Australian Government

Department of Health

MSAC Application 1705

Structured Prenatal Risk Assessment for Preterm 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 structured prenatal risk assessment for preterm preeclampsia in early pregnancy

Component	Description
Population	All pregnant women who are 11^{+0} to 13^{+6} weeks' gestation
Prior tests	None required, but a normal dating ultrasound may have occurred (MBS items 55700, 55703)
Intervention	A structured prenatal risk assessment conducted at a specific stage of gestation (between 11^{+0}-13^{+6} weeks') for identifying risk levels of preterm preeclampsia: • Medical history (specific characteristics) • Maternal Mean Arterial Pressure (MAP) • Biochemical measurement of maternal serum concentration of Placental Growth Factor (PlGF) • Ultrasound assessment of uterine perfusion (Doppler measurement of uterine artery pulsatility index) and • Risk computation (high risk [risk≥1% for preterm preeclampsia], or moderate/low risk)[1] Two models of care were proposed for implementation: 1) Ultrasound service risk calculation* and 2) Pathology service risk calculation**
Comparator/s	Current standard of care (involves assessment of risk for preterm preeclampsia through clinical examination and medical history (no formal timelines but typically performed between 8 and 20 weeks' gestation)) Prediction algorithms which are based predominantly on patient characteristics, medical and obstetric history alone: • The National Institute for Health and Care Excellence (NICE)[2], and • The American College of Obstetrics and Gynaecology (ACOG)[3]. The use of PAPP-A instead of PlGF in the FMF model.
Reference standard	Diagnosis of preterm preeclampsia: new onset hypertension (blood pressure ≥140mmHg systolic and/or ≥90mmHg diastolic; (Brown and Lindheimer, 2001)) arising after 20 weeks' gestation and before 37 weeks' gestation, and accompanied by one or more of the following signs of organ involvement (Lowe et al., 2015): • Renal involvement (any of the following: proteinuria – a spot urine protein/creatinine ratio ≥ 30mg/mmol; Serum or plasma creatinine > 90 µmol/L; Oliguria: <80mL/4 hr)

[1] Rolnick, D. L.et al 2017. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. New England Journal of Medicine, 377, 613-622.

[2] National Collaborating Centre for Women's and Children's Health (UK). Hypertension in Pregnancy: The Management of Hypertensive Disorders During Pregnancy. London: RCOG Press, 2010 (updated 2019).

[3] American College of Obstetricians and Gynecologists. Gestational hypertension and preeclampsia. ACOG Practice Bulletin No. 222. Obstet Gynecol 2020; 135: e237 – e244.

* Model 1: Ultrasound service risk calculation: medical history conducted by an ultrasonographer; mean arterial blood pressure measured by an ultrasonographer or phlebotomist; and collation of investigation findings and calculation of risk for preterm preeclampsia carried out by an ultrasonographer.

** Model 2: Pathology laboratory service risk calculation : medical history conducted by an ultrasonographer; mean arterial blood pressure measured by an ultrasonographer or phlebotomist; and collation of investigation findings and calculation of risk for preterm preeclampsia carried out by pathology staff.

Component	Description
	• Haematological involvement (any of the following: Thrombocytopenia <100,000 /µL; Haemolysis: schistocytes or red cell fragments on blood film, raised bilirubin, raised lactate dehydrogenase >600mIU/L, decreased haptoglobin; Disseminated intravascular coagulation) • Liver involvement (any of the following: Raised serum transaminases; Severe epigastric and/or right upper quadrant pain). • Neurological involvement (any of the following: Convulsions (eclampsia)); Hypereflexia with sustained clonus; Persistent new headache; Persistent visual disturbances (photopsia, scotomata, cortical blindness, posterior reversible encephalopathy syndrome, retinal vasospasm); Stroke • Pulmonary oedema • Fetal growth restriction (FGR)
Outcomes	**Safety outcomes:** • Adverse events associated with test • Anxiety associated with the finding of increased risk of PE • Adverse events associated with treatment **Clinical effectiveness outcomes** • Reduction in incidence and severity of preterm preeclampsia • Uptake of preeclampsia prophylaxis treatment based on risk assessment • Preeclampsia related maternal outcomes (e.g. eclamptic fit, renal and hepatic impairment, HELLP syndrome, placental abruption, etc) • Preeclampsia related preterm birth/gestational age at birth • Preeclampsia related adverse neonatal outcomes (morbidity and mortality) **Test accuracy & clinical utility** • Diagnostic accuracy (Sensitivity, Specificity, Negative Predictive Value (NPV), Positive Predictive Value (PPV)) • Diagnostic yield among the test population (number of high risk patients identified) **Health care resources:** • Total number of services and cost of the testing program • Number and cost of additional medical practitioner consultations (e.g., pre-test and post-test follow-up, monitoring, etc) • Number and reduction of cost in treatment • Reduction in maternal admissions to intensive care • Reduction in admissions to NICU or special care **Cost-effectiveness:** • Cost per high risk patients identified (before cost offset) • Cost per high risk patients identified (with cost offsets) • Cost per quality-adjusted life years **Total Australian Government health care costs:** • Total cost to the Medicare Benefits Schedule (MBS), Pharmaceutical Benefits Scheme (PBS) and other government health budgets.
Assessment questions	What is the safety, effectiveness and cost-effectiveness of structured prenatal risk assessment for preterm preeclampsia versus the current standard of care in women in the early stage of pregnancy (between 11^{+0} and 13^{+6} weeks' gestation)?

Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of Structured prenatal risk assessment for preterm preeclampsia to be used as a screening tool in asymptomatic populations and to provide information about prognosis was received from Professor REDACTED/Roche by the Department of Health.

The clinical claim is that the use of a structured prenatal risk assessment for predicting preterm preeclampsia to be used as a screening tool in asymptomatic populations results in superior health outcomes compared to the comparator/standard practice which involves the assessment of risk for preterm preeclampsia through taking a medical history.

PICO criteria

Population

The proposed target population for a structured preterm preeclampsia risk assessment is all pregnant women at 11^{+0} to 13^{+6} weeks' gestation (this is the same time at which it is already recommended that all pregnant women are offered an aneuploidy screen (HGSA/RANZCOG Joint Committee, 2015).

PASC confirmed the population to be all pregnant women who are at 11^{+0} to 13^{+6} weeks' gestation.

Definition and burden of disease

Preeclampsia is a pregnancy specific condition that affects multiple organ systems. It is most typically defined as a condition with new onset elevated blood pressure (above 140mmHg systolic and/or 90mmHg diastolic) combined with functional maternal anomalies in at least one of:

- renal, hepatic, haematological, neurological or respiratory systems or
- evidence of progressively worsening placental insufficiency and fetal growth restriction or risk of in utero death (Lowe SA et al., 2014).

Once preeclampsia develops it becomes progressively worse until delivery. Preterm preeclampsia occurring before 37 weeks' gestation commonly represents a more severe and complicated form of preeclampsia than preeclampsia occurring at term, that causes more cardiovascular morbidity for mothers in later life (Von Dadelszen et al., 2003).

