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1. Title of the project

Placental growth factor (PlGF)-based testing to help diagnose suspected pre-eclampsia - update of NICE diagnostic guidance 23.

2. Name of External Assessment Group (EAG) and project lead

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3. Plain English Summary

Pre-eclampsia is a serious condition that some people develop during pregnancy, usually in the second or third trimesters. It is important that it is timely and accurately diagnosed, as, without treatment, it can lead to significant health risks to mothers and foetuses. In routine antenatal care pregnant people are assessed for their level of risk for and signs of pre-eclampsia. People with suspected pre-eclampsia undergo further tests and if they are diagnosed with the condition they are closely monitored, and sometimes may be admitted to hospital. A type of test, known as the placental growth factor (PlGF) test, is available for use with or without soluble fms-like tyrosine kinase (sFlt), alongside standard assessments and clinical follow-up to help doctors to 'rule in' (i.e. to diagnose pre-eclampsia) or 'rule out' the condition (i.e. pre-eclampsia is not diagnosed). The PlGF test measures the amount of placental growth factor in a person's blood. If levels are low, this may indicate pre-eclampsia. Use of this test may provide more accurate and timely diagnosis of pre-eclampsia and help identify people at lower risk of developing the condition, which could help avoid admission to hospital.

In 2016 the National Institute for Health and Care Excellence (NICE)[1] recommended two types of PlGF tests - the Triage PlGF test and the Elecsys immunoassay sFlt 1/PlGF ratio - for use in the NHS in England, for ruling out pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation. NICE did not recommend two other available tests - The DELFIA Xpress PlGF 1-2-3 test and BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio - for routine use. Currently no test is recommended for ruling in pre-eclampsia. NICE's guidance suggests that further research is done to find out if the DELFIA and BRAHMS tests are accurate in diagnosing pre-eclampsia. The guidance also recommends more research to find out if the Triage PIGF test and the Elecsys immunoassay sFlt-1/PIGF ratio test can accurately rule in pre-eclampsia. Since 2016 new research evidence has become available which potentially addresses NICE's recommendations.

We previously carried out a review of the available research evidence and constructed an economic model to determine the benefits and costs of these tests to patients and the NHS to inform the NICE guidance. In our current project, we will be updating the review and the economic model. We will search medical research databases to find new, relevant studies. We will then review the studies in detail, in an organised way using standard research methods. We will summarise and critically appraise the methods and results of the studies and judge whether any of them might be biased, and whether we can trust the results they give.

4. Decision problem

4.1 Purpose of the decision to be made

Pre-eclampsia is a serious condition that can occur during pregnancy, mostly in the second and third trimesters. Without timely and accurate diagnosis, monitoring and intervention it can lead to significant health risks to the mother and fetus. Pre-eclampsia is a heterogeneous and unpredictable condition, and the established method of diagnosis is assessment of standard key clinical signs and symptoms, including blood pressure measurement for hypertension, urinalysis to detect proteinuria and foetal monitoring for evidence of uteroplacental dysfunction with fetal growth restriction. People with suspected pre-eclampsia may be admitted to acute maternity units for initial evaluation and monitoring.

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

Use of PlGF-based tests (i.e. PlGF or sFlt-1/PlGF tests) to aid standard clinical assessments may provide an earlier and more accurate diagnosis in people who have signs and symptoms of possible pre-eclampsia. In turn, this can inform care decisions, such as avoiding hospital admission in people with low risk of developing pre-eclampsia.

4.2 Existing NICE diagnostics guidance

NICE diagnostics guidance 23[1], published in 2016, recommends two commercially available PlGF tests for use in the NHS: **the Triage PlGF test** and the **Elecsys immunoassay sFlt-1/PlGF ratio**. Both tests are to be used alongside standard clinical assessment and subsequent clinical follow-up, to help *rule-out* pre-eclampsia in women presenting with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation. There was insufficient evidence available on these two tests to support a recommendation for the tests to be used to diagnose (*rule-in*) pre-eclampsia in women presenting with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation. However, the guidance notes that these tests "show promise" for rule-in and further research to investigate this was recommended (research recommendation 6.2).

NICE diagnostics guidance 23[1] did not recommend the two other available tests - **The DELFIA Xpress PlGF 1-2-3 test** and **BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio**, for routine adoption in the NHS. The guidance recommends further research from the companies to demonstrate the clinical effectiveness of the tests, including their diagnostic accuracy and analytical validity (research recommendation 1.3 in DG23).

The use of repeat PlGF-based testing for suspected pre-eclampsia was considered in NICE diagnostics guidance 23.[1] However, a practice recommendation could not be made due to the lack of diagnostic accuracy data for repeat use of the tests. Instead, a recommendation was made for research on the different scenarios in which repeat testing may be indicated; the appropriate intervals between PlGF-based tests; and the diagnostic accuracy of PlGF-based testing in women with suspected pre-eclampsia who have previously had one or more negative PlGF-based test results (research recommendation 6.1).

