Give the size of the treatment effect used in the evaluation

Intervention Costs
Were the cost data derived from: a single (observational) study, a review/ synthesis of previous studies expert opinion? Were the methods for deriving these data adequately described (give sources if using data from other published studies)? List the direct intervention costs and other direct costs used in the evaluation – include resource estimates (and sources for these estimates, if appropriate) as well as sources for unit costs used.

indicate the source for individual cost values (if appropriate)

Indirect Costs (costs due to lost productivity, unpaid inputs to patient care)
Were indirect costs included:

Health state valuations/ utilities (if study uses quality of life adjustments to outcomes)
Were the utility data derived from: a single (observational) study, a review/ synthesis of previous studies expert opinion. Were the methods for deriving these data adequately described (give sources if using data from other published studies)?

List the utility values used in the evaluation

indicate the source for individual cost values (if appropriate)

Modelling

If a model was used, describe the type of model used (e.g. Markov state transition model, discrete event simulation). Was this a newly developed model or was it adapted from a previously reported model? If an adaptation, give the source of the original. What was the purpose of the model (i.e. why was a model required in this evaluation)? What are the main components of the model (e.g. health states within a Markov model)? Are sources for assumptions over model structure (e.g. allowable transitions) reported – list them if reported.

Extract transition probabilities for [natural history/disease progression] model and show sources (or refer to table in text).

What is the model time horizon?

What, if any, discount rates have been applied in the model? Same rate for costs and outcomes?

Results/ Analysis

What measure(s) of benefit were reported in the evaluation?

Provide a summary of the clinical outcome/ benefits estimated for each intervention/ strategy assessed in the evaluation

Provide a summary of the costs estimated for each intervention/ strategy assessed in the evaluation

Synthesis of costs and benefits – are the costs and outcomes reported together (e.g. as cost-effectiveness ratios)? If so, provide a summary of the results.

Give results of any statistical analysis of the results of the evaluation.

Was any sensitivity analysis performed – if yes, what type(s) (i.e. deterministic (one-way, two-way etc) or probabilistic).

What scenarios were tested in the sensitivity analysis? How do these relate to structural uncertainty (testing assumptions over model structure such as relationships between health states), methodological uncertainty (such as choices of discount rate or inclusion of indirect costs) or parameter uncertainty (assumptions over values of parameters in the model, such as costs, quality of life or disease progression rates)?

Give a summary of the results of the sensitivity analysis – did they differ substantially from the base case analysis. If so, what were the suggested causes?

Conclusions/ Implications

Give a brief summary of the author's conclusions from their analysis

What are the implications of the evaluation for practice?

SHTAC Commentary

Selection of comparators:

Validity of estimate of measure of benefit:

Validity of estimate of costs:

Appendix 4: Quality assessment criteria for full economic evaluations

Table 1 Critical appraisal checklist of economic evaluation (Questions in this checklist based on Philips et al[1])

	Item	Study 1	Comments
1	Is there a clear statement of the decision problem?		
2	Is the comparator routinely used in UK NHS?		
3	Is the patient group in the study similar to those of interest in UK NHS?		
4	Is the health care system comparable to UK?		
5	Is the setting comparable to the UK?		
6	Is the perspective of the model clearly stated?		
7	Is the study type appropriate?		
8	Is the modelling methodology appropriate?		
9	Is the model structure described and does it reflect the disease process?		
10	Are assumptions about model structure listed and justified?		
11	Are the data inputs for the model described and justified?		
12	Is the effectiveness of the intervention established based on a systematic review?		
13	Are health benefits measured in QALYs?		
14	Are health benefits measured using a standardised and validated generic instrument?		
15	Are the resource costs described and justified?		
16	Have the costs and outcomes been discounted?		
17	Has uncertainty been assessed?		
18	Has the model been validated?		

Yes / No / ? (unclear)