Australian Government

Department of Health

MSAC Application 1706

Angiogenic and anti-angiogenic markers for identification and management of preeclampsia

Ratified PICO Confirmation

Summary of PICO/PPICO criteria to define question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC).

Table 1: PICO for angiogenic and anti-angiogenic markers for the identification and management of preeclampsia

Component	Description
Population	1) Pregnant women presenting from 24^{+0} weeks' gestation (triage testing population): (i) with signs and symptoms suggestive of preeclampsia (PE); or (ii) at increased risk of PE, due to maternal, gestational or other factors, in the absence of signs and symptoms suggestive of PE. 2) Pregnant women from 24^{+0} weeks' gestation with a confirmed diagnosis of PE using current standard tests (prognostic testing population for severity assessment).
Prior tests	Antenatal clinic BP checks: • New onset Hypertension (systolic blood pressure, >140 mm Hg, or diastolic blood pressure, >90 mmHg, on at least two occasions 4 hours apart, experienced after 20^{+0} weeks gestation in previously normotensive women). • Severe hypertension: systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥110 mm Hg on at least 2 occasions 6 hours apart. Assessment of proteinuria • spot urinalysis: If urine dipstick is positive (≥1+) then confirm with spot urine protein:creatinine ratio, which is abnormal if protein: creatinine ratio ≥ 30 mg/mmol or albumin: creatinine ≥ 8 mg/mmol.
Intervention	sFlt-1/PlGF ratio test, also known as the PE ratio test (PERT), to: Population 1 categorise the *likelihood* of PE in: (i) women with signs and symptoms suggestive of PE, or (ii) asymptomatic women at increased risk of PE. Population 2 categorise the *severity* of PE in women with a confirmed diagnosis of PE made using the current standard tests.
Comparator	Population 1 No triage testing ± current standard tests that are repeated for diagnosing PE at 24^{+0} to 36^{+6} weeks gestation, including • Urine protein: creatinine ratio test • Proteinuria reagent strip test • Full blood count • Renal function test • Serum electrolytes • Hepatic transaminases Population 2 No prognostic testing plus standard medical management of PE (which may include repeat current standard tests for monitoring PE severity).

Reference standard	The diagnosis of PE, defined as: Maternal hypertension (systolic blood pressure is 140 mmHg or more OR diastolic blood pressure is 90 mmHg or more) developing after 20 weeks of gestation and the co-existence of one or more of the following new-onset conditions: 1. Proteinuria 2. Other maternal organ dysfunction, including at least one of the following: a) Renal insufficiency (creatinine ≥ 90 µmol/L) b) Liver involvement (elevated transaminases and/or severe right upper quadrant or epigastric pain) c) Neurological complications (e.g., hyperreflexia and/or clonus, eclampsia, visual disturbance, blindness, stroke) d) Haematological complications (thrombocytopenia, DIC, haemolysis) e) Uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery Doppler ultrasound)
Outcomes	• **Diagnostic performance**: sensitivity, specificity, positive and negative predictive values. Assessment of the extent and implications of discordance between Australian PE testing guidelines/practices, test-retest reliability, test failure rate. • **Prognosis**: prognostic utility of tests. • **Clinical effectiveness outcomes:** Reduction in incidence and severity of preterm PE; Uptake of PE prophylaxis treatment based on risk assessment; PE related maternal outcomes (e.g., eclamptic fit, renal and hepatic impairment, HELLP syndrome, placental abruption, etc); Preterm birth/gestational age; PE related adverse neonatal outcomes (morbidity and mortality), reduction in hospital admission and over treatment. • **Safety**: misclassification of the risk of PE; adverse events associated with incorrect risk stratification and the follow-up diagnostic and treatment work ups. • **Costs**: cost of testing and any cost offsets, costs associated with hospitalisation, outpatient appointments, antihypertensive medication, therapeutic intervention prior to delivery and treating complications in the mother and infant. • **Cost-utility**: cost per quality-adjusted life year. • **Financial implications**: number and cost of patients tested.
Assessment questions	What is the safety, cost and clinical effectiveness of the sFlt-1/PlGF ratio test in women at 24^{+0} weeks gestation to: 1. categorise the *likelihood* of PE in: (i) women with signs and symptoms of PE, or (ii) asymptomatic women at increased risk of PE 2. categorise the *severity* of PE in women with a confirmed diagnosis of PE made using the current standard tests

PE= preeclampsia; BP= blood pressure; sFlt-1= soluble fms-like tyrosine kinase-1; PlGF= placental growth factor; mg/mmol = micrograms per millimole; mmHg = millimetres of mercury; µmol/L= micromoles per litre; DIC = Disseminated intravascular coagulation; HELLP=Hemolysis, Elevated Liver enzymes and Low Platelets; ±= in addition/ replace.

Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of the placental soluble fms-like tyrosine kinase-1 (sFlt-1) / placental growth factor (PlGF) ratio test which was described as to be used to determine the likelihood of the onset of preeclampsia (PE) in pregnancies from 24^{+0} weeks gestation and the prognosis of the disease for women with a confirmed PE diagnosis was received from Professor **REDACTED**/Roche by the Department of Health.

The use of the proposed technology is claimed to result in superior health outcomes compared to the nominated comparators.

PICO criteria- angiogenic and anti-angiogenic markers for the diagnosis of PE

Population

The proposed populations are:

1) Pregnant women presenting from 24^{+0} weeks of gestation with (i) signs and symptoms suggestive of PE or (ii) at increased risk of PE, due to maternal, gestational or other factors, in the absence of signs and symptoms suggestive of PE (triage testing population).
2) Pregnant women presenting from 24^{+0} weeks of gestation with a confirmed diagnosis of PE using current standard tests (prognostic testing population for severity assessment).

PE is a multisystem pregnancy disorder characterised by variable degrees of placental malperfusion. The release of soluble factors into the circulation causes maternal vascular endothelial injury leading to hypertension and multi-organ injury [1]. The Task Force on Hypertension in Pregnancy considers the diagnosis of PE as new onset blood pressure >140/90 mmHg after 20 weeks of pregnancy and either proteinuria ≥300 mg/24 hours or protein: creatinine ratio ≥0.3 mg/24 hours or one of the following: thrombocytopenia, elevated liver transaminases, pulmonary oedema, new-onset renal insufficiency, or cerebral or visual disturbances [2].

PE can be subclassified (not mutually exclusive) into [3]:
1. Early-onset PE (with delivery at $<34^{+0}$ weeks of gestation).
2. Preterm PE (with delivery at $<37^{+0}$ weeks of gestation).
3. Late-onset PE (with delivery at $\geq 34^{+0}$ weeks of gestation).
4. Term PE (with delivery at $\geq 37^{+0}$ weeks of gestation).

The placental disease can trigger fetal growth restriction and stillbirth. PE is a significant cause of maternal and perinatal mortality and morbidity, especially in low-income and middle-income countries [3, 4]. For the mother, PE is associated with a two- to four-fold increased risk of long-term hypertension, a doubling of cardiovascular mortality and major adverse cardiovascular events, and an increased risk of stroke [3, 5]. For the fetus, this means there is an increased risk antenatally of intra-uterine growth restriction, preterm birth (most commonly iatrogenic), oligohydramnios, placental abruption, fetal distress, and fetal death in utero [1, 3, 5, 6].

<u>Incidence of PE</u>

The incidence of PE in the general population is 2% to 3% in developed countries, which rises to almost 20% in high-risk pregnant women [7, 8]). Others have stated that PE affects 3–8% [9] and ≈2% to 10% [10] of pregnant women. Thornton et al. [11] found an overall prevalence of PE between 2000 and 2008 of around 3% with datasets of singleton births in New South Wales.

Existing chronic hypertension is a risk factor for PE, and it is becoming more prevalent in women of childbearing age and the Indigenous population in Australia. Between 2008 and 2012, complications from PE accounted for 18.4% (9 out of 49) of direct maternal deaths in Australia [12]. According to the Maternity and Neonatal Clinical Guideline of Queensland, there were 364,194 pregnancies between 2014–2019 and among them, gestational hypertension affected 9,692 women, and PE affected 8,463 women (2.3%) [13].

The application indicated that approximately 1,200 infants are born prematurely (<34 weeks) in Australia because of maternal PE each year (p18 of the application). According to the Australian preterm birth prevention alliance[1], more than 26,000 Australian babies are born preterm each year. The latest annual report from the Australian and New Zealand Neonatal Network[2] indicated that in 2019, there were 947 infants liveborn <34 weeks to mothers with hypertension in pregnancy, and 518 with intrauterine growth retardation (among 11,195 infants liveborn <34 weeks' gestation).

PASC confirmed that the triage testing population (Population 1) is women presenting from 24^{+0} weeks of gestation: (i) with signs and symptoms suggestive of PE, or (ii) at increased risk of PE, due to maternal, gestational or other factors, in the absence of signs and symptoms suggestive of PE.

PASC confirmed that the prognostic testing population (Population 2) is women presenting from 24^{+0} weeks of gestation with a confirmed diagnosis of PE using current standard tests.

Causes and symptoms of PE

The cause of PE remains unclear [14, 15]. Nonetheless, women at high risk of developing PE are more likely to have the following characteristics: hypertensive disease during a previous pregnancy, chronic kidney disease, autoimmune diseases such as systemic lupus erythematosus or antiphospholipid syndrome, type 1 or type 2 diabetes, age >40, pre-pregnancy body mass index (BMI) >30, use of assisted reproductive technology and existing chronic hypertension [16, 17]. Moderate risk factors are first pregnancy, a pregnancy interval greater than ten years, body-mass index of 35 kg/m² or more, polycystic ovarian syndrome, family history of PE, and multiple pregnancies [1, 18]. In addition, a diagnosis of schizophrenia or bipolar disorder increases the likelihood of having PE by five-fold [19].

The symptoms of PE include severe headache, sudden blindness, drowsiness, severe pain just below the ribs, vomiting, and sudden swelling of the face and hands or feet [20, 21]. The key signs of evolving PE are proteinuria, elevated blood pressure (≥140 mmHg systolic or ≥90 mmHg diastolic),

[1] Australian preterm birth prevention alliance: https://www.pretermalliance.com.au/About-Preterm-Birth/Preterm-Facts-and-FigureS.
[2]Chow SSW, Le Marsney R, Creighton P, Kander V, Haslem R, Lui K. Report of the Australian and New Zealand Neonatal Network 2015. Sydney: Australian and New Zealand Neonatal Network; 2017. Available from https://www.anznn.net/Portals/0/AnnualReports/Report%20of%20the%20Australian%20and%20New%20Zealand%20Neonatal%20Network%202019.pdf (Accessed March 2022).

derangement in biochemistry or haematology (e.g., solitary thrombocytopenia), fetal growth restriction or abnormal fetal biophysical profile [21, 22].

Some clinical and lifestyle factors assist in predicting PE in early pregnancy. These include elevated mean arterial pressure at 15 weeks of gestation, family history of coronary heart disease or PE, and vaginal bleeding for more than five days in the current pregnancy [23]. This study also stated that previous single miscarriage with the same partner, time to conception of at least 12 months, and high fruit consumption reduced the risk of PE [23].

The utilisation of the proposed test

The application estimated the number of patients at risk of clinical and/or biochemical symptoms and signs suggestive of PE, eligible for an sFlt-1/PlGF test in Year 1 as 30,583 (p26 of the application). The average number of sFlt-1/PlGF tests performed per eligible patient will be two, and the total utilisation of the test is estimated to be 61,166 per year (Table 2) (p19 of the application). The application also assumed that the number of births, and hence the number of tests per year, would remain identical in Years 1, 2 and 3. The number of births per year is taken from the Australian Bureau of Statistics (ABS). Noticeably, the application has used the total number of births per year as a proxy for the total number of pregnancies per year. The ABS data indicated that the total number of births registered in Australia was 305,832 in 2019 and 294,369 in 2020. In 2020, there were 4,202 confinements resulting in multiple births. Of these, 4,148 were twins, and 54 were triplets and higher-order births.

PASC noted that the assessment will need to define the number of pregnancies beyond 24^{+0} weeks in scope based on the proportion of pregnancies:births beyond 24^{+0} weeks gestation. This data should be available given that ABS statistics capture all registered births beyond 20^{+0} weeks gestation.