In 2020 NICE reviewed research evidence published since 2015 on the use of these tests, to assess whether sufficient evidence has become available to address the research recommendations made by the guidance (see Appendix 1 for our tabulation of key study characteristics). NICE's review identified a number of recently published studies, and studies in progress, which could inform an update of the guidance, in respect of:

- Research recommendation 6.2 - rule in pre-eclampsia using the Triage PlGF test, and the Elecsys immunoassay sFlt-1/PlGF ratio:
    - There are at least eight recent studies, including UK/Irish randomised controlled trials, using the Triage PlGF test (four studies) and the Elecsys immunoassay sFlt-1/PlGF ratio (four studies).
    - Some of these studies assess the diagnostic accuracy of the tests, other studies report a range of intermediate outcome measures (e.g. time to events; hospital admissions) and, importantly, some of them provide data on clinical outcomes including morbidity and mortality (maternal, fetal, neonatal).
    - At least four of the studies provide data to inform a 'rule in' pre-eclampsia diagnosis.
- Research recommendation 1.3 - diagnostic accuracy and analytical validity of the DELFIA Xpress PlGF 1-2-3 test and BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio.
    - At least six studies have been identified which report diagnostic accuracy and analytical validity of these two tests.
    - Studies are observational in design, some of which are prospective and some retrospective in data collection and analysis.

- The studies compare the different commercially available immunoassays, in terms of outcomes including diagnostic accuracy. Both pairwise and multiple comparisons of tests are made.

- Research recommendation 6.1 – use of repeat testing for suspected pre-eclampsia.
  - At least two studies have investigated use of repeat testing: one study used the Triage PlGF test and the other used the Elecsys immunoassay sFlt-1/PlGF ratio. A third study (an RCT in progress) is likely to provide data on repeat testing, but publication of results is not expected until January 2022.

Given the availability of this new evidence, NICE has scheduled an update of diagnostics guidance 23 to address the unanswered questions on use of PlGF-based testing. The purpose of this research protocol is to describe, a priori, the scope and methods of the update to the diagnostic assessment report (DAR)[2] which will inform the guidance.

4.2 Aim and objectives

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

The objectives of this diagnostic assessment are to update the published systematic review of diagnostic test evaluations, the systematic review of cost-effectiveness studies and the economic evaluation which informed NICE's 2016 diagnostic guidance (23)[1]

Each test will be evaluated when used alongside standard clinical assessment, to diagnose pre-eclampsia between 20 weeks and 36 weeks and 6 days of pregnancy. The tests are: the Triage PlGF test; the Elecsys immunoassay sFlt-1 / PlGF ratio; the DELFIA Xpress PlGF 1-2-3 test with or without the DELFIA Xpress sFlt-1 kit, and the BRAHMS sFlt-1 Kryptor / PlGF plus Kryptor PE ratio.

4.3 Clear definition of the intervention

The four tests are described in more detail below (NB. this description has been taken directly from the NICE scope for this assessment; diagnostic cut off values for each test have not been reproduced here but are stated in the NICE scope). Where evidence is available, each test will be assessed when used once per episode of suspected pre-eclampsia, and also when the tests are repeated in people with suspected pre-eclampsia who have had a PlGF-based test for suspected pre-eclampsia that was negative.

No additional commercial PlGF-based tests for pre-eclampsia were identified by NICE's review of new evidence. Likewise, there have been no changes to the CE marked indications for the existing four tests (as regards their use in the second and third trimesters), or technical changes to the tests, since the previous diagnostic guidance (with the exception of the new DELFIA Xpress sFlt-1 kit – see below)

4.3.1 The Triage PlGF test

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

4.3.2 Elecsys immunoassay sFlt-1 / PlGF ratio

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

The sFlt-1/PlGF ratio is intended for use as an aid in the diagnosis of pre- eclampsia in conjunction with other diagnostic and clinical information. In addition, the sFlt-1/PlGF ratio is intended for use as an aid in short-term prediction of preeclampsia (rule-out and rule-in) in pregnant women with suspicion of preeclampsia in conjunction with other diagnostic and clinical information.

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

4.3.3 DELFIA Xpress PlGF 1-2-3 test / DELFIA Xpress sFlt-1 kit

The DELFIA Xpress PlGF 1-2-3 (Perkin Elmer) can be used as a stand-alone test or in combination with the Perkin Elmer DELFIA Xpress sFlt-1 test.

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

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

Using the DELFIA Xpress PlGF 1-2-3 test alone, the process time for first results is 30 minutes. Using both DELFIA Xpress PlGF 1-2-3 and sFlt-1 together takes approximately 31,5 minutes for the first sFlt-1/PlGF ratio result. The instrument is able to process samples simultaneously, leading to approximately 40 results per hour throughput.

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

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

The BRAHMS PlGF plus Kryptor test (ThermoFisher) can be used as a stand-alone test or together with ThermoFisher BRAHMS sFlt-1 Kryptor test.

The BRAHMS sFlt-1 Kryptor / BRAHMS PlGF plus Kryptor PE ratio is formed by combining the results from 2 automated immunofluorescent sandwich assays, the BRAHMS sFlt-1 Kryptor and BRAHMS PlGF plus Kryptor assays. The assays are indicated for the quantitative determination of sFlt-1 and PlGF in serum samples and are compatible with the BRAHMS Kryptor compact plus analyser and the Kryptor Gold immunoanalyser. The BRAHMS sFlt-1 Kryptor / BRAHMS PlGF plus KRYPTOR PE ratio is intended to be used to confirm or exclude diagnosis of pre-eclampsia after 20 weeks gestation.

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

The BRAHMS sFlt-1 Kryptor assay has a limit of detection of 22 picograms/millilitre (measuring range 22 to 90,000 picograms/millilitre) and a limit of quantitation of 34 picograms/millilitre. The BRAHMS PlGF 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.

4.4 Populations and relevant subgroups

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

Key relevant subgroups of interest include people with comorbidities such as chronic hypertension, severe hypertension, pre-existing or gestational diabetes, renal disease, and/or autoimmune disease; gestational stage (between 20 weeks and 34 weeks plus 6 days of pregnancy; between 35 weeks and 36 weeks and 6 days of pregnancy), and multiple pregnancy.