Preeclampsia has been identified as being severe (blood pressure ≥160mmHg systolic and/or 110mmHg diastolic) or mild/moderate (140-159mmHg systolic and/or 90-109mmHg diastolic)(Visintin et al., 2010) or as preeclampsia with severe features where one or more of the following apply (American College of Obstetricians and Gynecologists, 2020):

- Systolic blood pressure of 160 mm Hg or more, or diastolic blood pressure of 110 mm Hg or more on two occasions at least 4 hours apart (unless antihypertensive therapy is initiated before this time)
- Thrombocytopenia (platelet count less than 100,000 × 109/L)
- Impaired liver function that is not accounted for by alternative diagnoses and as indicated by abnormally elevated blood concentrations of liver enzymes (to more than twice the upper limit normal concentrations), or by severe persistent right upper quadrant or epigastric pain unresponsive to medications

- Renal insufficiency (serum creatinine concentration more than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease)
- Pulmonary edema
- New-onset headache unresponsive to medication and not accounted for by alternative diagnoses
- Visual disturbances

Preeclampsia can also be defined as early (develops before <34 weeks' gestation) or late (develops at or after 34 weeks' gestation) in onset (Raymond and Peterson, 2011). Based on (Park et al., 2013), 2.8% of pregnant women experience preeclampsia and approximately 0.7% of pregnant women developed pre-term preeclampsia in the ASPRE trial (Rolnik et al., 2017a).

Although the aetiology of preeclampsia is not fully understood, both the placenta and the maternal endothelium are centrally involved in the pathophysiology of the disease (Chaiworapongsa et al., 2014). The majority of cases that are severe and lead to early (<34 weeks' gestation) delivery are associated with placental insufficiency. Poor implantation causes placental hypoxia, altering release of angiogenic factors that impact both placental development and the maternal endothelium (Chaiworapongsa et al., 2014). 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 of preeclampsia is associated with further angiogenic dysregulation and exacerbation of disease. The health and wellbeing of the patient will continue to decline up to a point where the fetus and placenta are delivered. The identification of pre-clinical and clinical stages of disease provide an opportunity for identification of women at high risk and for intervention before a woman and her fetus become significantly affected.

Preeclampsia causes significant maternal and fetal mortality and morbidity. Mothers that develop preeclampsia may progress to an eclamptic fit and/or other neurological sequelae (such as a cerebrovascular accident), renal and hepatic impairment (Pollock et al., 2020, Thornton et al., 2013). Significant uncontrolled hypertension is also associated with placental abruption and haematological dysfunction can lead to peri- or post-partum haemorrhage.

The disease is the one of the commonest causes of maternal death in pregnancy and globally approximately 60,000 mothers die from the morbidities of preeclampsia each year. Whilst maternal deaths from preeclampsia are rare in Australia, this is partly due to clinical supervision and the decision to deliver the fetuses of women affected by severe preeclampsia to break the pathological cycle of disease (by delivering the placenta). Preterm delivery has a significant impact on the fetus/newborn child and is associated with 500,000 deaths worldwide (Poon et al., 2019). The applicant stated that; approximately 15% of admissions to neonatal intensive care units (NICU) and approximately 1,200 infants are born prematurely (<34 weeks' gestation) in Australia due to maternal preeclampsia each year. Based on the results from Rolnick et al 2017 there is the potential to reduce the incidence of preeclampsia by 80% if prophylactic treatment can be initiated in the at-risk population (Rolnik et al., 2017b).

Up to 20% of women who develop severe preeclampsia will develop a condition called HELLP syndrome characterised by haemolysis, raised liver enzymes (transaminases) and low platelets with or without other pre-eclamptic features (Haram et al., 2009, Lowe SA et al., 2014). Often only two of the three components are present. HELLP may occur in normotensive women but this is atypical. Women who develop preeclampsia during pregnancy have an increased risk of being hypertensive in later life and of other cardiovascular disease and stroke (Arnott et al., 2020). The risk is most significant in those women who have early/severe preeclampsia. Hypertensive disorder of pregnancy carries an increased risk of cardiovascular event (Hazard ratio 2.56; 95% CI; (2.21, 2.96)) compared to smoking alone (HR 1.56; 95%CI

(1.33, 1.84)) (Arnott et al., 2020). Preterm birth is also associated with increased risks for the infant and child. This includes neurodevelopmental disability, increased special educational needs and ongoing cardiovascular, respiratory and metabolic disease (Marlow et al., 2005).

Population size expected to use proposed health technology

The applicant presented data from the Hunter New England Local Health District (HNELHD) patient database which found that 89.26% of pregnant women had visited a general practitioner (GP) prior to 14^{+0} weeks' gestation (Park et al., 2021). It was assumed that all of these presentations would lead to preeclampsia screening; this seems reasonable but may slightly overestimate uptake. The estimated eligible population based on the number of births in 2019 is slightly higher than 2020 and doesn't take into account multiplicity. The estimated eligible population size has been adjusted to accommodate this (the projections have been assumed to be steady for the next 5 years as prior to 2019 COVID pandemic births were increasing, but have decreased since then). These estimates may need to be refined during the development of the assessment report.

Table 2 Estimated eligible population size and 3-year utilisation estimates

Item	Year 1	Year 2	Year 3	*Year 4*	*Year 5*
Births per year (ABS, 2021b)	*294,369*	*294,369*	*294,369*	*294,369*	*294,369*
Number of confinements (ABS, 2021a)	*290,272*	*290,272*	*290,272*	*290,272*	*290,272*
Uptake	89.26%	89.26%	89.26%	89.26%	89.26%
Risk assessment utilisation per year	*259,097*	*259,097*	*259,097*	*259,097*	*259,097*
Cumulative utilisation	*259,097*	*518,194*	*777,290*	*1,036,387*	*1,295,484*

Source: Constructed during development of the PICO based on estimates provided in p27 of Application form

Intervention

The proposed health technology is a risk algorithm and its clinical components which together are an investigative screening tool for preterm preeclampsia. The clinical factors are all entered into a computer risk algorithm that calculates a risk for preterm preeclampsia. This risk is interpreted (high risk or low risk) and reported to the referring clinician. This technology will also provide relevant information about prognosis. All pregnant women will be screened only once within the gestational window of the 11^{+0} to 13^{+6} week when the intervention (preeclampsia prophylaxis) is deemed the most useful. The applicant recommends that the screening for preeclampsia can be conducted in tandem with first trimester screening for common forms of chromosomal abnormality.

PASC noted the applicant's advice that pre– and post- test counselling is currently included in the service model.

PASC noted that noninvasive prenatal testing (NIPT) does not impact this intervention.

The applicant states that the proposed algorithm, Fetal Medicine Foundation (FMF) algorithm (Fetal Medicine Foundation, 2021)[4], is the risk algorithm used by most Australian centres that offer combined first trimester screening. The algorithm has been made available by FMF to a number of commercial ultrasound reporting software providers including the Astraia and Viewpoint products commonly used in

[4] https://www.fetalmedicine.org/research/assess/preeclampsia/first-trimester

Australia to generate risks for first trimester screening for aneuploidy. The risk calculator is also freely available to use online through the FMF website. The risk calculator outputs a risk calculation, with a risk of 1 in 100 (1%) considered to be high risk (Rolnik et al., 2017b)

PASC considered that the applicant needed to provide evidence that the protocol prescribed by the Fetal Medicine Foundation (FMF) for determining MAP was superior to the standard procedure recommended by professional bodies such as the National Heart Foundation of Australia (NHFA) or the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ).

There are other risk calculators available that were not included in the application (e.g., Predictor®Software by PerkinElmer (PerkinElmer, 2015), Wolfson Institute of Preventative Screening (Wald et al., 2012) and Medicina Fetal Barcelona (Gratacos, 2020)). The aforementioned algorithms use similar approaches to the FMF algorithm though can include additional biomarkers; Medicina Fetal Barcelona includes sEng, Inhibin A and PP13, and Predictor®Software includes PP13. The applicant suggests that a similar stance that was taken for aneuploidy be applied for preeclampsia in that a variety of algorithms can be used provided their performance has been validated in an Australian population. This is based on a similar stance taken in the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) statement for aneuploidy which accepts all tests that have been demonstrated to perform above a level of screening efficacy (70% detection for a 5% screen positive rate) (HGSA/RANZCOG Joint Committee, 2015). However, the application only provided evidence for the FMF algorithm, and this may need to be addressed in the assessment report.