Table 2: Estimated utilisation of sFlt-1/PlGF tests in Australia (suspected PE)

Three-year estimates for utilisation	Year 1	Year 2	Year 3
Births per year (ABS) (gestation >20 weeks)	305,832	305,832	305,832
Percentage of pregnancies estimated to become eligible for sFlt-1/PlGF testing due to clinical signs and symptoms indicative of PE.	10%	10%	10%
Total eligible patient population	30,583	30,583	30,583
The average number of sFlt-1/PlGF tests performed per eligible patient	2	2	2
sFlt-1/PlGF utilisation per year	61,166	61,166	61,166
Cumulative utilisation	61,166	122,333	183,499

ABS = Australian Bureau of Statistics, PE = preeclampsia; sFlt-1= soluble fms-like tyrosine kinase-1; PlGF= placental growth factor.
Source: p26 of the application.

The application also estimated that 10% of pregnancies would become eligible for sFlt-1/PlGF testing due to clinical signs and symptoms of PE. This figure was based on data from the Royal Women`s Hospital Melbourne. Several previous studies also concluded that hypertensive disorders occur in 10% of all pregnancies [5, 8, 16, 22, 24]. However, the estimation is likely to be underestimated. Depending on the clinician's interpretation of the test indication and defensive practice, education may be required around appropriate use.

During the pre-PASC meeting, it was discussed that MSAC application 1705 - Structured prenatal risk assessment for preterm PE will also be submitted for assessment. The listing of the test proposed in

1705 may impact the proportion of women who are eligible for 1706 (i.e., those identified before 14 weeks' gestation at high risk of PE and who are treated with prophylactic aspirin to lower their PE risk may have an altered risk of PE beyond 24^{+0} weeks' gestation).

It seems unlikely that every woman who is started on aspirin because of elevated risk of PE as determined by the test proposed in 1705 would not have an sFlt-1/PlGF ratio test from 24^{+0} weeks' gestation given that aspirin will not prevent 100% of PE cases. This means that some share of the high-risk population identified by 1705 may still be considered eligible for an sFlt-1/PlGF test so it is not necessarily the case that the size of the relevant patient population in the current application would drop.

PASC noted that if MSAC application 1705 is successful, the size of the relevant patient population in the current application may be impacted (in either direction). This should be investigated in the assessment report.

The application stated that clear clinical signs (disease progression and severity) indicate a need to admit the woman for monitoring regardless of the sFlt-1/PlGF ratio (p20 of the application). Based on the feedback provided by the applicant to the questions after the pre-PASC meeting, if the ratio test is low (<38), then a repeat ratio test may be required in 2-4 weeks. If it is high (>38), then the subsequent sequence will depend on the result/level of the ratio test and the gestation of the pregnancy [28]. The applicant also stated that as PE develops, there is a significant correlation between the ratio test result and other key markers of PE, in so far as the higher the ratio result, the higher the risk of PE associated adverse maternal and fetal complications (such as Haemolysis, Elevated Liver enzymes and Low Platelets syndrome, renal failure, placental abruption, refractory hypertension and eclampsia in the mother, and fetal growth restriction and prematurity in the baby).

Intervention

In Population 1, women with signs and symptoms suggestive of PE and asymptomatic women at increased risk of PE, the proposed intervention is as a triage test to consider the need for current standard diagnostic tests (and repeat sFlt-1/PlGF ratio test after 2-4 weeks if the ratio is <38, if required) for PE in pregnancies from 24^{+0} weeks gestation.

Recently, numerous studies have concluded that angiogenic factors (specifically sFlt-1 and/or PlGF) are good candidate biomarkers for predicting (or refuting) the diagnosis of PE occurring in the short term [21, 29-31]. Hence, in Population 1, the sFlt-1/PlGF ratio test is proposed to be used in addition to the current standard tests for diagnosing PE (in the triage testing population that are repeated to diagnose PE) at 24^{+0} to 36^{+6} weeks gestation (p19-23 of the application).

In Population 2, the applicant proposed the sFlt-1/PlGF ratio test as prognostic testing for assessing the severity (trajectory) of PE in women with an established diagnosis of PE (diagnosis made using the current standard tests) (p20 of the application). Therefore, the sFlt-1/PlGF ratio test is proposed to be used in addition to tests used to diagnose and monitor PE in the prognostic test population.

Based on the applicant's feedback to the questions after the pre-PASC meeting, once a woman is diagnosed with PE (before term), the rate of change of the ratio result (e.g., the results of two ratio

tests a week or so apart) indicates the rate of progression of the disease and hence its severity. The ratio test results can help the clinician in deciding when to deliver, that is, in weighing up the balance between the risks to the mother and fetus of continuing the pregnancy (because the complications of PE for both increase the longer the pregnancy continues) versus the risks of iatrogenic prematurity complications for the baby when the pregnancy is ended preterm to cure the condition [32].

The role of antiangiogenic factors in the diagnosis of PE

Preeclamptic pregnancies are characterised by ischemia and hypoperfusion of the placenta (as demonstrated by abnormal uterine artery Doppler ultrasound and/ or abnormal fetal growth/activity). These changes are accompanied by histologic markers of ischemia, including fibrin deposition, necrosis, atherosis, placental infarcts, and signs of endothelial damage [33]. Hypoperfusion of the placenta eventually results in placental production of the soluble factors such as sFlt-1 and sEng (two endogenous circulating antiangiogenic proteins) (see below), both of which have been implicated in maternal endothelial dysfunction [33]. The application indicated that both the placenta and the maternal vascular endothelium are centrally involved in the pathophysiology of the disease. Most severe cases that lead to early/preterm (<34 weeks' gestation) delivery are associated with placental insufficiency (p17 of the application). Poor placental perfusion causes placental hypoxia, altering the release of angiogenic factors that impact placental development and the maternal endothelium. Vascular endothelial dysfunction results in the end-stage features (vasoconstriction, hypertension, and organ dysfunction) seen in a woman who is symptomatic for the disease. The development of clinical symptoms and signs indicative of PE is associated with further angiogenic dysregulation and exacerbation of the disease (p17 of the application). The health and wellbeing of the patient will continue to decline until the pregnancy is delivered, including the delivery of the placenta.

Placental expression of sFlt-1 is increased in PE, and it is associated with a marked increase in the levels of maternal circulating sFlt-1 [34]. Circulating levels of sFlt-1 and PlGF are altered several weeks before the onset of clinical disease and correlate with the disease's severity [14]. sFlt-1 levels normalise within several days after delivery, coinciding with improvement in proteinuria and hypertension [35].

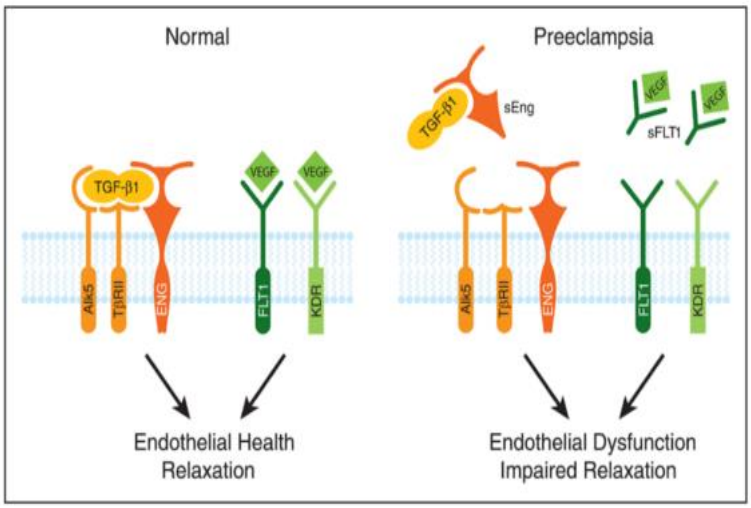

Figure 1: sFlt-1 and soluble endoglin (sEng) cause endothelial dysfunction by antagonising vascular endothelial growth factor and transforming growth factor-1 signalling.

Source: Image adapted from [36].

Literature has suggested that vascular endothelial growth factor (VEGF) and transforming growth factor-1 (TGF-β1) are required to maintain endothelial health in several tissues, including the kidney and other vascular beds. During normal pregnancy, vascular homeostasis is maintained by physiological levels of VEGF and TGF-β1 signalling in the vasculature (Figure 1) [36]. In PE, there is excess placental secretion of sFlt-1 and sEng inhibits VEGF and TGF-β1 signalling, respectively, in the vasculature. This results in endothelial cell dysfunction, including decreased prostacyclin, nitric oxide production, and release of procoagulant proteins [30].

The rate of change of the sFlt-1/PlGF ratio in consecutive tests indicates the severity of PE and the rate of progression of the disease, including earlier onset disease and placental dysfunction.

The application stated that the results of the sFlt-1 / PlGF test could be used to (p2 of the application):

1. Identify a cohort of women who have a low risk of the onset of PE and who can be managed along the normal antenatal pathway (the sFlt-1/PlGF test ratio <38).
2. Identify a cohort of women at intermediate risk of the onset of PE who would benefit from an increased level of outpatient assessment. This may include repeat sFlt-1/PlGF ratio testing later in the pregnancy (the sFlt-1/PlGF test ratio 38-85).
3. Identify a cohort of women at high risk of imminent PE (the sFlt-1/PlGF test ratio >85 before 37^{+0} weeks' gestation) and related adverse outcomes who can be managed through timely admission and preparation for delivery to mitigate these risks to maternal and fetal outcomes.

Some issues have been identified in previous studies related to the sFlt-1 / PlGF ratio test.

Widmer et al. [37] found that the sensitivity, specificity and likelihood ratios of the sFlt-1/PlGF ratio test were poor. Hence, the authors concluded that angiogenic biomarkers in the first half of pregnancy do not perform well enough in predicting the later development of PE. Honigberg et al. [38] found that measuring the trend in PlGF and sFlt-1 throughout pregnancy lacks clinically useful

predictive power. Honigberg et al. [38] suggested that PlGF and sFlt-1 levels have not been shown to predict the development of PE with acceptable accuracy. Honigberg et al. [38] yielded positive predictive values of 9 to 19% and negative predictive values of 93 to 97%; hence, the study concluded that changes in angiogenic factors throughout pregnancy lack clinically useful predictive power due to the low positive predictive values. In another study, McElrath et al. [39] concluded that the diagnosis of PE in early pregnancy was not possible using maternal angiogenic protein concentrations. Similarly, Malshe and Sibai [40] found that angiogenic factors' ability to diagnose PE is unclear. Past findings indicated that the ratio test has very high negative predictive values but low positive predictive values. The applicant may address these findings in the assessment report.

Several other studies have raised questions about the utility of the sFlt-1/PlGF ratio as a predictive marker in women with suspected PE:

1. All studies investigated the sFlt-1/PlGF ratio as a predictive marker focused on singleton pregnancies. There is a lack of test accuracy evidence for twin or non-singleton pregnancies [40-42].
   During the PASC meeting, the applicant stated that the ratio test is effective in predicting PE for multifetal gestation (as the results of the two components of the test are derived from the activity of syncytiotrophoblast, not the fetus(es)) until the third trimester. However, the applicant acknowledged that there is a lack of data to support this claim.
2. sFlt-1/PlGF ratio results are uncertain for twin pregnancies, obese and diabetic patients [35, 43].
3. Levine et al. [44] found that serum sFlt-1 levels were lower in smokers than in non-smokers throughout normal pregnancy, and levels of soluble endoglin were lower and PlGF higher at 10 through 20 weeks.
4. The 'optimal' time interval for a follow-up test (sFlt-1/PlGF ratio) remains unclear [28].
5. Klein et al. [45] concluded that the optimal cut-off ratio (sFlt-1/PlGF ratio cut-off of 85) to aid the diagnosis of PE might differ depending on which assays are used.
6. The use of cut-offs for the concentration of PlGF or the ratio of the concentrations of sFlt-1 and PlGF in predicting PE does not allow the flexibility of selecting different gestational age cut-offs for the categorisation of the severity of PE; they do not take into account the increasing effect size on biomarkers with the severity of the disease, and they cannot be expanded easily to include additional biomarkers that are measured at different stages in pregnancy [46].
7. The sFlt-1/PlGF ratio has also been shown to be useful for predicting a diagnosis of PE at a cut-off >85 for early-onset PE and >110 for late-onset PE. At ≥34 weeks, a significant increase in the sFlt-1/PlGF ratio is observed in hypertensive pregnant women without PE, but only in a minority of cases (<10%) values >110 are reached.

The applicant is advised to address the concerns above in the assessment report.