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

The place of PlGF testing for pre-eclampsia in the care pathway has not changed since the original diagnostic guidance (i.e. for suspected pre-eclampsia occurring between 20 weeks and 36 weeks and 6 days of pregnancy). This accords with recommendations on the use of PlGF testing specified in the NICE hypertension in pregnancy clinical guideline.[3]

4.6 Relevant comparators

The relevant comparator for PlGF tests is standard clinical assessment, which, as mentioned earlier, assesses standard key clinical signs and symptoms, including hypertension, proteinuria and fetal growth restriction.

4.7 Key factors to be addressed (e.g. clinical and cost outcomes, further considerations, problematic factors)

None.

4.8 Areas of agreement at the scoping workshop that are outside the scope of the appraisal and therefore do not require any detailed assessment (e.g. key factors for which evidence is already accepted).

As this will be an update of existing NICE diagnostic guidance, a scoping workshop was not considered necessary by NICE.

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

As there have been no significant changes to the scope of this NICE diagnostic assessment, the inclusion criteria for the systematic review of diagnostic test evaluations are likewise very similar to those of the original DAR.[2]

5.1 Population

The eligible population for this assessment is people between 20 weeks and 36 weeks plus 6 days of pregnancy who have suspected pre-eclampsia based on standard clinical assessment.

Sub-group analyses will be conducted for the following groups of people, where data are available:

- Between 20 weeks and 34 weeks plus 6 days of pregnancy
- Between 35 weeks and 36 weeks plus 6 days of pregnancy
- With chronic hypertension
- With severe hypertension (BP of 160/110 mmHg or more)
- With pre-existing or gestational diabetes
- With renal disease
- With an autoimmune disease
- With a multiple pregnancy (for example, twin or triplet pregnancy)

Test results may be impacted by ethnicity and maternal weight, where data are available these variables will be taken into account.

5.2 Interventions

The following tests, used alongside standard clinical assessment, to help diagnose pre-eclampsia and make subsequent decisions about care, are eligible for inclusion:

- Triage PlGF test
- Elecsys immunoassay sFlt-1/PlGF ratio
- DELFIA Xpress PlGF 1-2-3 test with or without the DELFIA Xpress sFlt-1 test
- BRAHMS sFlt-1 Kryptor / BRAHMS PlGF plus Kryptor PE ratio

Studies will be eligible if they report:

- Use of a test **once per episode** of suspected pre-eclampsia, to rule in and/or rule out pre-eclampsia (or to prompt further monitoring and assessment in the case of intermediate PlGF levels).

- A **repeat test** for a person with suspected pre-eclampsia who previously had a PlGF-based test that was negative for pre-eclampsia (ruled out) and who had no further subsequent indications of the condition.

We will only include studies reporting on the use of these tests in the between 20 weeks and 36 weeks and 6 days of pregnancy, as per the NICE scope.

5.3 Comparators

PlGF and sFlt-1/PlGF ratio tests, in conjunction with standard clinical assessment, will be compared only with standard clinical assessment alone (i.e. blood pressure measurement, urinalysis and fetal monitoring).

5.4 Outcomes

The following outcome measures will be included, where reported by included studies:

Intermediate outcomes

- Diagnostic accuracy
- Concordance between tests
- Prognostic accuracy
- Time to test result
- Impact of test result on clinical decision making
- Test failure rate
- Time to diagnosis
- Proportion of people diagnosed with pre-eclampsia
- Time to onset of pre-eclampsia and/or eclampsia
- Proportion of people returned to less intensive follow-up
- Number of people admitted to hospital / Length of in-patient hospital stay
- Time to delivery
- Gestation at diagnosis of pre-eclampsia
- Use of antihypertensive drugs

Clinical outcomes

- Maternal morbidity and mortality
- Foetal morbidity and mortality

- Neonatal morbidity and mortality

Patient-reported outcomes

- Health related quality of life

5.5 Study design

Relevant study designs for this systematic review will include randomised controlled trials, prospective or retrospective longitudinal cohort studies or cross-sectional studies. Given the range of study designs that could include diagnostic test assessments, the systematic review will not be limited to particular study designs. Instead, issues of study validity that may relate to the study design (specifically, influencing risk of bias and applicability of the study findings) will undergo validity assessment (Section 5.8).

5.6 Search strategy

The literature search strategy used in the previous DAR will be reviewed and adapted, as necessary, by an experienced information specialist for use in this update. Given that there have been no significant changes to the scope of this update from the scope of the original assessment, we only intend to revise the search strategies to reflect any changes in the search sources (e.g. to account for new/defunct databases) and changes in database search terms.

The following databases will be searched:

- Medline and Medline In-Process
- Embase
- The Cochrane Library (Cochrane Central Register of Trials and the Cochrane Database of Systematic Reviews)
- Science Citation Index, via Web of Science
- Conference Proceedings Index – Science, via Web of Science
- Centre for Reviews and Dissemination HTA database (NB. the previous DAR searched the Database of Abstracts of Reviews of Effects and NHS Economic Evaluations Database but these have not been updated since March 2015).

Whilst preparing this protocol we reviewed the Medline search strategy used in the previous DAR[2] and noted that a Medical Subject Heading (MeSH term) was introduced in 2017 for Placental Growth Factor. We have added this term to the search strategy for this update (see Appendix 2). We will repeat this review process for all the databases to be searched. The searches reported in the original DAR cover the time period from 2000 to July 2015. In this update we will run the searches from the start of 2015 to the present. The rationale for the small temporal overlap between these

two sets of searches is to ensure we identify any publications between January-July 2015 which had not yet been indexed in the databases at that time.