<u>The risk algorithm screening tool requires several key components to assess risk:</u>

Medical history – Details of maternal characteristics, medical history and obstetric history are collected and entered into a computer system so that precise likelihood ratios can be developed for each factor (rather than the current binary scoring system). These maternal features are used to generate an individualised 'a priori' risk.

- Pregnancy type (singleton or multiple)
- Pregnancy dating (fetal crown-rump length, examination date)
- Maternal characteristics (age, height, weight, ethnicity, smoking history, conception [spontaneous, IVF, etc]),
- Maternal medical History (chronic hypertension, diabetes [type I or II], maternal history of PE, systemic lupus erythematosus, anti-phospholipid syndrome, obstetric history [nulliparous/parous]).

Maternal mean arterial pressure – Maternal blood pressure is measured using a prescribed standardised protocol: positioning the rested patient appropriately and measuring blood pressure (if an electronic sphygmomanometer is used, it must be suitable for pregnancy). Two measurements are made in each arm. The mean value of these measures, the mean arterial pressure, is calculated for each arm using MAP = (SBP +2xDBP)/3 (most electronic BP machines report this as well as systolic and diastolic BP) and the average of the four calculations is recorded.

Mean uterine artery pulsatility index – The uterine arteries (left and right) are identified using ultrasound (either transabdominal or transvaginal) on the lateral aspect of the cervix at the level of the internal cervical os – using a standardised protocol. Measurement of these Doppler indices uses a standardised

technique by appropriately trained sonographers and needs to be reported by an appropriately trained radiologist/sonologist. The mean uterine artery pulsatility index is recorded.

Measurement of maternal serum placental growth factor (PlGF) – The maternal serum concentration of PlGF is measured using a standard biochemical assay, and expressed as multiples of the median value (MoM). The MoM depends on several factors including the assay platform (known to the pathology laboratory, but not necessarily to the referring clinician), and maternal factors such as gestational age, obesity, smoking history (known to the clinician, but not necessarily to the pathology laboratory).

Practical and Pragmatic Implementation:

As there are a number of different models of maternity care and a number of different models of access to ultrasound imaging and pathology testing, the applicant recommended a pragmatic approach to the introduction of the proposed screening program that would enable women to access components of the test and their risk result in an easy manner. The applicant noted that all 11^{+0} to 13^{+6} week referrals are made by general practitioners (GPs) as GP visits occur prior to allocation to maternity service model of care in each state.

The applicant proposes two potential models for implementation: 1) Ultrasound service risk calculation and 2) Pathology laboratory risk calculation. It is important to note that for both models, the GP or maternity service clinician refers patient for (i) BP assessment and fetal growth assessment (surrogate to determine gestational age)/uterine artery Doppler assessment and (ii) for maternal blood draw for PlGF test. Combined first trimester screening for aneuploidy provides a framework for this approach.

Model I: Ultrasound service risk calculation

The PlGF blood test result is reported to the GP/maternity service and the ultrasound service provider by the pathology service provider. The ultrasound service provider collects maternal demographics, maternal mean arterial pressure (alternatively this may be undertaken by the phlebotomist), and completes the ultrasound scan (measurement of gestational age [crown-rump length, CRL] and uterine artery pulsatility index). The ultrasound service also inputs the PIGF data received from the pathology services. The ultrasound service then collates these data in the risk algorithm and reports these to the GP/maternity service and the patient. This reflects, for example, the service model for combined first trimester screening (cFTS) for aneuploidy in NSW and Queensland.

Model II: Pathology laboratory risk calculation

The patient attends the ultrasound clinic, and the ultrasound service provider collects maternal demographics, maternal mean arterial pressure (alternatively this may be undertaken by the phlebotomist), and completes the ultrasound scan (measurement of CRL and uterine artery Doppler). These data are forwarded to the pathology service provider. The patient attends the pathology service for their PlGF blood test. The pathology service then collates these data in the risk algorithm and reports these to the GP/maternity service. This reflects, for example, the service model for cFTS for aneuploidy in Victoria and SA.

In both models the patient returns to the GP/maternity service who is responsible for discussing risk and for ongoing pregnancy management. There is a risk that either the ultrasound or pathology service will not receive the required PlGF blood test result or uterine artery pulsatility index from the appropriate service

in time and the risk calculation would therefore need to be conducted by the GP/maternity service provider.

PASC considered that measurement of BP (and hence calculation of MAP) should be considered as an integral part of routine antenatal care by the GP, obstetrician or midwife and it was therefore unclear why this measurement should be undertaken by an ultrasonographer or phlebotomist, or why it should attract a separate fee.

PASC had concerns about the MAP being performed during the appointment for the ultrasound examination or during attendance for phlebotomy as (i) BP measurement obtained in either of these unfamiliar and potentially stressful settings may not be valid and (ii) this would create interruptions to workflows of the ultrasound or phlebotomy services especially given that neither of these services are likely to be restricted to obstetric services.

PASC requested that if the scoring of risk is to be carried out by pathology or ultrasonography staff, how this is implemented in practice needs to be clarified, so that it is generalisable throughout Australia.

PASC considered that the applicant needs to justify why each element of the intervention is needed, e.g. PlGF vs. PAPP-A (which is already MBS funded under item 66750), and why each element should be funded separately under the MBS. In addition, PASC considered that alternative models of implementing the proposed intervention need to be considered, in particular a more clinician-led model. This would ensure that one model of care is demonstrated to be superior to another. PASC considered that as the proposal is requesting substantial changes to the way the MBS is presented, there needs to be clear justification for those items that are requested. PASC also noted that some service components (e.g. medical history and MAP) of the intervention could be unbundled to be covered by existing services or amendments to existing services (e.g. item 55707).

PASC queried whether a clinician led model should be used to obtain history, conduct MAP and compile the results in the multifactorial algorithm (rather than the proposed models of care).

<u>Other relevant considerations</u>

Training standard

To ensure that each measured variable (mean arterial pressure, uterine artery pulsatility index (PI) and biomarker PlGF) are measured to an appropriate standard, it is imperative that the assessments are conducted by trained members of medical staff. For example, uterine artery PI is assessable by a trained sonographer/sonologist. It important to note that the appropriate training standard is currently available through the RANZCOG Nuchal Translucency Ultrasound and Education Monitoring Program (RANZCOG NTUEMP). PlGF is a routine biomarker measured in a number of biochemistry laboratories, and is already widely available in Australia.

PASC suggested that appropriate training and a quality assurance system would need to be implemented and approved to ensure that measurements of the uterine artery pulsatility index are carried out appropriately by ultrasonographers and – if approved – MAP measurements are carried out correctly by ultrasonographers or phlebotomists.

Setting for conducting the test

This is a population-based screening test available to both public and private patients and the test can be performed in an outpatient setting, therefore it does not require inpatient admission. However, the biochemical component of the test is to be performed in a laboratory.

Comparator(s)

The current standard of care for the assessment of risk for preterm preeclampsia is based on clinical assessment of maternal characteristics and medical history (no formal timelines but typically done between 8 and 20 weeks' gestation). Clinicians use assessment tools recommended by NICE (National Collaborating Centre for Women's Children's Health, 2010) or the American College of Obstetrics and Gynaecology (ACOG) (American College of Obstetricians and Gynecologists, 2020) , which outline the following risk factors for preeclampsia (National Collaborating Centre for Women's Children's Health, 2010):

- *High risk factors for preeclampsia include:* Previous preeclampsia; Chronic hypertension; Chronic renal disease; Diabetes Mellitus; and Maternal systemic lupus erythematosus (SLE) or antiphospholipid syndrome.