The applicant should also address the issue of heterogeneity of the accuracy of the ratio test based on patient characteristics and the necessities of different cut-off rates based on gestation age and the assay type used.

The application should clarify which assay types (e.g., Elecsys, Kryptor) are likely to be used in Australian practice in the assessment report. During the PASC meeting, the applicant clarified that

the Roche assay platform is widely used in Australia, and it is the most likely assay to be used for the ratio test.

Lastly, Klein et al. [45] concluded that the sFlt-1/ PlGF ratio test has not been evaluated as a universal screening test and is not intended to replace other techniques for assessing patients at risk of PE; the triage test should only be offered to women who have signs and symptoms suggestive of PE or are considered at an increased risk of PE and should be used in the context of other established diagnostic tools.

In contrast, several other studies have concluded that the sFlt-1/PlGF ratio is a useful predictive marker in women with suspected PE.

The application stated that women with PE have abnormal levels of angiogenic and anti-angiogenic factors with low levels of PlGF and high levels of sFlt-1 (p2 of the application). The sFlt-1/PlGF ratio increases several weeks before the onset of clinical symptoms and signs of PE and is more marked in cases of early-onset and severe disease and can be used to improve recognition and management of this disease and reduce costs of health care (p2 of the application).

The application also stated that in the absence of the sFlt-1/PlGF ratio testing, pregnant women with suspected PE would be managed through increased monitoring, including repeat diagnostic testing, clinical assessments, pregnancy day-care monitoring, and pre-emptive hospitalisations. While the biochemical comparators (e.g., urine protein/creatinine ratio test, Proteinuria reagent strip test) help diagnose PE, the applicant claimed that none of them has the predictive capacity of the sFlt-1/PlGF ratio test (p23 of the application).

Agrawal et al. [7] conducted a meta-analysis and systematic review that included 15 studies, 534 cases with PE and 19,587 controls. The study found that the sFlt-1/PlGF ratio has a pooled sensitivity of 80% (95% confidence interval, 0.68–0.88), specificity of 92% (95% confidence interval, 0.87–0.96), the positive likelihood ratio of 10.5 (95% confidence interval, 6.2–18.0), and negative likelihood ratio of 0.22 (95% confidence interval, 0.13–0.35) in predicting PE in both high- and low-risk patients. Hence, the study concluded that the sFlt-1/PlGF ratio could be a valuable screening tool for PE and may also help in decision-making, treatment stratification, and better resource allocation. Another meta-analysis included 15 relevant studies to conclude that the pooled odds ratios for the association between the high level of sFlt-1 and low level of PlGF and subsequent development of PE among women were 5.20 (95% CI: 1.24–9.16) and 2.53 (95% CI: 1.33– 3.75), respectively [47]. Hence, it concluded that increased levels of sFlt-1 and reduced levels of PlGF might predict the subsequent development of PE [47].

In an observational study with a cohort of 500 women, Zeisler et al. [48] evaluated the performance of the sFlt-1/PlGF ratio in women who presented with suspected PE. The study showed that a ratio ≤38 conferred a negative predictive value of 99.3% (95% CI, 97.9–99.9) for developing PE within seven days, whereas a ratio >38 conferred a positive predictive value of 36.7% (95% CI, 28.4–45.7) for developing PE within four weeks. Similarly, Caillon et al. [41] also found that the test had high predictive performances for ruling out PE for patients with ongoing pregnancies between 20 and 37 weeks gestation with prespecified risk factors (e.g., abnormal uterine artery Doppler, multiple pregnancies, previous pre-eclampsia, BMI >30 kg/m², vascular intra-uterine growth restriction, Thrombophilia etc.). Among the 67 patients included, 53 had the sFlt-1/PlGF ratio lower than 38;

none developed subsequent PE, leading to a negative predictive value of 100%. The positive predictive value was 21% at one week and 18% at four weeks using the same threshold (sensitivity was 100%, and specificity was 85%). The study concluded that using the ratio in the routine management of PE may improve clinical care and avoid inappropriate hospitalisation. Rana et al. [42] demonstrated that among women with suspected PE presenting at <34 weeks, the circulating sFlt1/PlGF ratio predicts adverse outcomes occurring within two weeks. The authors suggested that the accuracy of this test is substantially better than that of current approaches and may be helpful in risk stratification and management.

PASC noted that the intervention for both populations is the sFlt-1/PlGF ratio test (PERT).

PASC clarified that in Population 1, the sFlt-1/PlGF ratio test is not a predictive test but is used to categorise the likelihood of PE in (i) women with signs and symptoms suggestive of PE, or (ii) asymptomatic women at increased risk of PE; a ratio < 38 makes PE highly unlikely at the time of testing, and PE is unlikely to develop in the subsequent 2-4 weeks.

In Population 2, sFlt-1/PlGF ratio test is used for prognostication in women with a confirmed diagnosis of PE:

1. a ratio > 85 indicates severe PE and flags the need for urgent admission +/- delivery;

2. a ratio 38-85 indicates the need for more intensive monitoring and management of the pregnancy.

PASC noted the possibility that more than one ratio test may be required for Populations 1 and 2 based on the patient's gestational age and clinical presentation. PASC confirmed that once a patient is judged to be at low risk of developing PE (sFlt-1/PlGF ratio<38), no ratio test is required for at least the next 2-4 weeks (Population 1). Nonetheless, a low ratio on the proposed test does not categorically exclude a diagnosis of PE for the entirety of the pregnancy for an individual patient and therefore, serial testing may still be likely.

PASC noted that the frequency of ratio testing was an important clinical question to resolve and in particular:

- *The usefulness of very frequent testing (if a change in ratio is indicative of immediacy of risk).*
- *The likelihood of serial testing given the incremental value of knowing.*
- *The implications for frequency of use in multiple pregnancies compared to singletons.*

PASC noted that the Roche assay platform is widely used in Australia, and it is the most likely assay to be used for the ratio test.

PASC noted that the ratio test may be effective for multiple pregnancies (as the results of the two components of the test are derived from the activity of syncytiotrophoblasts, not the fetus(es)) up to the third trimester of pregnancy. However, evidence supporting the use of sFlt-1/PlGF ratio tests in multifetal gestation is limited and should be presented separately from the evidence in singleton pregnancies in the assessment report.

<u>Regulatory information</u>

The table below presents commercial tests registered on the Australian Register of Therapeutic Goods (ARTG) (Table 3).

Table 3: sFlt-1 and PlGF tests on the Australian Register of Therapeutic Goods

Test	Laboratory-based test
sFlt-1 Roche Diagnostics Australia Pty Limited	ARTG 181222, Class 3 IVD, Specific Protein IVDs.
PlGF Roche Diagnostics Australia Pty Limited	ARTG 181221, Class 3 IVD, Clinical chemistry hormone IVDs

ARTG = Australian Register of Therapeutic Goods; IVD = in vitro diagnostic medical device.
Source: Provided to the Department by the Therapeutic Goods Administration.

Comparator

There are no universally accepted tests with sufficiently strong performance characteristics to reliably predict PE in pregnant women, especially at term gestations (37 to 42 weeks), where the most significant disease burden exists [49].

During the PASC meeting, the applicant stated that the sFlt-1/PlGF ratio test may not be necessary for pregnant women after 37 weeks of gestation as curative delivery of the baby and placenta is associated with less risk than before 37 weeks.

Past literature indicated that tests for diagnosis of PE involve an initial assessment of blood pressure, proteinuria (first by urine dipstick and then confirmed by urine protein:creatinine ratio if the dipstick is positive), urine microscopy and culture, baseline blood tests (complete blood count, urea and electrolytes, liver function tests, and clotting), as well as physical examination and cardiotocography [26, 29]. Another study concluded that the combination of maternal characteristics, mean arterial pressure, late first-trimester uterine artery Doppler pulsatility index, placental growth factor, and pregnancy-associated plasma protein-A in maternal blood was successful in predicting about 95% of cases of early-onset PE and had a false-positive rate of 10% (sensitivity 93% [95% CI 76–98%]; specificity 95% [94–96%]) [50].

Table 4 represents various diagnostic criteria for diagnosing PE based on the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) guidelines for managing hypertensive disorders of pregnancy [6].

Table 4: General diagnostic criteria for PE (SOMANZ guidelines)

Factor (dysfunction)	Outcome measures
Gestational hypertension	Hypertension (systolic blood pressure, >140 mmHg, or diastolic blood pressure, >90 mmHg, on at least two occasions 4 hours apart, was experienced after 20 weeks gestation in previously normotensive women. Severe hypertension: blood pressure of 160/110 mmHg or more
Plus, one or more of the following signs of organ involvement.	
Renal involvement	Significant proteinuria – a spot urine protein/creatinine ratio ≥ 30 mg/mmol Serum or plasma creatinine >90 µmol/Ld Oliguria: <80 mL/4 hour
Proteinuria	Initial assessment with automated dipstick urinalysis. If unavailable, visual analysis can be used. If dipstick is positive (≥1+), confirmed with spot urine, which is abnormal if Protein:Cr ≥ 30 mg/mmol or Albumin:Cr ≥ 8 mg/mmol

Factor (dysfunction)	Outcome measures
Haematological involvement	Thrombocytopenia <100 000/μL Haemolysis: schistocytes or red cell fragments on the blood film, raised bilirubin, raised lactate dehydrogenase >600 mIU/L, decreased haptoglobin
Liver involvement	Raised serum transaminases Severe epigastric and/or right upper quadrant pain.
Neurological involvement	Convulsions (eclampsia) Hyperreflexia with sustained clonus Persistent new headache Persistent visual disturbances (photopsia, scotomata, cortical blindness, posterior reversible encephalopathy syndrome and retinal vasospasm) Stroke
Uteroplacental dysfunction	Fetal growth restriction, abnormal umbilical artery Doppler wave form analysis, stillbirth

PE= preeclampsia; SOMANZ= Society of Obstetric Medicine of Australia and New Zealand; mg/mmol = micrograms per millimole; mmHg = millimetres of mercury; μmol/L= micromoles per litre.

Source: Fox et al., [5], Lowe et al., [6]. SOMANZ guidelines for the management of hypertensive disorders of pregnancy 2014.

Past studies have attempted to identify which features are predictive. Several problems have been identified with standard diagnostic testing for PE. The International Society for the Study of Hypertension in Pregnancy (ISSHP) suggested a consensus that factors determining the severity of PE include difficulty in controlling blood pressure and deteriorating clinical condition, impending eclampsia, and worsening thrombocytopenia or worsening fetal growth restriction. However, there is less concern regarding increasing proteinuria [51]. Previous research indicated that dipstick testing is not accurate in confirming or excluding significant proteinuria (≥300 mg/24 h): sensitivities of 22–82% have been reported; hence, a spot urine protein:creatinine ratio is recommended for confirmation or exclusion of proteinuria when PE is suspected [52]. Serum/plasma creatinine usually falls in normal pregnancy and levels even at the upper end of the normal range (70–100 mmol/L), indicate impaired renal function. Therefore, some guidelines have used cut-offs up to >100– 110 mmol/L to indicate renal impairment in PE [51, 53]. Lastly, a reduction in platelet count is typical in pregnancy. However, a platelet count of <100 000/μL is reported in 4.5% of women with proteinuric and 9.9% with non-proteinuric PE and only 1% of normal pregnant women [54].

Chappell et al. [1] stated that once diagnosed, PE is often a progressive condition and maternal organ function deteriorates with time. No drug has been discovered that clearly slows disease progression, and the only option to stop the disease is to deliver the fetus and placenta. Therefore, the overall approach to management is to deliver the baby and placenta at term, or, if preterm PE is diagnosed, to individualise the active management of the pregnancy (antenatal antihypertensives, steroids, magnesium infusion, support organ dysfunction, delivery in an appropriate centre) until a more advanced gestation is reached. The National Institute for Health and Care Excellence [25] suggested monitoring maternal kidney function, bilirubin, electrolytes, full blood count, and transaminases several times a week after a PE diagnosis. Other studies which reported management and tests for women diagnosed with PE did not include the sFlt-1/PlGF ratio test are [4]; [1]; [26]; [16]; [13] and [27].

PASC noted that the comparator of the ratio test for Population 1 is no triage testing ± current standard tests that may be repeated for diagnosing PE at 24^{+0} to 36^{+6} weeks, including the urine protein: creatinine ratio test, proteinuria reagent strip test, full blood count, renal function test,

serum electrolytes and hepatic transaminases; and for Population 2 it is no prognostic testing and standard medical management of PE (which may include repeat standard diagnostic tests for monitoring PE severity).