We will use the Preferred Reporting Items for a Systematic Review and Meta-analysis (PRISMA) Statement[4] and the PRISMA Diagnostic Test Accuracy Studies (DTA) Statement[5] to ensure reporting of our review's methods and results is comprehensive, transparent and informative.

5.7 Data extraction strategy

Relevant data will be extracted on the study and population characteristics, details of the technologies under comparison and outcome measures. 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 to avoid any errors (see Appendix 3 for sample data extraction form). 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. References that refer to the same primary study will be assessed together, to avoid double-counting of information.

5.8 Validity assessment strategy

The methodological validity of the included studies will be assessed by one reviewer and checked by a second reviewer, with any disagreements resolved by consensus or, if necessary, with arbitration by a third reviewer. The validity of studies reporting diagnostic accuracy will be assessed using the QUADAS-2 tool.[6] The validity of studies reporting other intermediate and/or clinical outcomes will be assessed using standard criteria appropriate to specific study designs, as necessary e.g. the Cochrane Risk of Bias tool for randomised controlled trials (version 1)[7], and the Cochrane Effective Practice and Organisation of Care (EPOC) suggested risk of bias criteria for non-randomised studies.

5.9 Methods of analysis/synthesis

Included studies will be synthesized through a structured narrative review with tabulation of all relevant study outcomes as listed in section 5.4 above (e.g. *intermediate outcomes* such as diagnostic accuracy, time to events, step-up/step-down in care intensity, use of antihypertensive drugs; *clinical outcomes* including morbidity and mortality and *patient reported outcomes*). The studies included in the original DAR were diverse in design and other key characteristics and a narrative synthesis was used, as a meta-analysis was not possible. In this update, where appropriate and necessary data are available, meta-analysis will be used to synthesise outcome data including test sensitivity and specificity.

The appropriateness and feasibility of doing a meta-analysis will be determined by assessing the degree of clinical and statistical heterogeneity across the primary studies. It will also be informed by critical appraisal of the primary studies (section 5.8) (e.g. sensitivity analyses may be conducted to assess the effect of study validity 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, R, or R Shiny[8] - an App developed by the NIHR Complex Reviews Support Unit.

Synthesis of outcomes may include summary receiver operating characteristic (sROC) curves to illustrate the trade-off between test sensitivity and specificity for different diagnostic thresholds. [9] 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)[10] (Chapter 2: Systematic reviews of Clinical Tests) the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy,[11] and the NICE Diagnostics Assessment Programme Manual.[12]

6. Report methods for synthesising evidence of cost effectiveness

6.1 Identifying and systematically reviewing published cost-effectiveness studies

For the review of cost-effectiveness studies, the relevant population, interventions and comparators will be the same as for the systematic review of diagnostic test evaluations (as described in sections 5.1, 5.2 and 5.3), with the exception of study design and outcomes. Studies will be included if they are full economic evaluations, assessing both the costs and consequences of the tests. Outcomes will include intermediate outcomes (e.g. 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 piloted standardised forms, with data extracted from each study by one reviewer and checked by a second reviewer. The characteristics of the studies and their results will be tabulated and discussed in a structured narrative review.

HRQoL data, where available, will be extracted from included cost-effectiveness studies and supplemented with any patient reported outcome data relating to quality of life from the systematic review of diagnostic test evaluations (section 5). In addition, a targeted literature search will be

conducted specifically for publications reporting HRQoL or health state utility for people undergoing medical management for suspected pre-eclampsia.

The quality of the included economic evaluations will be assessed using a critical appraisal checklist based upon that proposed by Drummond et al[13] and Philips et al.[14] (see Appendix 4).

6.2 Development of a health economic model

6.2.1 Model structure

A comparison of the costs and consequences of alternative approaches to diagnosing pre-eclampsia will be made using a decision analytic model. The structure of the model will be based on the approach taken in the original DAR[2] and updated, as necessary, to incorporate the additional outcome data that has been generated since the original DAR (as discussed earlier in section 4.1). Decisions on changes to the model structure will be informed by data from the systematic review of diagnostic test evaluations; the systematic review of cost-effectiveness; targeted literature searches for specific model input data; clinical guidelines and expert opinion. Adaptations to the model structure will also take into account the use of repeat testing for suspected pre-eclampsia (section 4.1)

The model will be constructed according to standard modelling guidelines.[14 15] The model used in the previous DAR[2] was a decision tree approach, incorporating the management of clinical symptoms of suspected pre-eclampsia, the timing and mode of delivery, and maternal and neonatal outcomes. A schematic of the decision tree is shown in Figure 1. A full explanation of our methods for formulating model structure and deriving parameter values will be given in the updated DAR.

The perspective of the economic evaluation will be that of the NHS and Personal Social Services (PSS). The cost effectiveness of the tests will be expressed as the cost per incremental QALY gained.