- *Moderate risk factors include:* First ongoing pregnancy; Maternal age >35 years; Maternal BMI >30kg/m^2; Interpregnancy interval >10 years; Family history of preeclampsia; non-Caucasian background or lower socioeconomic status.

The applicant states that the current standard of care has poor sensitivity and specificity and that there is data to show that this approach has been ineffective in modifying the prevalence of this disease. Additionally the applicant stated that it is not cohesively applied in clinical practice (due to lack of framework for application) and is typically not completed at an appropriate gestation to optimise the effect of prophylactic treatment. The applicant also stated that the intervention should be the sole screening tool and the new test would become standard of care for all pregnant women.

However, this may not be the case in practice, as it is likely that practitioners that are used to assessing risk for preterm preeclampsia in their patients would use the risk algorithm as an additional screening test. If a clinician is comfortable with their assessment that a patient is at high risk of preterm preeclampsia they may initiate treatment and not refer patients for screening. This may affect the overall sensitivity, specificity, NPV and PPV of the test in practice as the testing population will have a lower prevalence of preterm preeclampsia than the general population; this should be explored in the assessment report.

PASC queried whether pregnant women assessed at high risk for preeclampsia by standard of care would also require the intervention but noted that there may be some benefits to high risk patients receiving the proposed service.

PASC noted that as the intervention is composed of individual elements and these are proposed to be delivered through various models of care, standard care for each of those elements needs to be the comparator.

PASC considered that the standard risk assessment tools recommended by NICE and the American College of Obstetrics and Gynaecology (ACOG) for preterm preeclampsia through clinical examination and medical history should also be explicitly defined as comparators.

Currently PAPP-A assessment is reimbursed in MBS item 66750 as a component of the first trimester aneuploidy risk assessment. PAPP-A may also be used to assess the risk for PE. PASC considered that MBS-

reimbursed PAPP-A (in conjunction with maternal history, MAP +/- uterine artery pulsatility index) should be considered a valid comparator for the proposed PlGF measurement, and the evaluation should include a cost-effectiveness analysis of measuring PAPP-A vs. PlGF (vs. both).

Table 3 PASC suggested additional comparisons for the proposed intervention models of care

Intervention	***Comparator***
Medical history conducted by a sonographer.	*Medical history obtained by a health professional (e.g. midwife, GP, obstetrician) responsible for the care of the individual.*
Mean arterial blood pressure measured by a sonographer or phlebotomist.	*Mean arterial blood pressure measured by a health professional (e.g. midwife, GP, obstetrician) responsible for the care of the individual.*
Collation of investigation findings and calculation of risk for preterm preeclampsia carried out by a pathologist/ultrasound provider (depending on the delivery model).	*Collation of investigation findings and calculation of risk for preterm preeclampsia carried out by a health professional (e.g. midwife, GP, obstetrician) responsible for the care of the individual.*

Items currently used to assess preterm preeclampsia risk

There are several antenatal item numbers that could be used currently to assess preterm preeclampsia (16400, 16401, 16404, 16500, 91850, 91853, 91855, 91858, 82100, 82105, 82110, 91211, 91212, 91218, 91219) Item 16400 is presented below, for the full description of each item see Appendix 1: Existing MBS items.

Category 1 (Professional Attendances) –
MBS item 16400 ANTENATAL CARE Antenatal service provided by a midwife, nurse or an Aboriginal and Torres Strait Islander health practitionerif: (a) the service is provided on behalf of, and under the supervision of, a medical practitioner; (b) the service is provided at, or from, a practice location in a regional, rural or remote area; (c) the service is not performed in conjunction with another antenatal attendance item (same patient, same practitioner on the same day); (d) the service is not provided for an admitted patient of a hospital; and to a maximum of 10 service per pregnancy
Fee: $28.35 Benefit: 85% = $24.10

Reference standard (for investigative technologies only)

PASC considered that the reference standard should include a more detailed definition of preeclampsia that incorporated multi-organ assessment, such as proteinuria, along with hypertension and this has been updated in the text and PICO.

PASC considered that the types of pre-eclampsia predicted and potentially averted by aspirin prophylaxis need to be clearly defined, i.e.:

- *very early-onset PE – with delivery at <32 weeks' gestation*
- *early-onset PE – with delivery at <34 weeks' gestation*
- *late-onset PE- with delivery at ≥34 weeks' gestation*
- *pre-term PE – with delivery at <37 weeks' gestation (the primary end-point of the ASPRE trial)*
- *term PE – with delivery at ≥37 weeks' gestation since the adverse consequences of delivery at each of these gestational ages will differ.*

A diagnosis of preeclampsia can be made when new onset hypertension (blood pressure ≥140mmHg systolic and/or ≥90mmHg diastolic; (Brown and Lindheimer, 2001)arises after 20 weeks' gestation and is accompanied by one or more of the following signs of organ involvement (Lowe et al., 2015):

- Renal involvement (any of the following: proteinuria – a spot urine protein/creatinine ratio ≥ 30mg/mmol; Serum or plasma creatinine > 90 µmol/L; Oliguria: <80mL/4 hr)
- Haematological involvement (any of the following: Thrombocytopenia <100,000 /µL; Haemolysis: schistocytes or red cell fragments on blood film, raised bilirubin, raised lactate dehydrogenase >600mIU/L, decreased haptoglobin; Disseminated intravascular coagulation)
- Liver involvement (any of the following: Raised serum transaminases; Severe epigastric and/or right upper quadrant pain).
- Neurological involvement (any of the following: Convulsions (eclampsia); Hypereflexia with sustained clonus; Persistent, new headache; Persistent visual disturbances (photopsia, scotomata, cortical blindness, posterior reversible encephalopathy syndrome, retinal vasospasm); Stroke
- Pulmonary oedema
- Fetal growth restriction (FGR)

Outcomes

*PASC considered that one of the proposed clinical effectiveness outcomes 'Preterm birth/gestational age at birth' should be amended to be '**Preeclampsia-related** preterm birth/gestational age at birth.'*

Safety outcomes

Outcomes that relate to the direct safety of the health technology or comparator:

- Adverse events associated with test
- Anxiety associated with the finding of increased risk of PE
- Adverse events associated with treatment

Clinical effectiveness

- Reduction in incidence and severity of early or preterm preeclampsia
- Uptake of prophylactic aspirin based on risk assessment
- Preeclampsia related maternal morbidity and mortality outcomes (e.g. hypertension, eclamptic fit, renal and hepatic impairment, HELLP syndrome, placental abruption, etc)
- Preeclampsia related preterm birth/gestational age at birth
- Preeclampsia related neonatal outcomes (morbidity and mortality, see below)

Test accuracy & clinical utility

- Diagnostic accuracy (Sensitivity, Specificity, Negative Predictive Value (NPV), Positive Predictive Value (PPV))
- Diagnostic yield among the test population (number of high risk patients identified)

Health care resources:

- Total number of services and cost of the testing program
- Number and cost of additional medical practitioner consultations (e.g., pre-test and post-test follow-up, monitoring, etc)
- Number and reduction of cost in treatment
- Reduction in maternal admissions to intensive care
- Reduction in admissions to NICU or special care

Cost-effectiveness:

- Cost per high risk patients identified (before cost offset)
- Cost per high risk patients identified (with cost offsets)
- Cost per quality adjusted life years

Total Australian Government health care costs:

- Total cost to the Medicare Benefits Schedule (MBS), Pharmaceutical Benefits Scheme (PBS) and other government health budgets

Clinical outcomes associated with preterm preeclampsia.