PASC noted that whether the ratio test is a substitute or in addition to the current standard (diagnostic) tests will depend in part on the patient's gestational age, and without this information, the pathologist will have difficulty in interpreting the ratio test results. The applicant was advised to clarify this in the assessment report.

Reference standard

The ISSHP defines PE as new onset hypertension present after 20^{+0} weeks of gestation combined with proteinuria (>300 mg/day), other maternal organ dysfunction, such as renal insufficiency, liver involvement, neurological or haematological complications, uteroplacental dysfunction, or fetal growth restriction [27].

Acceptable reference standards for PE were persistently high systolic (≥ 140 mm Hg) or diastolic (≥ 90 mm Hg) blood pressure and proteinuria (≥ 0.3 g of protein in 24-hour urine collection, or dipstick test result of ≥ 1+ [equivalent to 30 mg/dL in single urine sample]) of new-onset after 20 weeks of gestation [55]. PE is defined as a systolic blood pressure of 160 mm Hg or greater or a diastolic blood pressure of 110 mm Hg or greater plus a high level of proteinuria (≥ 2.0 g of protein in 24-hour urine collection or dipstick test result of ≥ 3+), before 34 weeks' gestation in a patient with chronic hypertension [55]. On the other hand, superimposed PE is defined as proteinuria (≥ 0.3 g of protein in 24-hour urine collection or dipstick test result ≥ 1+) developing after 20 weeks of gestation in patients with chronic hypertension. Other signs of PE are: liver involvement (blood concentration of transaminases to twice the normal level), neurological complications (e.g. cerebral or visual symptoms), thrombocytopenia (platelet count <100 000/μL), pulmonary oedema [6, 56] and CNS symptoms (e.g., altered mental status, blurred vision, or blindness [57].)

Maternal hypertension and/or proteinuria with or without clinical symptoms may be sufficient to diagnose PE, or these signs may also occur in combination with fetal growth restriction and/or signs of biochemical or haematological impairment [25].

The SOMANZ study stated that a diagnosis of PE could be made when hypertension arises after 20 weeks of gestation and is accompanied by one or more of the signs of renal involvement, haematological involvement, liver involvement or neurological involvement [6].

Another study stated that the reference standard for the diagnosis of PE is clinical assessment, guided by a combination of the following clinical information: a) maternal hypertension (categorised as mild, moderate or severe); b) quantitative proteinuria test; c) clinical symptoms suggestive of PE (e.g. headache, oedema or visual disturbances); d) fetal growth restriction [58].

The National Institute for Health and Care Excellence [16] recommended that women diagnosed with PE should have regular fetal monitoring, including an initial assessment to confirm fetal well-being. In the presence of fetal growth restriction, a recommended schedule for serial fetal surveillance with ultrasound is detailed within these recommendations. The study also suggested continuous maternal monitoring to assess risk (e.g., BP monitoring, repeated assessments for

proteinuria if it is not already present, clinical assessment including clonus, and a minimum of twice-weekly blood tests for hemoglobin, platelet count, and tests of liver and renal function).

The applicant may confirm what is the most relevant reference standard for Population 1 and Population 2.

Outcomes

The evidence base for the sFlt-1/PlGF ratio testing (women with suspected PE) mainly consists of observational studies, which are discussed briefly below.

Patient relevant

Diagnostic performance

Sensitivity, specificity, positive predictive value, and negative predictive value compared to the reference standard in women with likelihood of PE, test-retest reliability (confirmation or ruling out of PE), evidence of stability in risk level (diagnostic measurement for risk), test failure rate (unsatisfactory or uninterpretable results).

Clinical outcomes associated with PE.

Structured prenatal risk assessment for preterm PE facilitates improved clinical management of pregnancies identified as high-risk, or symptomatic of PE. Hospital admission and over treatment. There are a number of adverse maternal outcomes associated with PE that should be explored, these include:

- eclamptic fit and/or other neurological sequelae (such as a cerebrovascular accident)
- renal and hepatic impairment
- haematological dysfunction and postpartum haemorrhage
- HELLP syndrome (Haemolysis, Elevated Liver enzymes and Low Platelets)
- placental abruption

PE is also associated with preterm birth, which increases risks of numerous adverse neonatal outcomes that should also be explored.

The most commonly reported adverse outcomes, which predominately affect babies < 32 weeks gestation when PE is not identified and properly managed are:

- Early onset sepsis (starting <48 hours after delivery)
- Late onset sepsis (starting >48 hours after delivery)
- Hyaline membrane disease – lung immaturity requiring ventilation (the incidence of which is significantly reduced by administration of antenatal steroids)
- Chronic lung disease (CLD) (also called bronchopulmonary dysplasia) – long term lung disease occurring as a result of prematurity and adverse effects of requiring ventilation
- Intracerebral haemorrhage (IVH) – acute bleeding in the brain (the incidence of which is ameliorated by antenatal magnesium sulphate administration to the mother)
- Periventricular leukomalacia – persistent brain abnormality typically arising from IVH

- Necrotising enterocolitis – infection of the lining of the bowel that may require antibiotics and or surgical resection
- Persistent patent ductus arteriosus – this is where a vessel that is required in utero between the two main outflow vessels of the heart fails to shut once the baby is born, requiring medical or surgical closure
- Poor neurodevelopment as assessed at 2 years of age

Prognosis	Prognostic utility of testing in women with PE.
Safety	Misclassification of the risk of PE; adverse events associated with incorrect risk stratification and the follow-up diagnostic and treatment work ups.
<u>Healthcare system</u>	
Costs	Cost of testing and any cost offsets; costs associated with-hospitalisation, outpatient appointments, antihypertensive medication, and preventing and treating complications.
Cost-utility	Incremental cost per life-year gained, the incremental cost per quality-adjusted life-year.
Financial implications	Number and cost of patients tested.

Value of Knowing

There could be several potential benefits and harms associated with a knowledge of the diagnosis of PE. The application did not present any analysis of the value of knowing test results. Many studies have explained the value of additional information generated by the ratio test and its positive impact on the health outcome of women with likelihood of PE [34, 50, 56]. The ratio test also provides valuable information on disease progression or severity for women diagnosed with PE.

The applicant should comment on any potential value of knowing issues in the assessment report for Population 1 and Population 2.

PASC advised that clinical outcomes related to both mother and fetus should be addressed in the assessment report.

Assessment framework

Two assessment frameworks linking the sFlt-1/PlGF ratio test to relevant health outcomes are presented in Figure 2 (Population 1) and Figure 3 (Population 2).

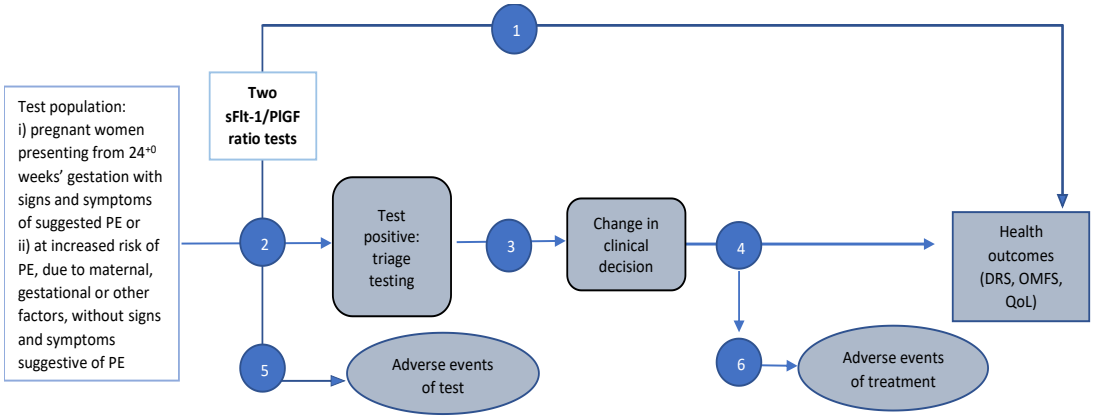

Figure 2: Assessment framework showing the links from the test population to health outcomes (Population 1)

sFlt-1= soluble fms-like tyrosine kinase-1; PlGF= placental growth factor; OMFS = overall maternal and fetal survival; DRS = disease-related survival (maternal and fetal); QoL = quality of life.
1: direct from test to health outcomes evidence; 2: concordance of sFlt-1/PlGF ratio testing with pregnant women with symptoms of PE; 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: adverse events due to testing; 6: adverse events due to treatment
Source: Adapted from p80, Figure 8, MSAC Guidelines for preparing assessments for the Medical Services Advisory Committee 2021.

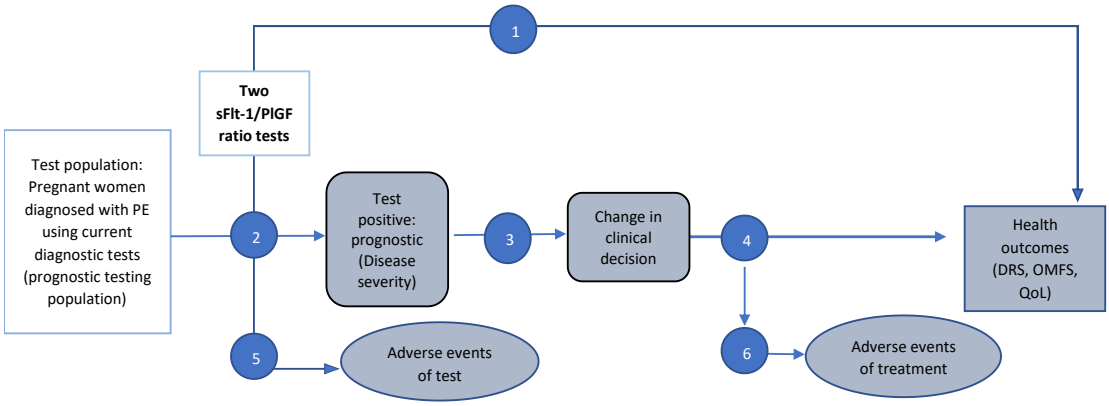

Figure 3: Assessment framework showing the links from the test population to health outcomes (Population 2)

sFlt-1= soluble fms-like tyrosine kinase-1; PlGF= placental growth factor; OMFS = overall maternal and fetal survival; DRS = disease-related survival (maternal and fetal); QoL = quality of life.
1: direct from test to health outcomes evidence; 2: concordance of sFlt-1/PlGF ratio testing with pregnant women with symptoms of PE; 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: adverse events due to testing; 6: adverse events due to treatment
Source: Adapted from p80, Figure 8, MSAC Guidelines for preparing assessments for the Medical Services Advisory Committee 2021.

The main assessment question for a claim of superiority is whether the addition of the sFlt-1/PlGF ratio test to the current testing regimen results in the claimed superior health outcomes?

Clinical management algorithm

PASC advised developing one clinical management algorithm for Population 1 and another algorithm for Population 2.

Current clinical management algorithms

Modified versions of the current management algorithm including for women with signs and symptoms suggestive of PE along with asymptomatic women with an elevated risk of PE (Population

1) and women with a confirmed diagnosis of PE (Population 2) prepared during the PICO development are shown in Figures 4 and 5, respectively. Patients with the following maternal characteristics are at high risk: hypertensive disease during a previous pregnancy, chronic kidney disease, autoimmune diseases such as systemic lupus erythematosus or antiphospholipid syndrome, type 1 or type 2 diabetes, age >40, pre-pregnancy body mass index (BMI) [58]. The symptoms of PE include severe headache, sudden blindness, drowsiness, severe pain just below the ribs, vomiting, sudden swelling of the face and hands or feet. In addition, the key signs are proteinuria, marginally increased blood pressure (≥140 mmHg systolic or ≥90 mmHg diastolic), white coat hypertension, adverse biochemistry (e.g., solitary thrombocytopenia), or fetal growth restriction [6-8]. Lastly, women diagnosed with PE are cared for using standard clinical management for the risk assessed and disease severity, based on the current prognostic tests. For women with PE diagnosed at 24-28 gestational age, care includes regular blood tests (1–2 a week), ultrasound every 2 weeks or more frequently if indicated (e.g., the presence of coexisting fetal growth restriction), and regular cardiotocograph. On the other hand, severe PE diagnosis after week 37 should include planned birth within 24–48 hours [4]; [1]; [26];[16] and [27]. Further information on the current clinical management practices for women diagnosed with PE is presented in the appendix.