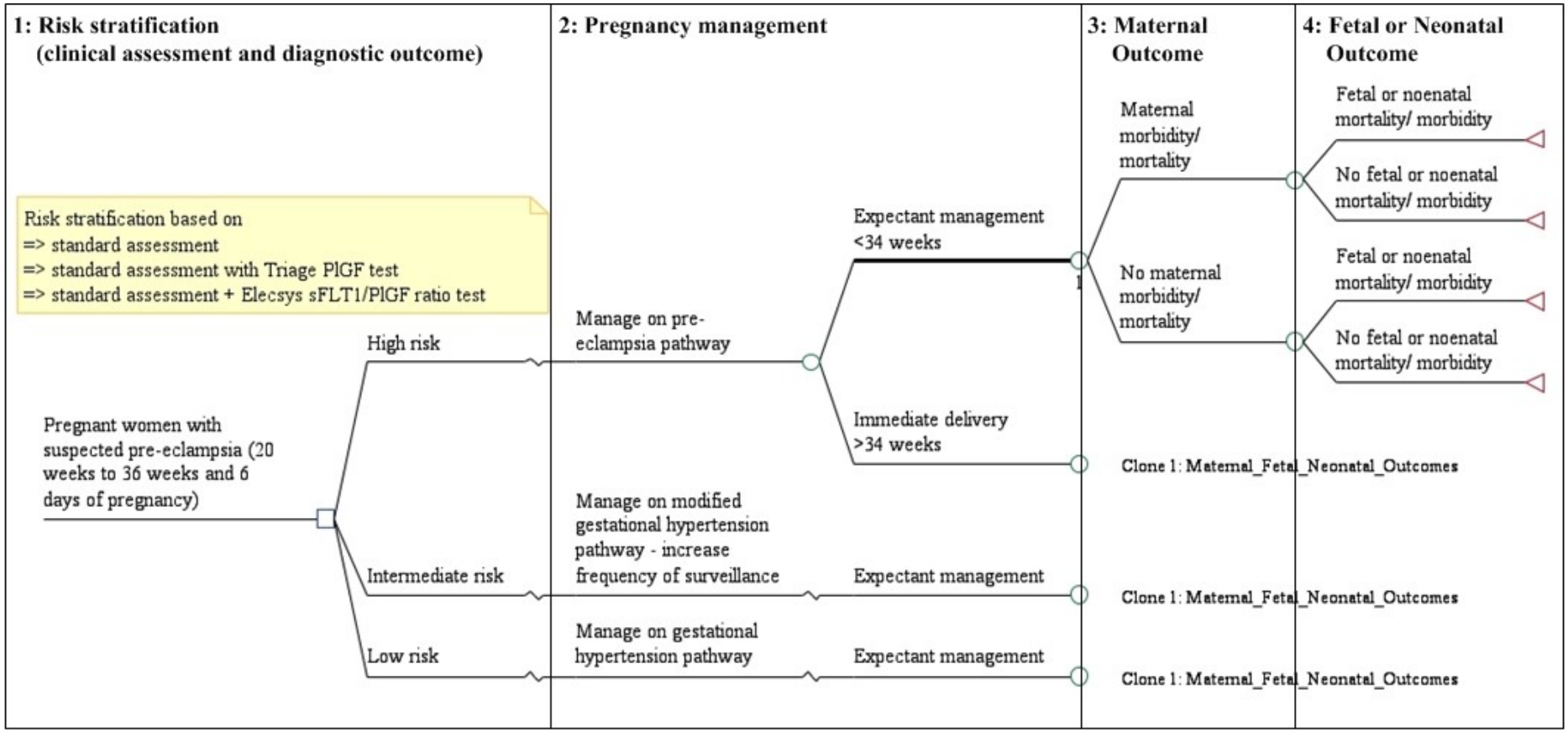

Figure 1 Schematic outline of the economic model used in the original diagnostic assessment report (DAR)

6.2.2 Model input parameters and assumptions

The model will include cost data relating to the PlGF and sFlt1 tests (e.g. equipment, reagents and consumables); the medical management of people with suspected/diagnosed pre-eclampsia; delivery procedures and in-hospital monitoring. Cost information will be identified from any data available in costing studies, diagnostic test evaluation studies, information supplied by the test manufacturers, and national and local NHS unit costs data. All costs will be updated to price year 2019/20.

All other existing input parameter values will be reviewed and updated, where necessary, with data identified from our systematic reviews of diagnostic test evaluations and cost-effectiveness studies. The source of, and justification for, all parameter values will be explicitly stated.

Our preliminary scoping searches for this protocol identified four economic evaluations of diagnostic tests within the scope of this assessment. All four studies describe themselves as cost-effectiveness analyses, three of which are evaluations of the Elecsys sFlt-1 / PlGF ratio test[16-18] and one an evaluation of the Triage PlGF test.[19] Three use short-term decision trees to model the cost of managing people with suspected pre-eclampsia according to current practice compared with diagnosis based on a specific diagnostic test combined with current practice.[16-18] The remaining study uses a Monte Carlo simulation.[19]

Only one of the models includes maternal and neonatal outcomes;[19] the other three focus on potential cost savings associated with improved patient management decisions arising from the addition of PlGF-based testing to standard clinical assessment.[16-18] In particular, the studies suggest that including diagnostic tests alongside standard clinical assessment has the potential to reduce maternal adverse events and lower the proportion of people receiving inappropriate treatment (mainly hospitalisation) due to false-positive diagnoses.

We will review the models used in these studies, and any further models used in studies included in the systematic review of cost effectiveness, to inform any necessary adjustments to assumptions or structure of the model used in the previous DAR[2]. The existing models will be formally assessed for the appropriateness of their structural assumptions, and for their included parameters and associated values.