Structured prenatal risk assessment for preterm preeclampsia facilitates improved clinical management of pregnancies identified as high-risk, or symptomatic of preeclampsia. There are a number of adverse maternal outcomes associated with preterm preeclampsia 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 (Hemolysis, Elevated Liver enzymes and Low Platelets)
- placental abruption

Preterm preeclampsia is also associated with preterm birth which increases risks of numerous neonatal outcomes that should also be explored.

The most commonly reported adverse outcomes, which predominately affect babies < 32 weeks' gestation when preeclampsia are 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 pathology typically arising from IVH
- Necrotising enterocilitis – infection of the lining of the bowel that may require antibiotics and or surgical resection
- Persistent patent ductus artriosus – 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
- Neurodevelopment as assessed at 2 years of age
- Death

Early anticipation of preterm birth allows timely administration of evidence based interventions that optimise the outcome of premature infants, such as; corticosteroid and magnesium treatments to improve respiratory and neurological function and outcomes.

Cost-effectiveness:

Considering clinical superiority has been proposed and the likelihood that the intervention is more costly than standard care, a cost effectiveness approach is appropriate. The assessment report could consider whether a stepped approach may be helpful for decision making:

Step 1: cost per high risk patients identified; where the applicant considers just the cost of testing (i.e. not including any perceived cost offset from downstream reduction in preeclampsia and the clinical outcomes)

Step 2: cost per high risk patients identified; where the applicant includes the cost offsets due to consequences of changes in the clinical management of a patient.

Step 3: cost per quality-adjusted life years.

Assessment framework (for investigative technologies)

Assessment Framework

The assessment framework is depicted in Figure 1.

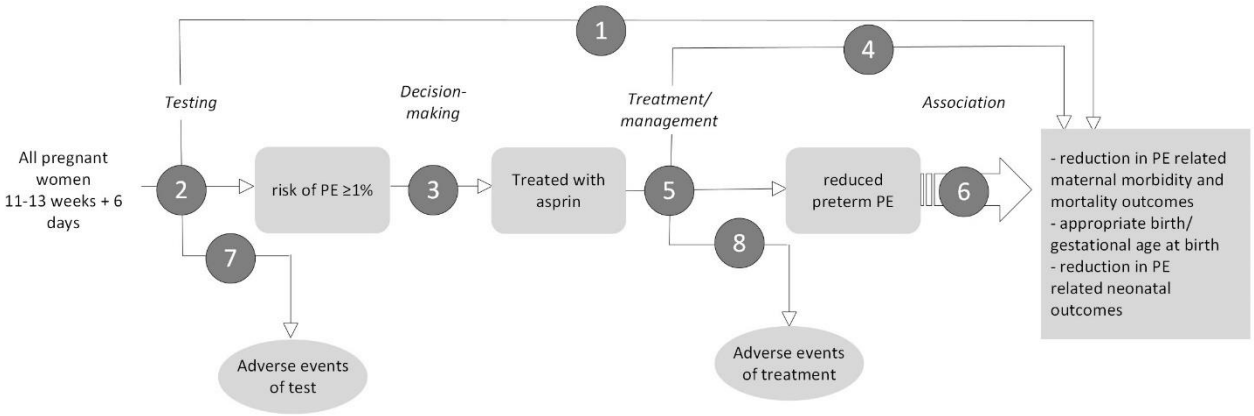

Figure 1 Assessment framework

Figure notes: 1: direct from test to health outcomes evidence; 2: test accuracy; 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: influence of the change in management on intermediate outcomes; 6: association of intermediate outcomes with health outcomes; 7: adverse events due to testing; 8: adverse events due to treatment; PE = preeclampsia

Clinical management algorithms

Patient journey

The applicant proposes that the screening test is carried out in conjunction with the current early pregnancy screening test for common forms of chromosomal abnormality (aneuploidy). This process is well established and involves identification of pregnancy by GPs or obstetricians/gynaecologists, followed by GP/obstetrician referral for ultrasound and biochemical testing and risk calculation in either ultrasound or biochemistry laboratories. The risk information would then be reported to the referring GP/obstetrician who would act on the result. Women deemed high-risk for early onset preeclampsia would be prescribed aspirin (150mg PO nocte) as prophylaxis against this condition. Implementation studies have shown that no further detailed follow-up/change of antenatal surveillance is needed (Park et al., 2013), although reinforcement of the value of the intervention likely improves compliance and the impact of treatment (Park et al., 2015). There is no other difference between the two risk arms and patients would continue to receive routine pregnancy care appointments (midwife or doctor). Patients that are treated with aspirin are still able to develop preterm preeclampsia.

Current clinical management pathway

Women are currently identified as being high risk for preterm preeclampsia by assessment of maternal characteristics, medical and obstetric history. This is traditionally done within the GP practice or by a midwife or obstetrician after referral, at the time of the booking visit. There is no formal timeline for this process, which normally occurs in 'early pregnancy' but may be anywhere between 8 and 20 weeks' gestation.

Recognised risk factors are grouped into high-risk factors and moderate-risk factors.

High risk factors for preterm preeclampsia include: Previous preeclampsia; Chronic hypertension; Chronic renal disease; Diabetes Mellitus; and Maternal SLE or antiphospholipid syndrome.

Moderate risk factors include: First ongoing pregnancy; Maternal age >35 years; Maternal BMI >30kg/m^2; Interpregnancy interval >10 years; Family history of preeclampsia; non-Caucasian background or lower socioeconomic status.

Women who have one high-risk or two moderate-risk factors are deemed high risk and should be prescribed aspirin for prophylaxis against preeclampsia. The management pathway is the same for high-risk patients generated through either approach to screening, namely, high risk patients will be prescribed Aspirin 150mg PO nocte. Aspirin is recognised as being of value in reducing the risk of preeclampsia. Aspirin has been shown to be most effective if prescribed <16 weeks' gestation and is most effective at preventing severe early onset preeclampsia leading to delivery <34 weeks' gestation.

Clinical Management algorithms

Figure 2 presents the clinical management algorithm for the comparator (standard care). Once a patient is identified as high risk for preterm preeclampsia, they are prescribed aspirin. There is no other difference between the two risk arms and patients would continue to receive routine pregnancy care appointments (midwife or doctor). Patients that are treated with aspirin are still able to develop preterm preeclampsia.

PASC noted the applicant's advice that the intervention's algorithm uses a cut-off of 1% to determine that a patient is at high risk of PE (i.e. a patient with a 1% risk of developing preeclampsia based on the algorithm is considered to be at high risk), which equates to approximately 10.5% of the screened population (Rolnik et al., 2017a). This was updated in the proposed algorithm.