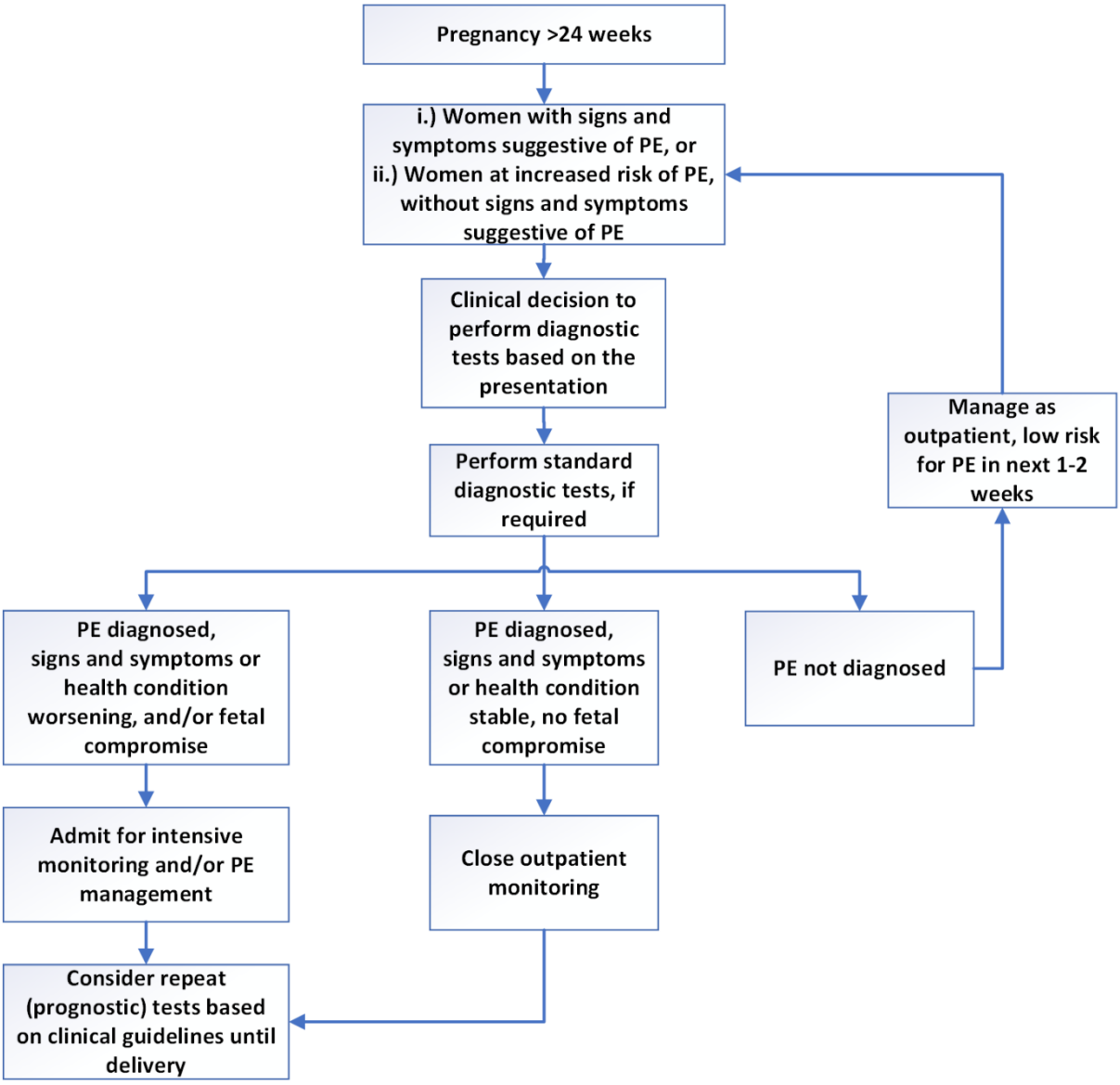

Figure 4: Current clinical management algorithm for Population 1 prepared during the PICO development

PE = Preeclampsia.

Source: Modified version of the current clinical management algorithm developed during the PICO preparation based on the PASC and Department of Health feedback and figure (Attachment: sFlt-1_PlGF ratio clinical pathway diagram) provided in the application.

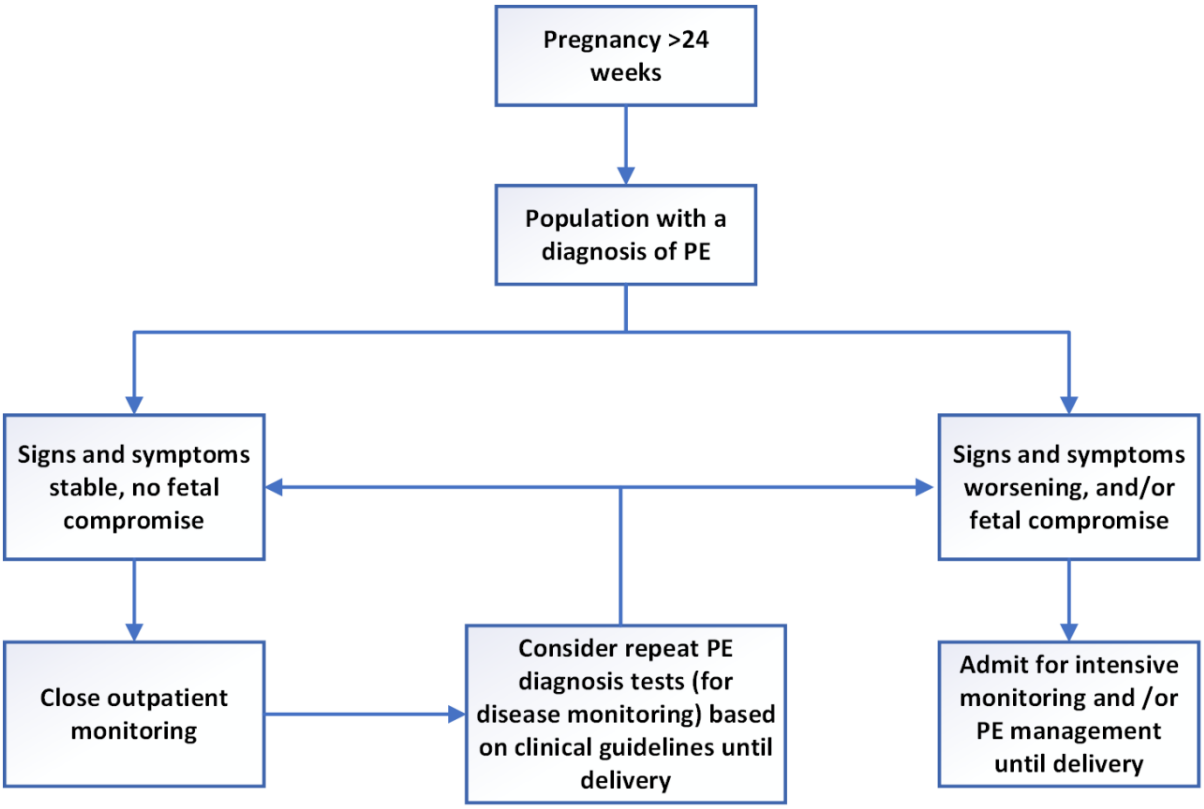

Figure 5: Current clinical management algorithm for Population 2 prepared during the PICO development

PE = Preeclampsia.
Source: Modified version of the current clinical management algorithm developed during the PICO preparation based on the PASC and Department of Health feedback and figure (Attachment: sFlt-1_PlGF ratio clinical pathway diagram) provided in the application.

Proposed clinical management algorithm

The application proposed the sFlt-1/PlGF ratio test to be used to predict the onset of PE in pregnancies from 24^{+0} weeks gestation. Based on the discussion during the pre-PASC teleconference and PASC meeting, modified versions of the proposed clinical management algorithms were developed during the PICO preparation (Figures 6 and 7). The test is aimed at pregnant women with signs and symptoms suggestive of PE (but in whom PE is not already diagnosed), along with asymptomatic women at increased risk of PE and women with an established diagnosis of PE. The application indicated that clinical suspicion of PE could be due to the following reasons (p18 of the application):

- New onset of increased blood pressure
- Exacerbation of pre-existing hypertension
- New onset proteinuria
- Exacerbation of pre-existing proteinuria
- PE related clinical features (epigastric pain, excessive oedema, headache, visual disturbances, sudden weight gain)
- Abnormal uterine artery Doppler sonography
- Fetal growth restriction.

The applicant's response to questions after the pre-PASC meeting stated that the ratio test is primarily a prediction test for PE in so far as its excellent NPV and reasonable (and better than any

comparator) PPV help clarify the likelihood of a woman with clinical features suggestive but not diagnostic of PE going on to develop actual PE in the following month [43]. Therefore, if the ratio test is low (<38), then no subsequent diagnostic testing is required within the next 2-4 weeks. If it is high (>38), then the subsequent sequence will depend on the result/level of the ratio test and the gestation of the pregnancy. On the other hand, for women diagnosed with PE, the test result will indicate the rate of progression of the disease and hence, its severity.

For both Populations 1 and 2, repeated sFlt-1/PlGF ratio tests might be required subject to disease severity and gestational age. Figure 6 presents the clinical management algorithm for Population 1, as developed during the PICO preparation.

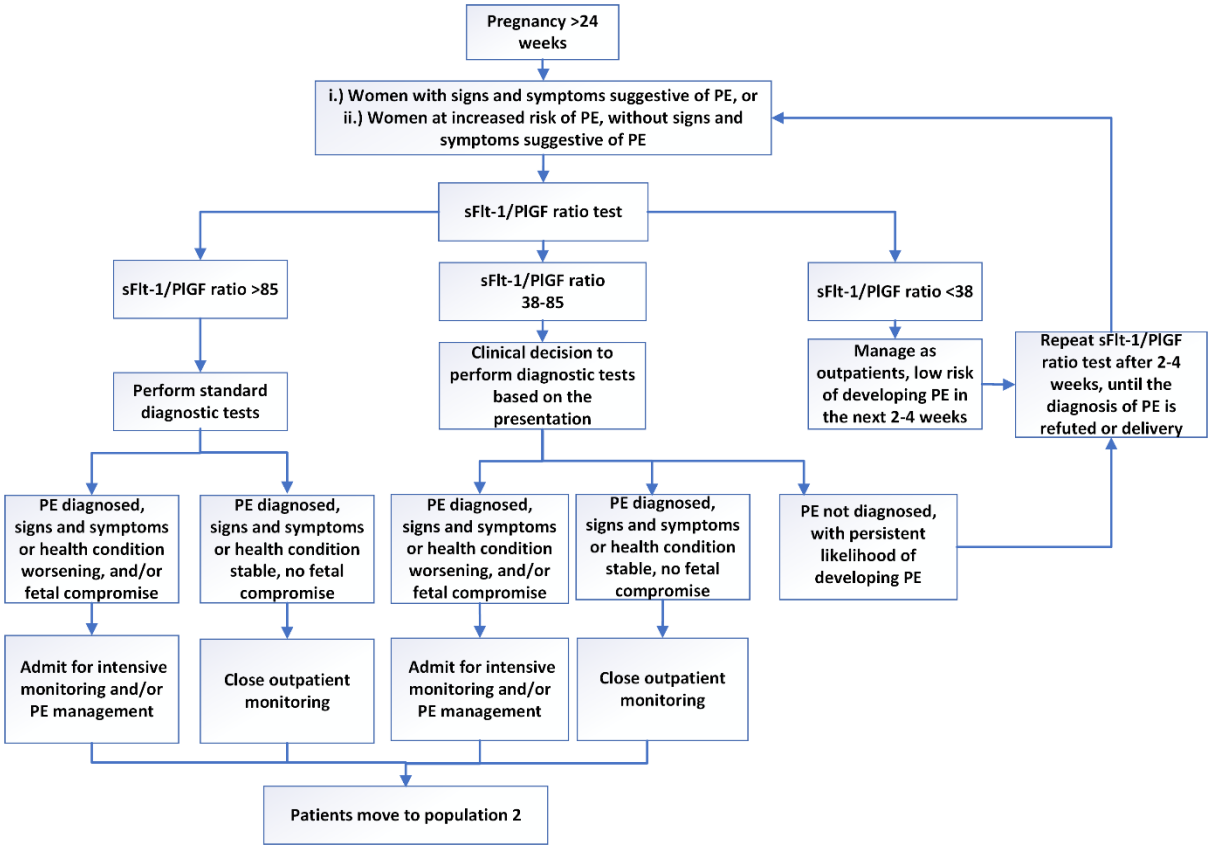

Figure 6: Proposed clinical management algorithm for Population 1 developed during the PICO preparation

PE = Preeclampsia; sFlt-1= soluble fms-like tyrosine kinase-1; PlGF= placental growth factor.