6.2.3 Addressing uncertainty

Uncertainty in model inputs and structure will be explored through deterministic one-way sensitivity analyses and scenario analyses. The model used in the previous DAR did not include a probabilistic sensitivity analysis (PSA). We will assess the feasibility of including a PSA if the available data and the

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

7. Handling information from the companies

Any data submitted by the companies who produce the PlGF-based tests will be considered for inclusion in this assessment if received by the EAG no later than 11th March 2021. Data received after this date will not necessarily be considered. All data meeting the inclusion criteria for the systematic reviews of diagnostic test evaluations and cost-effectiveness studies will be formally extracted and critically appraised using the methods and criteria specified earlier (section 5.7 and 5.8, and section 6.1, respectively).

Any specified 'commercial in confidence' data provided by a company involved in this assessment which is reproduced in the updated DAR will be highlighted in blue and underlined (followed by an indication of the relevant company name e.g. in brackets). Any academic in confidence information supplied by a company or another source will be highlighted in yellow and underlined.

8. Competing interests of authors

The authors confirm they have no competing interests

9. Timetable/milestones

Milestone	Date to be completed
Progress report to NIHR NETSCC	29/01/2021
Draft version of DAR and executable economic model sent by EAG to NICE	08/04/2021
EAG deliver's final DAR to NICE, and NETSCC	07/05/2021

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11. Appendices

Appendix 1 – Potentially relevant diagnostic test evaluation evidence for inclusion in this diagnostic assessment update

The studies listed in this table were identified during the scoping phase by NICE, and by the EAG's MEDLINE scoping searches, as potentially relevant to the DAR update, pending formal inclusion screening assessment.

Test (manufacturer)	New evidence (since original DAR)[a]				References	Outcomes																	
	Study name and identifier	Rule out PE	Rule in PE	Repeat testing		Diagnostic accuracy	Test concordance	Prognostic accuracy	Time to result	Impact on clinical decision	Test failure rate	Time to diagnosis	% diagnosed with PE	Time to onset of PE and/or E	% with less intensive follow-up	No. hospital admissions / stay length	Time to delivery	Gestation at diagnosis of PE	Use of antihypertensive drugs	Maternal morbidity and mortality	Fetal morbidity and mortality	Neonatal morbidity and mortality	HRQoL
Triage PlGF test (Quidel)	PARROT ISRCTN16842031	✓	✓		Duhig, KE et al. (2019) Placental growth factor testing to assess women with suspected pre-eclampsia: a multicentre, pragmatic, stepped-wedge cluster-randomised controlled trial. *Lancet* 393(10183): 1807-1818[20]							✓	✓			✓				✓	✓	✓	
	PARROT (Ireland) NCT02881073		✓		Protocol: Hayes, D et al. (2019) PARROT Ireland: Placental growth factor in Assessment of women with suspected pre-eclampsia to reduce maternal morbidity: a Stepped Wedge Cluster Randomised Control Trial								✓					✓	✓	✓		✓	✓

Test (manufacturer)	New evidence (since original DAR)[a]				References	Outcomes																	
	Study name and identifier	Rule out PE	Rule in PE	Repeat testing		Diagnostic accuracy	Test concordance	Prognostic accuracy	Time to result	Impact on clinical decision	Test failure rate	Time to diagnosis	% diagnosed with PE	Time to onset of PE and/or E	% with less intensive follow-up	No. hospital admissions / stay length	Time to delivery	Gestation at diagnosis of PE	Use of antihypertensive drugs	Maternal morbidity and mortality	Fetal morbidity and mortality	Neonatal morbidity and mortality	HRQoL
					Research Study Protocol. *BMJ Open* 9(2): e023562[21]																		
	Ormesher et al. (2018)		✓		Ormesher, L et al. (2018) A clinical evaluation of placental growth factor in routine practice in high-risk women presenting with suspected pre-eclampsia and/or fetal growth restriction. *Pregnancy Hypertension* 14: 234-239[22]	✓				✓							✓							
	PARROT-2 (on-going) ISRCTN85912420			✓	Ongoing – trial record states due to finish 01/11/2021 No publications found Outcomes extracted from trial record								✓			✓				✓	✓	✓	
Elecsys immunoassay sFlt-1/PlGF ratio	INSPIRE ISRCTN87470468	✓	✓		Cerdeira, AS et al. (2019) Randomized Interventional Study on Prediction of Preeclampsia/Eclampsia in Women With Suspected	✓						✓	✓			✓						✓	

Test (manufacturer)	New evidence (since original DAR)[a]				References	Outcomes																
	Study name and identifier	Rule out PE	Rule in PE	Repeat testing		Diagnostic accuracy	Test concordance	Prognostic accuracy	Time to result	Impact on clinical decision	Test failure rate	Time to diagnosis	% diagnosed with PE	Time to onset of PE and/or E	% with less intensive follow-up	No. hospital admissions / stay length	Time to delivery	Gestation at diagnosis of PE	Use of antihypertensive drugs	Maternal morbidity and mortality	Fetal morbidity and mortality	Neonatal morbidity and mortality	HRQoL
(Roche Diagnostics)					Preeclampsia: INSPIRE. Hypertension 74(4):983-990[23]																		
	PROGNOSIS			✓	Zeisler et al. (2019) Soluble fms-like tyrosine kinase-1 to placental growth factor ratio: ruling out pre-eclampsia for up to 4 weeks and value of retesting. Ultrasound Obstet Gynecol. 53(3): 367–375[24]	✓							✓								✓		
	Cheng et al. (2019) **NB. Population is not women with suspected pre-eclampsia; includes pregnant women attending for Down's syndrome screening**				Cheng, YKY et al. (2019) Inter-manufacturer comparison of automated immunoassays for the measurement of soluble FMS-like tyrosine kinase-1 and placental growth factor. Pregnancy Hypertens. 17:165-171[25]		✓																
	Stepan et al. (2019) **NB. Enrolled women with preeclampsia/HELLP**				Stepan, H et al. (2019) Elecsys and Kryptor immunoassays for the measurement of sFlt-1 and PlGF to aid preeclampsia	✓																	