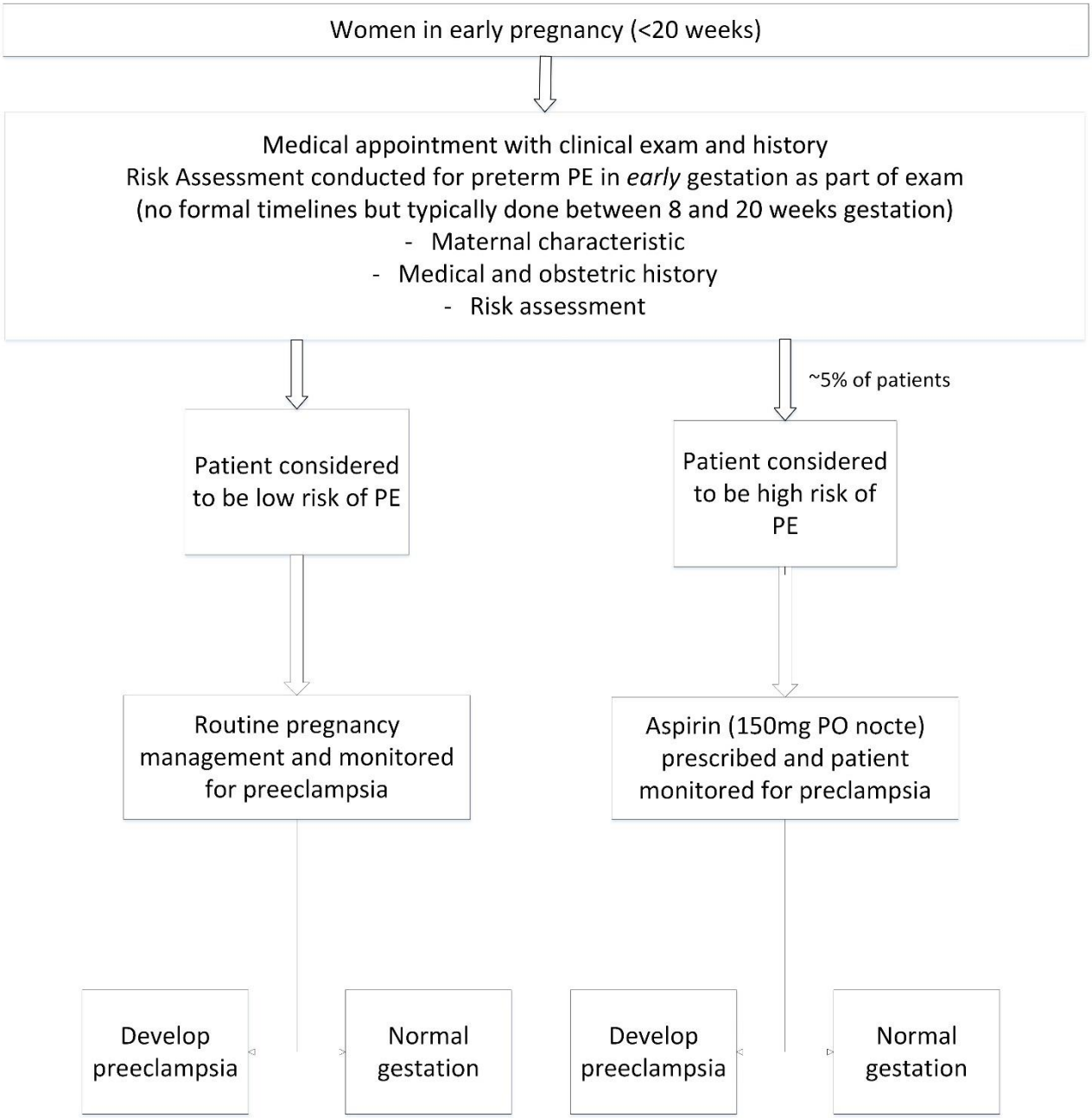

Figure 2 Current management for identifying preeclampsia in early pregnancy (comparator)

PE = Preeclampsia; PO = Per OS; nocte = At night.

The clinical management algorithm for the intervention

Figure 3 presents the clinical management algorithm for the intervention.

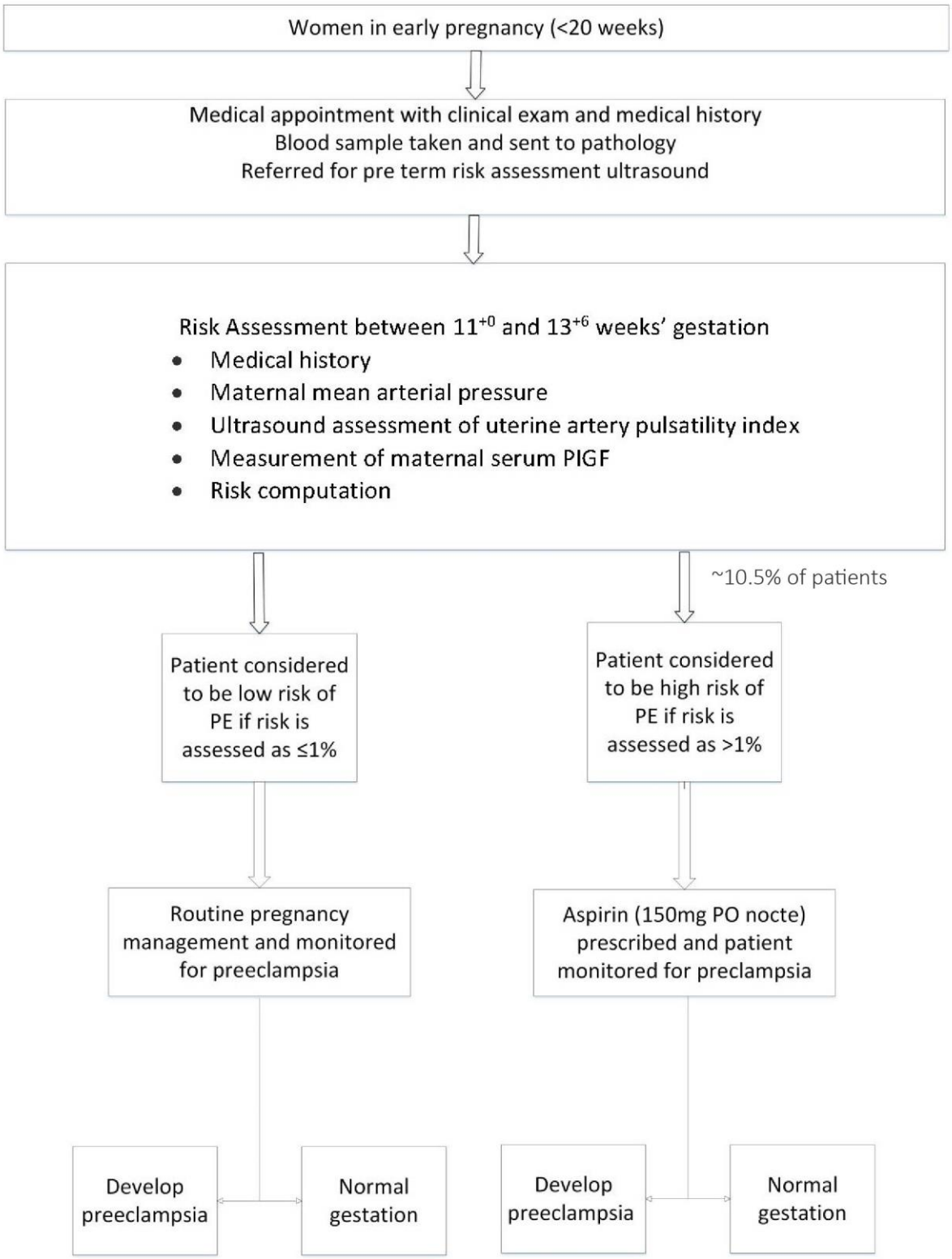

Figure 3 Proposed management for the identification of preeclampsia in early pregnancy (intervention)

PE = Preeclampsia; PO = Per OS; nocte = At night.

The main difference between the comparator and the proposed intervention is the timing of the intervention and that the intervention will identify more patients at high risk of preeclampsia (approximately 10.5% of women) compared to standard care (approximately 1.1% of women tested). Due to increased detection more patients would be treated with aspirin (data are rough estimates based on the diagnostic and detection rates from Park et al (2013)). Based on the false positive rate from Rolnik et al. (2017a) 9.2% of these women would unnecessarilybe treated with aspirin. If considered to have superior efficacy; less patients would develop and hence be treated for preeclampsia in later pregnancy. Patients that are treated with aspirin are still able to develop preterm preeclampsia (6.44% according to (Park et al., 2015)).