Source: Developed during PICO preparation based on the algorithm provided in the application (Attachment: sFlt-1_PlGF ratio clinical pathway diagram) and departmental feedback.

Figure 7 presents the clinical management algorithm for Population 2, developed during PICO evaluation.

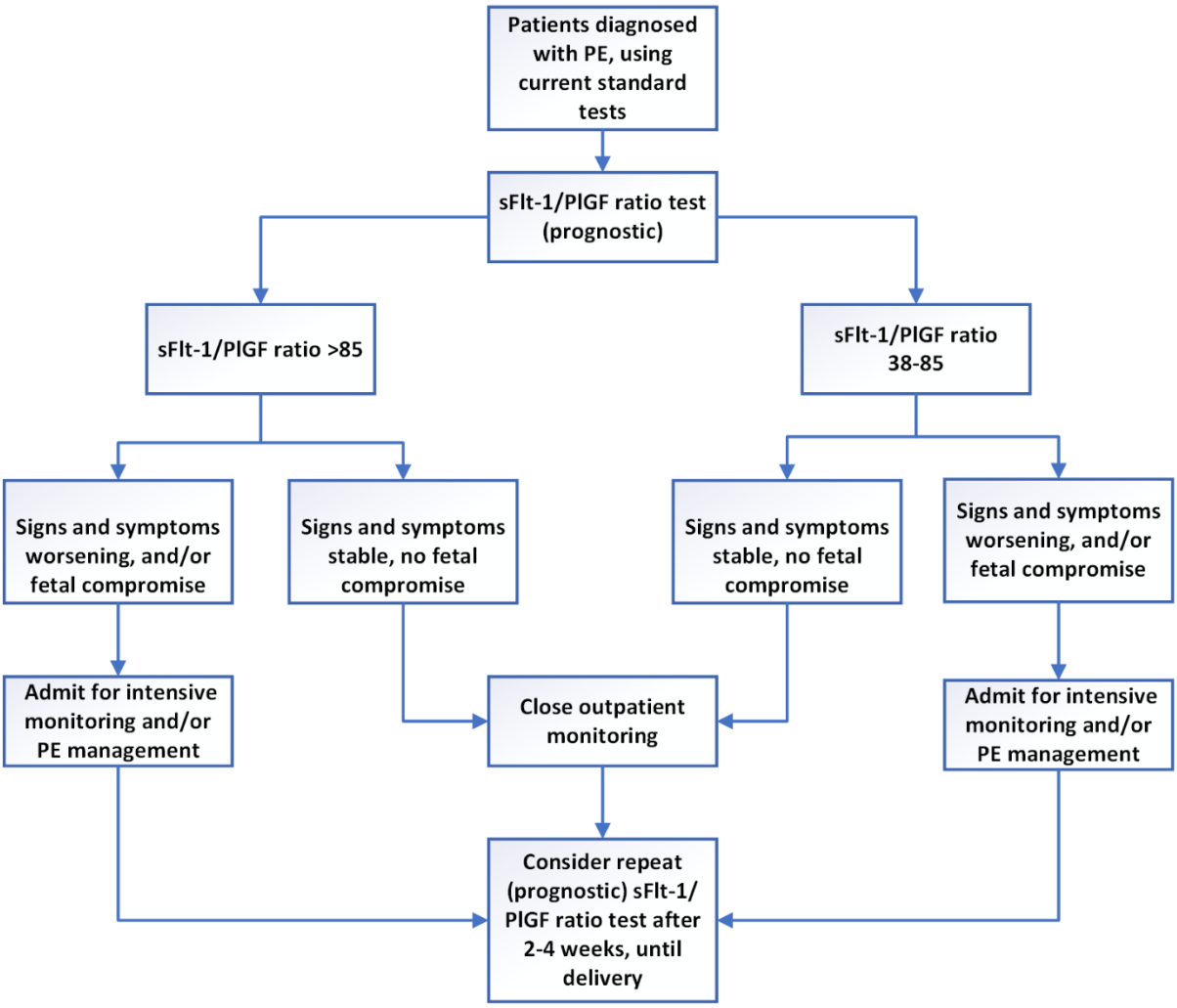

Figure 7: Proposed clinical management algorithm for Population 2 developed during the PICO preparation

PE = Preeclampsia; sFlt-1= soluble fms-like tyrosine kinase-1; PlGF= placental growth factor.
Source: Developed during PICO preparation based on the algorithm provided in the application (Attachment: sFlt-1_PlGF ratio clinical pathway diagram) and departmental feedback.
Note: The assessment report could also investigate clinical management for patients with sFlt-1/PlGF ratio < 38.

Use of the sFlt-1/PlGF ratio for pregnant women with signs and symptoms suggestive of PE and asymptomatic pregnant women at high risk of PE

According to the established cut-off values of the sFlt-1/ PlGF-ratio, women with a ratio >85 are classified as high-risk, a ratio between 38 and 85 are defined as intermediate-risk, and a ratio <38 as low risks [5, 27, 32, 59, 60].

Stepan et al. [28] and Frampton et al. [58] demonstrated implementing the sFlt-1/PlGF ratio for predicting and diagnosing PE in a singleton pregnancy and its implications for clinical practice. According to these studies:

1. The sFlt-1/PlGF ratio <38 rules out PE, irrespective of gestational age, for at least one week. Further management is according to the clinician's discretion. sFlt-1/PlGF ratio retesting should cease upon cessation of clinical features of PE.
2. The sFlt-1/PlGF ratio of 38–85 (early-onset PE) or 38–110 (late-onset PE) provides extra information on which women are at moderate risk or at high risk of developing PE within four weeks. Early-onset: Consider a follow-up sFlt-1/PlGF test in 1–2 weeks, according to the individual clinical situation. Late-onset: An intermediate result of the sFlt-1/PlGF ratio suggests impending placental dysfunction. Health practitioners should consider lowering the threshold for induction of delivery [28].
3. Women with an elevated sFlt-1/PlGF ratio >85 (early-onset PE) or >110 (late-onset PE) are highly likely to have PE or some form of placenta-related disorder. They should be managed according to local clinical /guidelines.
4. Severely elevated sFlt-1/PlGF ratios (>655 at <34+0 weeks; >201 at ≥34+0 weeks) are associated closely with the need to deliver within 48 hours. Close surveillance and (if <34 weeks) prompt initiation of antenatal corticoids to accelerate fetal lung maturation are mandatory [28].

The application stated that individualised management would depend on other clinical and ultrasound risk factors: if no new symptoms occur, most clinics will review the patient in 2–4 weeks (p19 of the application).

Based on the proposed algorithm, the ratio test might replace or be used in addition to standard diagnostic tests based on the patient's clinical condition (ratio and other test results, maternal or fetal condition). The applicant should address the following questions in the PICO assessment report.

The applicant may clarify what percentage of ratio tests performed will be an addition to the standard tests and what percentage of ratio tests performed will replace existing standard tests for the diagnosis of PE?

The applicant may also clarify, in practice, would the ratio test be performed simultaneously as the standard diagnostic tests in all patients, given the time-sensitive nature of making a definitive diagnosis?

Comparison of the current and proposed guidelines/algorithms

In the proposed algorithm developed during the PICO preparation, the sFlt-1/PlGF ratio test has been added as a triage test for women with signs and symptoms suggestive of PE, along with asymptomatic women at high risk of PE and as a prognostic test for women diagnosed with PE. The ratio test can provide a result indicative of impending PE while other key markers of PE remain within their normal ranges. The rate of change of the sFlt-1/PlGF ratio in consecutive tests indicates the severity of PE and the rate of progression of the disease, including earlier onset disease and placental dysfunction (p19 of the application). The ratio test is particularly useful between 24+0 to 34+6 weeks of gestation, facilitating the very complex, individually-based and integrated clinical decision-making process regarding the optimal timing of a likely preterm delivery (p21 of the application). The increased level of outpatient monitoring in the proposed algorithm includes repeating sFlt-1/PlGF ratio testing later in the pregnancy.

Proposed economic evaluation

The application has proposed a superior clinical claim (p25 of the application*).* During the development of this PICO, the applicant clarified that the claim is for superior effectiveness and superior safety. Based on these claims, the appropriate type of economic evaluation would be cost-effectiveness or cost-utility analysis (Table 5).

Table 5: Classification of comparative effectiveness and safety of the proposed intervention, compared with its comparator, and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	**Uncertain[a]**	**Noninferior[b]**	**Superior**
Inferior	Health forgone: need other supportive factors.	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain[a]	Health forgone possible: need other supportive factors.	?	?	? Likely CEA/CUA
Noninferior[b]	Health forgone: need other supportive factors.	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis.
? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis
[an] 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations.
[b] An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence.

PASC noted that the applicant claims superior effectiveness and superior safety of the ratio test.

Proposal for public funding

The application indicated that this is a new item proposing a way of clinically delivering a new service to the MBS (in terms of new technology) (p3). This is a pathology service used to determine PlGF and sFlt-1 quantitatively to predict, identify or manage PE in pregnancies from 24+0 gestational weeks.

The proposed MBS item descriptor is for a laboratory-based sFlt-1/PIGF ratio test for women who have a likelihood of developing PE (Table 6). The proposed test does not have an existing MBS item, and the proposed service is not seeking any public funding other than MBS. A fee structure is yet to be provided for the proposed test.

Tables 6 and 7 represent proposed MBS item descriptors for Populations 1 and 2, respectively. The item descriptor for Population 1 has been updated and a new item descriptor for Population 2 has been developed based on the suggestions made during the PASC meeting.

Table 6: Proposed MBS Item Descriptor for Population 1

Category 6 - PATHOLOGY SERVICES
Laboratory-based quantitative determination *of the ratio of* placental soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) from the beginning of the 24th week of pregnancy to *evaluate the likelihood of pre-eclampsia (PE)* in pregnancies where there are signs and symptoms suggestive of PE, or where there is an increased risk of PE.
Fee: $**.**

Source: Compiled during development of this PICO

During the pre-PASC meeting, the applicant mentioned that the cost of the PIGF test for the Australian health system ranges from $50-$100. *PASC advised that a fee structure should be proposed in the assessment report*.

Table 7: Proposed MBS Item Descriptor for Population 2

Category 6 - PATHOLOGY SERVICES
Laboratory-based quantitative determination *of the ratio of* placental soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) from the beginning of the 24th week of pregnancy *for the management (by categorising the severity) of* diagnosed preeclampsia in preterm pregnancies.
Fee: $**.**

Source: Compiled during development of this PICO.

PASC advised that the item descriptors should clearly mention that the clinical judgment should be based on the sFlt-1/PlGF ratio rather than the individual values of sFlt-1 and PlGF.

PASC also advised that the interpretation of the ratio test results (or guidelines) should be included in the item descriptor. However, the information may best be referenced in a note. PASC noted that the pathology report is unlikely to interpret the ratio test results as the pathologist will be unaware of the patient's gestational age. The applicant was advised to address this in the assessment report.

PASC also advised that a fee structure and justification should be proposed in the assessment report.

Summary of public consultation input

Consultation Feedback

PASC noted and welcomed consultation input from three (3) professional organisations, one (1) consumer organisation and five (5) individuals, of whom two (2) were consumers and three (3) medical professionals. Consultation input was received from the following organisations:

- *Australian Action on Preeclampsia Inc (AAPEC)*

- *Australian Pathology (AP)*
- *Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)*
- *Society of Obstetric Medicine Australia and New Zealand (SOMANZ).*

The consultation feedback received was broadly supportive of public funding for angiogenic and anti-angiogenic markers for identification and management of preeclampsia.

Clinical need and public health significance
The main benefits of public funding received in the consultation feedback included:

- Accurate diagnosis and monitoring of pre-eclampsia would help to improve health outcomes for both mothers-to-be and their newborns. Clinicians would get a clear indication of placental malfunction and of the diagnosis of preeclampsia.
- Patients would benefit from a reduction in unnecessary hospital admissions and tests. Earlier diagnosis would provide patients and their families with greater capacity to deal with diagnosis and make plans.
- Reduced costs to the healthcare system.
- Equity of access for patients through increased availability of the test, especially for women in rural and remote locations.