Test (manufacturer)	New evidence (since original DAR)[a]				References	Outcomes																	
	Study name and identifier	Rule out PE	Rule in PE	Repeat testing		Diagnostic accuracy	Test concordance	Prognostic accuracy	Time to result	Impact on clinical decision	Test failure rate	Time to diagnosis	% diagnosed with PE	Time to onset of PE and/or E	% with less intensive follow-up	No. hospital admissions / stay length	Time to delivery	Gestation at diagnosis of PE	Use of antihypertensive drugs	Maternal morbidity and mortality	Fetal morbidity and mortality	Neonatal morbidity and mortality	HRQoL
	syndrome; women who were normotensive during pregnancy and had normal pregnancy outcomes were matched controls				diagnosis: are they comparable? Clin Chem Lab Med. 57(9):1339-1348[26]																		
Delfia Xpress PlGF 1-2-3 test (Perkin Elmer)	COMPARE	✓	✓		McCarthy, FP et al. (2019). Comparison of three commercially available placental growth factor-based tests in women with suspected preterm pre-eclampsia: the COMPARE study. Ultrasound in obstetrics & gynecology 53(1): 62-67.[27]								✓				✓		✓			✓	
	Black et al. (2019a) **NB. "Asymptomatic patient population"** Black et al (2019b) **NB. "General pregnant population". Women affected by PE in the cohort**				Black, C et al. (2019a) Midpregnancy testing for soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PlGF): An inter-assay comparison of three automated immunoassay platforms. Placenta 86: 11–14[28]	✓	✓																

Test (manufacturer)	New evidence (since original DAR)[a]				References	Outcomes																	
	Study name and identifier	Rule out PE	Rule in PE	Repeat testing		Diagnostic accuracy	Test concordance	Prognostic accuracy	Time to result	Impact on clinical decision	Test failure rate	Time to diagnosis	% diagnosed with PE	Time to onset of PE and/or E	% with less intensive follow-up	No. hospital admissions / stay length	Time to delivery	Gestation at diagnosis of PE	Use of antihypertensive drugs	Maternal morbidity and mortality	Fetal morbidity and mortality	Neonatal morbidity and mortality	HRQoL
	were compared to those not affected by PE in the same cohort Black et al 2019a and 2019b appear to be reports of the same study				Black, C et al. (2019b) Midpregnancy prediction of pre-eclampsia using serum biomarkers sFlt-1 and PlGF. Pregnancy Hypertension 16: 112–119[29]																		
BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio (Thermo Fisher Scientific)	Dröge et al. (2017)		✓		Dröge, LA et al. (2017) Diagnosis of preeclampsia and fetal growth restriction with the sFlt-1/PlGF ratio: Diagnostic accuracy of the automated immunoassay Kryptor. Pregnancy Hypertens. 8:31-36[30]	✓																	
	Cheng et al. (2019) **NB. Population is not women with suspected pre-eclampsia; includes pregnant women attending for Down's**				Cheng, YKY et al. (2019) Inter-manufacturer comparison of automated immunoassays for the measurement of soluble FMS-like tyrosine kinase-1 and placental growth factor.		✓																

Test (manufacturer)	New evidence (since original DAR)[a]				References	Outcomes																	
	Study name and identifier	Rule out PE	Rule in PE	Repeat testing		Diagnostic accuracy	Test concordance	Prognostic accuracy	Time to result	Impact on clinical decision	Test failure rate	Time to diagnosis	% diagnosed with PE	Time to onset of PE and/or E	% with less intensive follow-up	No. hospital admissions / stay length	Time to delivery	Gestation at diagnosis of PE	Use of antihypertensive drugs	Maternal morbidity and mortality	Fetal morbidity and mortality	Neonatal morbidity and mortality	HRQoL
	syndrome screening who were randomised to undergo phlebotomy				Pregnancy Hypertens. 17:165-171[25]																		
	Stepan et al. (2019) **NB. Enrolled women with preeclampsia/HELLP syndrome. Women who were normotensive during pregnancy and had normal pregnancy outcomes were matched controls**				Stepan, H et al. (2019) Elecsys and Kryptor immunoassays for the measurement of sFlt-1 and PlGF to aid preeclampsia diagnosis: are they comparable? Clin Chem Lab Med. 57(9):1339-1348[26]	✓	✓																
	Chan et al. (2018) **NB. Patient population not described; study of the analytical performance of sFlt1 and PlGF on the KRYPTOR Compact Plus automated immunoassay platform (a table top analyser)**				Chan et al. SL et al. (2018) Analytical validation of soluble fms-like tyrosine and placental growth factor assays on B·R·A·H·M·S KRYPTOR Compact Plus automated immunoassay platform. Pregnancy Hypertens. 11:66-70[31]																		
	Black et al. (2019a)				Black, C et al. (2019a) Midpregnancy testing for	✓	✓																