During the pre-PASC meeting it was discussed that MSAC application 1706- *Angiogenic and anti-angiogenic markers for identification and management of preeclampsia* is also under application for funding, the listing of 1705 may lead to a smaller proportion of women being eligible for 1706 (i.e. those identified at high risk in 1705 and treated with prophylactic aspirin may be at lower risk for PE beyond 24 weeks' gestation).

Proposed economic evaluation

The applicant confirmed in the pre-PASC response that the claim is for superior effectiveness and superior safety outcomes. The applicant claimed that the new screening tool would:

- Improve screening efficacy (sensitivity and specificity) for identifying women at high risk for early onset preeclampsia
- Complete preeclampsia risk assessment by 13^{+6} weeks' gestation in all pregnant women
- Enable prophylactic aspirin treatment commencement by 15^{+6} weeks' gestation in all high-risk women
- Provide formal information about preeclampsia risk status to women, improving compliance with intervention
- Reduce the prevalence of preterm preeclampsia (delivery < 37 weeks' gestation) by 60%
- Reduce numbers of admissions and length of stay of admissions to NICU or special care
- Improve long term health outcomes of women (by reducing prevalence of preeclampsia; not formally proven)
- Reduce childhood morbidity and mortality related to preterm delivery

Based on the clinical claim of superior health outcomes compared to the current standard of care, a cost-effectiveness or cost-utility analysis would be appropriate.

Table 4 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main 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

[a] '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 agreed with the approach for economic evaluation.

Proposal for public funding

The applicant is proposing a structured prenatal risk assessment for preterm preeclampsia to be publicly funded through the MBS. In the application form the applicant proposed four MBS item descriptors, for professional attendances for assessment of mean arterial pressure (Item no 1), diagnostic imaging services (item no 2), pathology services (item no 3), and professional attendances for collation of investigation findings and calculation of risk for preterm preeclampsia (see Items below).

Item no 1: Mean arterial pressure

Category 1 – PROFESSIONAL ATTENDENCES
Standardised assessment of mean arterial pressure to predict preeclampsia in pregnancies 11^{+0} to 13^{+6} weeks' gestation. Measurement to be performed within a quality assured program. For use in conjunction with item numbers 2, 3, 4 as part of a structured prenatal risk assessment for preterm preeclampsia

Item no 2: Uterine artery PI

Category 5 – DIAGNOSTIC IMAGING SERVICES
Group I1 – Ultrasound Subgroup 5 - Obstetric And Gynaecological Ultrasound assessment of uterine artery pulsatility index to predict preeclampsia in pregnancies 11^{+0} to 13^{+6} weeks' gestation. Measurement to be performed within a quality assured program. For use in conjunction with item numbers 1, 3, 4 as part of a structured prenatal risk assessment for preterm preeclampsia

Item no 3: PlGF

Category 6 - PATHOLOGY SERVICES
Quantitative determination of maternal serum placental growth factor (PlGF) to predict preeclampsia in pregnancies 11^{+0} to 13^{+6} weeks' gestation. Measurement to be performed within a quality assured program. For use in conjunction with item numbers 1, 2, 4 as part of a structured prenatal risk assessment for preterm preeclampsia

Item no 4: Collation and communication

Category 1 - PROFESSIONAL ATTENDENCES
Collation of investigation findings and calculation of risk for preterm preeclampsia. Communication of this result to the patient and to the GP/Maternity service. To be performed within a quality assured program. For use in conjunction with item numbers 1, 2, 3 as part of a structured prenatal risk assessment for preterm preeclampsia.

Following advice at the pre-PASC meeting from the applicant and the Department, the Assessment Group evaluated options available for public funding including new item descriptors and whether it is possible to include the proposed services in already available items (see Items below).

At the pre-PASC meeting the applicant suggested that the maternal mean arterial blood pressure would be conducted at the time of the ultrasound appointment. The applicant also stated that alternatively the mean arterial blood pressure measurements could be performed at the time of the phlebotomy appointment or conducted by the GP prior to referral. As is current practice, it is proposed that the risk assessment be incorporated into the new ultrasound and pathology testing items (or existing items) and not presented as a separate item (though these options have been explored).

The Department of Health Pathology Services Section noted that it does not support a new MBS item for the sole purpose of the measurement of mean uterine artery pulsatility index. The Department reviewed several existing first trimester pregnancy related MBS ultrasound items, with a view to potentially

incorporating the addition of the measurement of mean uterine artery pulsatility index as part of the item descriptor should MSAC recommend public funding for this service. MBS item 55707 was identified as a possible item to which measurement of mean uterine artery pulsatility index could be added. The Department supports this as an option.

As an alternative to adding measurement of mean uterine artery pulsatility index to an existing item, the Department sought advice from PASC and the applicant on the viability of an all-encompassing new first trimester ultrasound item. The item could be conducted between 11 – 15 weeks' gestation and could be provided in lieu of several of the currently funded MBS scans including MBS items 55704 and 55707.

If a new item is thought to be a preferrable option, the Department noted that it could consider an appropriate fee for this service. In line with previous advice from the MSAC Review Taskforce, the Department recommended that a multiple pregnancies MBS item be made available also with a 50% fee increase to compensate for the additional complexity and reporting time.

PASC questioned the need for some of the proposed new MBS items and alternatively suggested that existing items could be modified:

- *PASC noted that modifying existing items for the ultrasound component was the preferred option.*
- *PASC noted that incorporating the pathology test into a revised MBS item #55707 was the most appropriate approach.*

Suggested approach to public funding by modifying existing items

The PICO suggests that the following approach may be the most appropriate based on context, pre PASC discussions and feedback from Pathology Services Section, Medical Benefits Division, Australian Government Department of Health. As GP consultations cover many aspects of pregnancy care and are not restricted to or focused on screening for preeclampsia, it is assumed that the initial consult would cover risk assessment and mean arterial blood preasure measurement under already approved item numbers for GP consultations. The relevant items are presented in Appendix 1: Existing MBS items.

Item for ultrasound - modification of item 55707 (*HTA group amendments in bold italicised*)

Addition of ultrasound for uterine artery PI to item 55707 is proposed. The fee for 55707 is $71.70; however, the revised fee incorporating uterine artery PI is likely to be more expensive. Also of note item 55707 is part of the bulk bill incentive.

Category 5 (Diagnostic Imaging Services)
MBS item 55707 Pelvis or abdomen, pregnancy related or pregnancy complication, ultrasound scan of, by any or all approaches**,** if: (a) the pregnancy (as confirmed by ultrasound) is dated ***at 11^{+0} to 13^{+6} weeks' gestation***; (b) nuchal translucency measurement is performed to assess the risk of fetal abnormality; and ***(c) uterine artery pulsatility index is performed to assess the risk of preeclampsia; and*** (d) the service is not performed with items 55700, 55703, 55704, 55705 or 55707 on the same patient within 24 hours (R) Applicable for any women in early pregnancies (one per pregnancy).
Fee: $TBC
Note: Maternal blood pressure is to be measured four times (twice in each arm) using an automated machine accredited for use in pregnancy.

Item 55704 could also be used to incorporate preeclampsia ultrasound. The existing items are presented in Appendix 1: Existing MBS items.