Most consultation feedback did not identify any disadvantages of public funding. One organisation noted the false-negative test rates as a disadvantage, but noted that this was similar to other tests, and stated that the proposed test had excellent negative predictive capacity.

Other services identified in the consultation feedback as being needed to be delivered before or after the intervention included:

- pre-intervention education regarding the test availability; and post-test counselling regarding interpretation of result, and
- appropriate ongoing obstetric management, based on maternal symptoms, examination and results.

Indication(s) for the proposed medical service and clinical claim
The consultation feedback ranged from 'agreeing' to 'strongly agreeing' with the proposed population(s).

The consultation feedback ranged from' agreeing' to 'strongly agreeing' with the proposed comparator(s).

- AAPEC agreed with the comparators and noted its members considered the existing comparators were not adequate for the prediction of preeclampsia compared to the proposed test, meaning there are often "missed opportunities" to identify the risk of preeclampsia and commence appropriate and timely interventions.
- SOMANZ noted that the proposed comparator is the current gold standard of practice but lacked any predictive capacity or sensitivity.
- AP noted there was additional diagnostic value to the tests listed in the comparators beyond simply the diagnosis and monitoring of pre-eclampsia. They considered that the test to quantify sFlt-1/PIGF ratio should not be considered a substitute for, or be mutually exclusive from, the listed tests.

The consultation feedback ranged from 'agreeing' to 'strongly agreeing' with the clinical claim.

- AAPEC considered that the documented performance of the proposed service indicated it was markedly more reliable than the comparator.

Cost information for the proposed medical service
The consultation feedback ranged from 'agreeing' to 'strongly agreeing' with the proposed service descriptor and proposed service fee.

- The AAPEC noted the documented costs do not address the costs associated with promoting the proposed intervention to consumers and all relevant providers and stated that they are firmly of the view that an associated public campaign would be beneficial to the implementation and take up of the service.
- SOMANZ suggested rewording the descriptor as the placental assay was not specific for placental sFLT-1, and that some literature supported testing from 22 weeks as below:

  Quantitative determination of placental growth factor (PlGF) and of ~~placental~~ soluble fms-like tyrosine kinase1 (sFlt-1) to predict, identify or manage preeclampsia in pregnancies from ~~24~~ **22** gestational weeks.

Additional comments
Additional comments were provided on associated interventions by AAPEC who considers the intervention to be readily implemented in a range of service models in all Australian states and territories. They went on to state that it will require adaptation in each jurisdiction and an associated professional and consumer education and awareness campaign.

The AAPEC was concerned about equality of access and ensuring those living in rural and remote areas, Aboriginal and Torres Strait Islander women and their families, and residents of non-English speaking backgrounds have access to the intervention. The AAPEC considered a public campaign could be considered with the implementation of the proposed intervention.

Individual Feedback

Health Professionals
All health professionals were in support of the public funding for the proposed service, stating that public funding would increase accessibility and would be more cost-effective than the comparator. They considered that the proposed service could reduce hospital or clinic visits, and hospital admission. Low risk patients would benefit from less intervention.

The health professionals agreed that the proposed service allows for planning by the patient and clinician in immediate and ongoing monitoring and management, including providing prognostic information, whether to begin treatments to protect the fetus and, whether the patient should be induced as opposed to awaiting spontaneous labour while also reducing the need for iatrogenic pre-term delivery. They further agreed that the proposed service may result in reduced morbidity and mortality associated with preeclampsia through early management, reducing resources required to manage the disease and its consequences. One health professional expanded on this stating that the proposed service allows for monitoring of high-risk patients in an outpatient setting. One health professional pointed out that the proposed service would be useful in ruling out pre-eclampsia in conditions that mimic it, reassuring patients and reducing the need for investigation and review in

these patients. One health professional stated that publicly funding the proposed service will have positive ramifications for ongoing research and improved guidance for clinicians, leading to optimal patient care.

Consumer submissions
Both consumers, one who also was a medical professional, had personal experience with the proposed medical service and were supportive of the proposed service.

The consumers considered that the proposed service would allow for increased identification of high-risk patients prior to the development of symptoms and would aid health care staff in decision making around admission, pregnancy management and monitoring. The consumers agreed that the proposed service allows patients and families to prepare for hospital admissions, interventions, likely pre-term births, and allowed families to stay together for as long as possible prior to hospital admission. Patients identified at low risk of preeclampsia would benefit from the ability to undertake usual activities, such as travel. One consumer further stated that the proposed service is an important test, not only for women during pregnancy, but for women's ongoing cardiovascular health.

Next steps

PASC noted that the applicant had not yet decided whether to proceed with the application as an ADAR (Applicant Developed Assessment Report) or a DCAR (Department Contracted Assessment Report) and will advise at a later stage.

Applicant comments on ratified PICO Confirmation

Nil.

References

1. Chappell, L.C., et al., Pre-eclampsia. The Lancet, 2021. 398(10297): p. 341-354.
2. American College of Obstetricians Gynecologists, Task Force on Hypertension in Pregnancy Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' task force on hypertension in pregnancy. Obstet Gynecol, 2013. 122(5): p. 1122-1131.
3. Poon, L.C., et al., *A literature review and best practice advice for second and third trimester risk stratification, monitoring, and management of pre-eclampsia: Compiled by the Pregnancy and Non-Communicable Diseases Committee of FIGO (the International Federation of Gynecology and Obstetrics).* 2021.
4. Mol, B.W.J., et al., *Pre-eclampsia.* The Lancet, 2016. **387**(10022): p. 999-1011.
5. Fox, R., et al., *Preeclampsia: Risk Factors, Diagnosis, Management, and the Cardiovascular Impact on the Offspring.* Journal of clinical medicine, 2019. **8**(10): p. 1625.
6. Lowe, S.A., et al., *SOMANZ guidelines for the management of hypertensive disorders of pregnancy 2014.* Australian and New Zealand Journal of Obstetrics and Gynaecology, 2015. **55**(5): p. e1-e29.
7. Agrawal, S., et al., *Meta-analysis and systematic review to assess the role of soluble FMS-like tyrosine kinase-1 and placenta growth factor ratio in prediction of preeclampsia: the SaPPPhirE study.* Hypertension, 2018. **71**(2): p. 306-316.
8. Campos, A., et al., *sFlt-1/PlGF ratio for the predictive diagnosis of preeclampsia: budget impact analysis from the public healthcare perspective in Portugal sFlt-1/PIGF no diagnóstico preditivo de pré-eclâmpsia: estudo de impacto económico em Portugal.* Acta Obstet Ginecol Port, 2019. **13**(2): p. 82-90.
9. Benzing, T., *Testing for pre-eclampsia: paving the way to early diagnosis.* Nature Reviews Nephrology, 2016. **12**(4): p. 200-202.
10. Ananth, C.V., K.M. Keyes, and R.J. Wapner, *Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis.* Bmj, 2013. **347**.
11. Thornton, C., et al., *The incidence of preeclampsia and eclampsia and associated maternal mortality in Australia from population-linked datasets: 2000-2008.* American journal of obstetrics and gynecology, 2013. **208**(6): p. 476. e1-476. e5.
12. AIHW, H.M., Bonello MR, Chughtai A, Macaldowie A, Harris K & Chambers GM, *Maternal deaths in Australia 2008–2012*, Australian Institute of Health and Welfare, Editor. 2015, AIHW: Canberra.
13. Queensland Clinical Guidelines, *Hypertension and pregnancy*, Queensland Clinical Guidelines Steering Committee and Statewide Maternity and Neonatal Clinical Network (Queensland), Editor. 2021, Queensland Health: Online.
14. Levine, R.J., et al., *Circulating Angiogenic Factors and the Risk of Preeclampsia.* New England Journal of Medicine, 2004. **350**(7): p. 672-683.
15. Agrawal, S., et al., *Predictive performance of PlGF (placental growth factor) for screening preeclampsia in asymptomatic women: a systematic review and meta-analysis.* Hypertension, 2019. **74**(5): p. 1124-1135.
16. National Institute for Health and Care Excellence, *Hypertension in pregnancy: diagnosis and management*, in *NICE guideline*. 2019, National Institute for Health and Care Excellence: Online.
17. Bartsch, E., et al., *Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies.* Bmj, 2016. **353**.
18. De Kat, A.C., et al., *Prediction models for preeclampsia: A systematic review.* Pregnancy Hypertension, 2019. **16**: p. 48-66.

19. Judd, F., et al., *Adverse obstetric and neonatal outcomes in women with severe mental illness: to what extent can they be prevented?* Schizophrenia Research, 2014. **157**(1-3): p. 305-309.
20. Perez-Cuevas, R., et al., *Critical pathways for the management of preeclampsia and severe preeclampsia in institutionalised health care settings.* BMC pregnancy and childbirth, 2003. **3**(1): p. 6-6.
21. Andersen, L.L.T., et al., *Decision Threshold for Kryptor sFlt-1/PlGF Ratio in Women With Suspected Preeclampsia: Retrospective Study in a Routine Clinical Setting.* Journal of the American Heart Association, 2021. **10**(17): p. e021376.
22. Figueira, S.F., et al., *Economic evaluation of sFlt-1/PlGF ratio test in pre-eclampsia prediction and diagnosis in two Brazilian hospitals.* Pregnancy Hypertension, 2018. **13**: p. 30-36.
23. North, R.A., et al., *Clinical risk prediction for pre-eclampsia in nulliparous women: development of model in international prospective cohort.* Bmj, 2011. **342**.
24. Duley, L. *The global impact of pre-eclampsia and eclampsia*. in *Seminars in perinatology*. 2009. Elsevier.
25. National Institute for Health and Care Excellence, *PlGF-based testing to help diagnose suspected preeclampsia (Triage PlGF test, Elecsys immunoassay sFlt-1/ PlGF ratio, DELFIA Xpress PlGF 1-2-3 test, and BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio)*, in *Diagnostics guidance*, National Institute for Clinical Excellence, Editor. 2016, NICE: UK.
26. Duhig, K., B. Vandermolen, and A. Shennan, *Recent advances in the diagnosis and management of pre-eclampsia.* F1000Research, 2018. **7**: p. 242-242.
27. Brown, M.A., et al., *Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice.* Hypertension, 2018. **72**(1): p. 24-43.
28. Stepan, H., et al., *Implementation of the sFlt-1/PlGF ratio for prediction and diagnosis of pre-eclampsia in singleton pregnancy: implications for clinical practice.* Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology, 2015. **45**(3): p. 241-246.
29. Cerdeira, A.S., et al., *Randomized Interventional Study on Prediction of Preeclampsia/Eclampsia in Women With Suspected Preeclampsia.* Hypertension, 2019. **74**(4): p. 983-990.
30. Karumanchi, A., *Angiogenic Factors in Preeclampsia.* Hypertension, 2016. **67**(6): p. 1072-1079.
31. Lam, C., K.-H. Lim, and S.A. Karumanchi, *Circulating Angiogenic Factors in the Pathogenesis and Prediction of Preeclampsia.* Hypertension, 2005. **46**(5): p. 1077-1085.
32. Zeisler, H., et al., *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 in Obstetrics & Gynecology, 2019. **53**(3): p. 367-375.
33. Steinberg, G., E.V. Khankin, and S.A. Karumanchi, *Angiogenic factors and preeclampsia.* Thrombosis Research, 2009. **123**: p. S93-S99.
34. Maynard, S.E., et al., *Circulating angiogenic factors in singleton vs multiple-gestation pregnancies.* American Journal of Obstetrics and Gynecology, 2008. **198**(2): p. 200.e1-200.e7.
35. Maynard, S.E. and S.A. Karumanchi, *Angiogenic factors and preeclampsia.* Seminars in nephrology, 2011. **31**(1): p. 33-46.
36. Powe, C.E., R.J. Levine, and S.A. Karumanchi, *Preeclampsia, a disease of the maternal endothelium: the role of anti-angiogenic factors and implications for later cardiovascular disease.* Circulation (New York, N.Y.), 2011. **123**(24).
37. Widmer, M., et al., *Accuracy of angiogenic biomarkers at ⩽20weeks' gestation in predicting the risk of pre-eclampsia: A WHO multicentre study.* Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health, 2015. **5**(4): p. 330-338.