Test (manufacturer)	New evidence (since original DAR)[a]				References	Outcomes																
	Study name and identifier	Rule out PE	Rule in PE	Repeat testing		Diagnostic accuracy	Test concordance	Prognostic accuracy	Time to result	Impact on clinical decision	Test failure rate	Time to diagnosis	% diagnosed with PE	Time to onset of PE and/or E	% with less intensive follow-up	No. hospital admissions / stay length	Time to delivery	Gestation at diagnosis of PE	Use of antihypertensive drugs	Maternal morbidity and mortality	Fetal morbidity and mortality	Neonatal morbidity and mortality	HRQoL
	NB. "Asymptomatic patient population" Black et al (2019b) **NB. "General pregnant population". Women affected by PE in the cohort were compared to those not affected by PE in the same cohort** Black et al 2019a and 2019b appear to be reports of the same study				soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PlGF): An inter-assay comparison of three automated immunoassay platforms. Placenta 86: 11–14[28] Black, C et al. (2019b) Midpregnancy prediction of pre-eclampsia using serum biomarkers sFlt-1 and PlGF. Pregnancy Hypertension 16: 112–119[29]																

Appendix 2 – Medline search strategy for systematic review of diagnostic test evaluation

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to October 13, 2020

NB. Search lines 28-34 will be updated to include all relevant brand and company names before this strategy is finalised and executed.

#	Searches	Results
1	Pre-Eclampsia/	31014
2	(preeclamp* or pre eclamp*).tw.	33895
3	(tox?emi* adj5 pregnan*).tw.	3500
4	gestosis.tw.	1226
5	(pregnan* adj3 hypertensi*).tw.	12569
6	(gestation* adj3 hypertensi*).tw.	4127
7	((maternal or maternity) adj3 hypertens*).tw.	1695
8	Hypertension, Pregnancy-Induced/	3384
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	54868
10	(PlGF and (triage or test* or assay* or immunoassay* or diagnos* or detect* or surveillance or screen* or measur* or analys* or analyz* or determin* or sensitivity or specificity or accuracy or accurate or assessment* or predict* or positive or negative or electrochemiluminescen*)).tw.	1820
11	("Placenta* growth factor" and (triage or test* or assay* or immunoassay* or diagnos* or detect* or surveillance or screen* or measur* or analys* or analyz* or determin* or sensitivity or specificity or accuracy or accurate or assessment* or predict* or positive or negative or electrochemiluminescen*)).tw.	2182
12	Placenta Growth Factor/	1705
13	(triage or test* or assay* or immunoassay* or diagnos* or detect* or surveillance or screen* or measur* or analys* or analyz* or determin* or sensitivity or specificity or accuracy or accurate or assessment* or predict* or positive or negative or electrochemiluminescen*).tw.	16084864
14	12 and 13	1347
15	Placenta Growth Factor/bl [Blood]	307
16	Vascular Endothelial Growth Factor Receptor-1/bl [Blood]	977
17	("VEGFR1" or "VEGFR 1").tw.	2942
18	diagnosis/ or early diagnosis/	44119
19	Diagnostic Tests, Routine/ or Diagnostic Equipment/ or "Diagnostic Techniques, Obstetrical and Gynecological"/ or Diagnostic Services/	15371
20	Maternal Serum Screening Tests/	484
21	Serologic Tests/	20534

22	Pregnancy Proteins/an, bl [Analysis, Blood]	2115
23	Membrane Proteins/bl [Blood]	3138
24	Biological Markers/bl [Blood]	124347
25	"fms-like tyrosine kinase*".tw.	2752
26	(("FLT 1" or "sFLT 1" or "FLT1" or "sFLT1") and (triage or test* or assay* or immunoassay* or diagnos* or detect* or screen* or measur* or analys* or analyz* or determin* or sensitivity or specificity or accuracy or accurate or "prognostic assessment*" or predict* or positive or negative or electrochemiluminescen*)).tw.	3089
27	("soluble fms-like tyrosine kinase" and (triage or test* or assay* or immunoassay* or diagnos* or detect* or measur* or analys* or analyz* or determin* or sensitivity or specificity or accuracy or accurate or assessment* or predict* or positive or negative or electrochemiluminescen*)).tw.	985
28	elecsys.af.	969
29	roche.af.	41559
30	alere.af.	691
31	delfia.af.	406
32	brahms.af.	588
33	kryptor.af.	178
34	thermo.af.	16945
35	10 or 11 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34	273202
36	9 and 35	3631
37	limit 36 to animals	344
38	36 not 37	3287
39	limit 38 to yr="2015 -Current"	1499
40	limit 39 to english language	**1461**

Appendix 3 Data extraction template for systematic review of diagnostic studies

(NB. this template may undergo minor iterative changes to its structure and format, where appropriate, to the suit the specific type(s) of data to be extracted from included 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)			

DIAGNOSTIC TEST ACCURACY OUTCOMES			
	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)		
OTHER TEST PERFORMANCE OUTCOMES		
Concordance between tests		
Prognostic accuracy		
Test failure rate		
Proportion of women diagnosed with pre-eclampsia		
TIME TO EVENT / TEMPORAL OUTCOMES		
Time to test result		
Time to diagnosis		
Time to onset of pre-eclampsia and/or eclampsia		
Time to delivery		
Gestation at diagnosis of pre-eclampsia		
IMPACT OF TEST RESULT ON CLINICAL DECISION MAKING		
Proportion of people returned to less intensive follow-up		
Number of pregnant people admitted to hospital		
Length of in-patient stay		
Use of antihypertensive drugs		
CLINICAL OUTCOMES		
Maternal morbidity and mortality		
Fetal morbidity and mortality		
Neonatal morbidity and mortality		
PATIENT REPORTED OUTCOMES		
Health related quality of life		

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)