38. Honigberg, M.C., et al., *Analysis of changes in maternal circulating angiogenic factors throughout pregnancy for the prediction of preeclampsia.* Journal of Perinatology, 2016. **36**(3): p. 172-177.
39. McElrath, T.F., et al., *Longitudinal evaluation of predictive value for preeclampsia of circulating angiogenic factors through pregnancy.* American Journal of Obstetrics and Gynecology, 2012. **207**(5): p. 407.e1-407.e7.
40. Malshe, A.K. and B.M. Sibai, *Angiogenic and Antiangiogenic Markers for Prediction and Risk Classification of Preeclampsia.* Clinical Obstetrics and Gynecology, 2017. **60**(1): p. 134-140.
41. Caillon, H., et al., *Evaluation of sFlt-1/PlGF Ratio for Predicting and Improving Clinical Management of Pre-eclampsia: Experience in a Specialized Perinatal Care Center.* alm, 2017. **38**(2): p. 95-101.
42. Rana, S., et al., *Angiogenic factors and the risk of adverse outcomes in women with suspected preeclampsia.* Circulation, 2012. **125**(7): p. 911-919.
43. Tardif, C., et al., *Angiogenic factors sFlt-1 and PlGF in preeclampsia: Prediction of risk and prognosis in a high-risk obstetric population.* Journal of Gynecology Obstetrics and Human Reproduction, 2018. **47**(1): p. 17-21.
44. Levine, R.J., et al., *Soluble endoglin and other circulating antiangiogenic factors in preeclampsia.* New England Journal of Medicine, 2006. **355**(10): p. 992-1005.
45. Klein, E., et al., *Influence of the sFlt-1/PlGF Ratio on Clinical Decision-Making in Women with Suspected Preeclampsia.* PLOS ONE, 2016. **11**(5): p. e0156013.
46. Wright, D., A. Wright, and K.H. Nicolaides, *The competing risk approach for prediction of preeclampsia.* American Journal of Obstetrics and Gynecology, 2020. **223**(1): p. 12-23.e7.
47. Veisani, Y., et al., *Angiogenic factors and the risk of preeclampsia: A systematic review and meta-analysis.* International journal of reproductive biomedicine, 2019. **17**(1): p. 1-10.
48. Zeisler, H., et al., *Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia.* New England Journal of Medicine, 2016. **374**(1): p. 13-22.
49. MacDonald, T.M., et al., *Clinical tools and biomarkers to predict preeclampsia.* EBioMedicine, 2022. **75**: p. 103780.
50. Poon, L.C. and K.H. Nicolaides, *First-trimester maternal factors and biomarker screening for preeclampsia.* Prenatal Diagnosis, 2014. **34**(7): p. 618-627.
51. Tranquilli, A.L., et al., *The definition of severe and early-onset preeclampsia. Statements from the International Society for the Study of Hypertension in Pregnancy (ISSHP).* Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health, 2013. **3**(1): p. 44-47.
52. Côté, A.-M., et al., *Diagnostic accuracy of urinary spot protein: creatinine ratio for proteinuria in hypertensive pregnant women: systematic review.* Bmj, 2008. **336**(7651): p. 1003-1006.
53. Magee, L.A., et al., *Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy: executive summary.* Journal of Obstetrics and Gynaecology Canada, 2014. **36**(5): p. 416-438.
54. Homer, C.S., et al., *Non-proteinuric pre-eclampsia: a novel risk indicator in women with gestational hypertension.* Journal of hypertension, 2008. **26**(2): p. 295-302.
55. Cnossen, J.S., et al., *Use of uterine artery Doppler ultrasonography to predict pre-eclampsia and intrauterine growth restriction: a systematic review and bivariable meta-analysis.* Cmaj, 2008. **178**(6): p. 701-711.
56. Tan, M., et al., *Comparison of diagnostic accuracy of early screening for pre-eclampsia by NICE guidelines and a method combining maternal factors and biomarkers: results of SPREE.* Ultrasound in Obstetrics & Gynecology, 2018. **51**(6): p. 743-750.
57. Sibai, B., G. Dekker, and M. Kupferminc, *Pre-eclampsia.* The Lancet, 2005. **365**(9461): p. 785-799.

58. Frampton, G.K., et al., *Placental growth factor (alone or in combination with soluble fms-like tyrosine kinase 1) as an aid to the assessment of women with suspected pre-eclampsia: systematic review and economic analysis.* Health Technol Assess, 2016. **20**(87): p. 1-160.
59. Dröge, L.A., et al., *Prediction of preeclampsia-related adverse outcomes with the sFlt-1 (soluble fms-like tyrosine kinase 1)/PlGF (placental growth factor)-ratio in the clinical routine: a real-world study.* Hypertension, 2021. **77**(2): p. 461-471.
60. Chantraine, F., et al., *Enhancing the value of the sFlt-1/PlGF ratio for the prediction of preeclampsia: Cost analysis from the Belgian healthcare payers' perspective.* Pregnancy Hypertension, 2021. **26**: p. 31-37.
61. Rana, S., et al., *Circulating Angiogenic Factors and Risk of Adverse Maternal and Perinatal Outcomes in Twin Pregnancies With Suspected Preeclampsia.* Hypertension, 2012. **60**(2): p. 451-458.
62. Chaemsaithong, P., D.S. Sahota, and L.C. Poon, *First trimester preeclampsia screening and prediction.* American Journal of Obstetrics and Gynecology, 2022. **226**(2, Supplement): p. S1071-S1097.e2.
63. Frusca, T., et al., *Budget impact analysis of sFlt-1/PlGF ratio as prediction test in Italian women with suspected preeclampsia.* The Journal of Maternal-Fetal & Neonatal Medicine, 2017. **30**(18): p. 2166-2173.
64. Hodel, M., et al., *sFlt-1/PlGF Ratio as a Predictive Marker in Women with Suspected Preeclampsia: An Economic Evaluation from a Swiss Perspective.* Disease markers, 2019. **2019**: p. 4096847-10.
65. Khosla, K., et al., *Cost effectiveness of the sFlt1/PlGF ratio test as an adjunct to the current practice of evaluating suspected preeclampsia in the United States.* Pregnancy Hypertension, 2021. **26**: p. 121-126.
66. Schnettler, W.T., et al., *Cost and resource implications with serum angiogenic factor estimation in the triage of pre-eclampsia.* BJOG: An International Journal of Obstetrics & Gynaecology, 2013. **120**(10): p. 1224-1232.
67. Hadker, N., et al., *Are there financial savings associated with supplementing current diagnostic practice for preeclampsia with a novel test? Learnings from a modeling analysis from a German payer perspective.* Hypertens. Pregnancy, 2013. **32**(4): p. 105–119.
68. Hadker, N., et al., *Financial impact of a novel pre-eclampsia diagnostic test versus standard practice: a decision-analytic modeling analysis from a UK healthcare payer perspective, J. Med. Econ. 13 (4) (2010) 728–737.* J. Med. Econ., 2010. **13**(4): p. 728-737.
69. Vatish, M., et al., *sFlt-1/PlGF ratio test for pre-eclampsia: an economic assessment for the UK.* Ultrasound in Obstetrics & Gynecology, 2016. **48**(6): p. 765-771.
70. Ohkuchi, A., et al., *Economic evaluation of the sFlt-1/PlGF ratio for the short-term prediction of preeclampsia in a Japanese cohort of the PROGNOSIS Asia study.* Hypertension Research, 2021. **44**(7): p. 822-829.

Appendix

Clinical management practices for women diagnosed with PE

The commonly used clinical management practices for women diagnosed with PE are discussed below

According to Queensland Clinical Guidelines [13], the management of patients diagnosed with PE should involve:

1. Liaison with consultant obstetrician, obstetric physician, physician and/or haematologist and anaesthetist
    - Contact other facilities/services if necessary
2. If greater than 34+0 weeks gestation and/or condition deteriorating, plan birth
    - Consider antenatal corticosteroids; however, urgent delivery should not be delayed purely for the benefit of the administration.
3. Magnesium sulphate infusion may be indicated.
4. Consider platelet transfusion if:
    - Thrombocytopenia presents a hazard to operative birth or
    - There is significant bleeding postpartum attributable to pre-eclamptic thrombocytopenia

Women diagnosed with PE should be assessed at each consultation by a healthcare professional trained in the management of hypertensive disorders of pregnancy and offered an integrated package of care that includes admission, testing and treatment that relates to the severity of hypertension. Tables 1A and 2A report the current clinical management of women with PE.

Table 1A: Management and tests for women diagnosed with moderate to severe PE

Gestational age	**Clinical management**
<23 weeks	Consider expectant management or discontinuation of pregnancy
23–28 weeks	Consider options depending on the limit of viability.
28–34 weeks	Offer expectant management • Monitor for severe features • Regular blood tests† (1–2 a week) • Ultrasound every 2 weeks or more frequently if indicated (eg, the presence of coexisting fetal growth restriction) • Consider regular cardiotocograph
34–37 weeks	Consider delivery or expectant management. Do not offer planned early birth before 37 weeks to women with chronic hypertension whose blood pressure is lower than 160/110 mmHg.
>37 weeks	Offer planned birth within 24–48 h. For women with chronic hypertension whose blood pressure is lower than 160/ 110 mmHg after 37 weeks, with or without antihypertensive treatment, timing of birth and maternal and fetal indications for birth should be agreed between the woman and the senior obstetrician
Key treatments	**Recommended actions**
Monitoring blood pressure	Regardless of the hypertensive disorder of pregnancy, blood pressure requires urgent treatment in a monitored setting when severe (>160/110 mmHg); acceptable agents for this include oral nifedipine or intravenous labetalol or hydralazine. BPs consistently at or >140/90 mm Hg in clinic or office (or ≥135/85 mm Hg at home) should be treated, aiming for a target diastolic BP of 85 mm Hg in the office (and systolic blood pressure of 110–140 mmHg) to reduce the likelihood of developing severe maternal hypertension and other complications

Gestational age	Clinical management
Care setting	Women with PE should be assessed in hospital when first diagnosed; thereafter, some may be managed as outpatients once it is established that their condition is stable, and the patient has the ability to report problems and monitor their BP.
Use of magnesium sulfate	Women with PE who have proteinuria and severe hypertension, or hypertension with neurological signs or symptoms, should receive magnesium sulfate (MgSO4) for convulsion prophylaxis.
Fetal monitoring	This should include an initial assessment to confirm fetal well-being. In the presence of fetal growth restriction, a recommended schedule for serial fetal surveillance with ultrasound is detailed within these recommendations
Maternal monitoring	should include blood pressure monitoring, repeated assessments for proteinuria if it is not already present, clinical assessment including clonus, and a minimum of twice weekly blood tests for hemoglobin, platelet count, and tests of liver and renal function.
Delivery	Should initiate delivery if they have reached 37 weeks' (and zero days) gestation or if they develop any of the following: • Repeated episodes of severe hypertension despite maintenance treatment with 3 classes of antihypertensive agents; • Progressive thrombocytopenia; • Progressively abnormal renal or liver enzyme tests; • Pulmonary edema; • Abnormal neurological features, such as severe intractable headache, repeated visual scotomata, or convulsions; • Nonreassuring fetal status.

Source: Compiled during PICO evaluation from [4]; [1]; [26];[16] and [27].

Abbreviations: mg/mmol = micrograms per millimole; mmHg = millimetres of mercury.

Table 2A: Tests and management of women with PE - NICE guidelines

Degree of hypertension	Mild (140/90 mmHg to 149/ 99 mmHg)	Moderate (150/100 mmHg to 159/ 109 mmHg)	Severe (160/110 mmHg or higher)
Admit to hospital	Yes	Yes	Yes
Treat	No	With oral labetalol as first-line treatment	With oral labetalol as first-line treatment
Measure blood pressure	At least 4 times a day	At least 4 times a day	More than 4 times a day
Test for proteinuria	Do not repeat quantification of proteinuria	Do not repeat quantification of proteinuria	Do not repeat quantification of proteinuria
Blood tests	Monitor the following twice a week: kidney function, bilirubin, electrolytes, full blood count, transaminases	Monitor the following 3 times a week: kidney function, bilirubin, electrolytes, full blood count, transaminases	Monitor the following 3 times a week: kidney function, bilirubin, electrolytes, full blood count, transaminases

Source: Compiled during PICO evaluation from [25].

Abbreviations: mg/mmol = micrograms per millimole; mmHg = millimetres of mercury.