Item for PIGF - modification of item 66750 (*HTA group amendments in bold italicised*)

Category 6 (Pathology Services)
MBS item 66750 Quantitation, in pregnancy, of any ***3*** of the following to detect fetal abnormality ***and for the assessment of risk of preeclampsia*** – total human chorionic gonadotrophin (total HCG), free alpha human chorionic gonadotrophin (free alpha HCG), free beta human chorionic gonadotrophin (free beta HCG), pregnancy associated plasma protein A (PAPP-A), ***serum placental growth factor (PIGF),*** unconjugated oestriol (uE_3), alpha-fetoprotein (AFP) – including (if performed) a service described in item 73527 or 73529 Applicable not more than once in a pregnancy
Fee: $55.25 Benefit: 75% = $41.45 85% = 47.00

If modification of item 66750 is preferred, item 66751 may also need to be modified ***(HTA group amendments in bold italicised).***

Category 6 (Pathology Services)
MBS item 66751 Quantitation, in pregnancy, of any ***four*** or more tests described in 66750 ***Applicable not more than once in a pregnancy***
Fee: $TBC

The existing items are presented in Appendix 1: Existing MBS items.

Possible alternative items based on new individual items for each stage of the assessment as per the MSAC application

PASC noted that it is possible to create a new item with all the elements as described (MAP, history, etc) and an appropriate fee would needto be derived and justified.

In this approach an individual item is proposed for each element: 1) ultrasound to estimate uterine artery PI; 2) MAP (conducted at time of ultrasound); 3) serum placental growth factor; 4) calculation of risk of preeclampsia using a pre-approved algorithm carried out by diagnostic imaging services; and 5) calculation of risk of preeclampsia using a pre-approved algorithm carried out by pathology services. Note, for each assessment, only one of 4 or 5 should be carried out, not both together.

Category 5 (Diagnostic Imaging Services)
MBS item AAAA Pelvis or abdomen, pregnancy related or pregnancy complication, ultrasound scan of, by any or all approaches, if: (a) the pregnancy (as confirmed by ultrasound) is dated at 11^{+0} to 13^{+6} weeks' gestation; (b) uterine artery pulsatility index is performed to assess the risk of preeclampsia; and (c) the service is not performed with items 55700, 55703, 55704, or 55705 on the same patient within 24 hours but may be preformed with item 55707. Applicable not more than once in a pregnancy Multiple Procedure Rule applies
Fee: $TBC

Item for mean arterial pressure

Category 5 (Diagnostic Imaging Services)
MBS item BBBB Calculation of maternal mean arterial pressure to assess the risk of preeclampsia, if: (a) the pregnancy (as confirmed by ultrasound) is dated by a fetal crown rump length of 45 to 84 mm; and (b) the service is performed with item AAAA Applicable not more than once in a pregnancy
Fee: $TBC
Note: Maternal blood pressure is to be measured four times (twice in each arm) using an automated machine accredited for use in pregnancy.

Category 6 (Pathology Services)
MBS item CCCC Calculation of maternal mean arterial pressure to assess the risk of preeclampsia, if: (a) the pregnancy (as confirmed by ultrasound) is dated at 11^{+0} to 13^{+6} weeks' gestation; and (b) the service is performed with item DDDD Applicable not more than once in a pregnancy
Fee: $TBC
Note: Maternal blood pressure is to be measured four times (twice in each arm) using an automated machine accredited for use in pregnancy.

Item for PIGF

Category 6 (Pathology Services)
MBS item DDDD Quantitation, in pregnancy, of serum placental growth factor (PIGF), in the assessment of preeclampsia Applicable not more than once in a pregnancy
Fee: $TBC

Separate items for calculation of risk assessment

By ultrasound service:

Category 5 (Diagnostic Imaging Services)
MBS item EEEE Calculation of risk of preeclampsia using a pre-approved algorithm, if the service is performed with items AAAA and BBBB Applicable not more than once in a pregnancy
Fee: $TBC

By pathology service:

Category 6 (Pathology Services)
MBS item FFFF Calculation of risk of preeclampsia using a pre-approved algorithm, if the service is performed with item DDDD Applicable not more than once in a pregnancy
Fee: $TBC

PASC noted that if scoring of risk was to be performed by the pathologist under a separate item, it would need to be explored and clarified how it would occur in practice so that a generalisable model that applies throughout Australia could be implemented.

Summary of public consultation input

The Department received responses to the consultation survey from five key stakeholders; Australia Action on Preeclampsia, Australian Society for Ultrasound in Medicine, The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG), The Royal College of Pathologists of Australasia (RCPA), the Society of Obstetric Medicine Australia and New Zealand (SOMANZ). All five groups supported the application.

Consultation feedback was received from four (4) professional organisations, one (1) consumer organisation and eight (8) individuals, of whom two (2) were consumers, five (5) medical professionals and one (1) was both a consumer and a medical professional. The five (5) organisations that submitted input were:

- The Australian Sonographers Association (ASA)
- The Royal Australia and New Zealand College of Radiologists (RANZCR)
- Australian Action on Preeclampsia Inc (AAPEC)
- Society of Obstetric Medicine Australia and New Zealand (SOMANZ)
- Royal Australian College of General Practitioners (RACGP).

All consultation feedback received was supportive of public funding for the proposed service.

Consumer Feedback

All health professionals and consumers were in support of public funding for structured prenatal risk assessment for preterm preeclampsia.

- The health professionals considered that the risk assessment could lead to improved detection of preeclampsia and allow for more intense and focused monitoring and targeted interventions for women at high risk, and thus reduce maternal and perinatal complications and stillbirth. Those with low risk of preeclampsia on the other hand would require less intensive monitoring.
- Public funding could ensure equity of access and ensure the standard of test provided.
- One specialist considered that GPs should be able to request the test as most women are seen by their GPs in their first trimester of pregnancy, and two other specialists considered that the test could be incorporated into first trimester screening for aneuploidy.

The consumers considered that the test should be available to all women and would lead to better health outcomes for mothers and babies. It also allows families to plan for a difficult pregnancy, especially for women outside metropolitan locations. Consumers considered that counselling and dietary advice should be available to women when they are determined to be at high risk of preeclampsia.

Organisational Feedback

Clinical need and public health significance

The main benefits of public funding received in the consultation feedback included:

- Decrease in maternal and infant mortality, prematurity and morbidity in at-risk pregnancies, especially for women who are pregnant for the first time;
- Early initiation of preventative treatment for women at high risk of pre-eclampsia
- Preventing preeclampsia may also prevent future cardiovascular disease for the mother and baby;
- Cost savings for the health care system through reduction in use of neonatal intensive care units, hospitalisations and medications
- Equity of access, noting that two organisations considered that equity of access should be considered in the implementation for patients from Aboriginal and Torres Strait Islander backgrounds, from rural and remote communities, lower socioeconomic and culturally and linguistically diverse communities.

The main disadvantages of public funding received in the consultation feedback included:

- Patient's anxiety about the identified risk of pre-eclampsia; which could be mitigated by appropriate counselling at the time of delivery of results, and
- Reliance of the multivariate test on all the components being done optimally and according to protocol to provide accurate and meaningful results.

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

- Pre-intervention education regarding availability of the test for pre-eclampsia, and
- Post-intervention counselling regarding interpretation of test result.

Indication(s) for the proposed medical service and clinical claim

The consultation feedback ranged from 'agreeing' to 'strongly agreeing' with the proposed population(s) and comparator. The RACGP considered that it would be of benefit to undertake modelling to determine if the entire pregnant population or only those with risk factors should be screened.

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

- The AAPEC considered that the documented performance of the proposed service is markedly more reliable than the service comparator.
- The RACGP recommended careful assessment of the effectiveness of introducing any screening service, to ensure benefits are maximised and harms minimised. The RACGP also noted that the

evidence did not provide any modelling on the harms of aspirin in the proportion of the population of pregnant women who are 'over diagnosed'.
- The RACGP recommended a systematic review such as that available from the Cochrane Library on Antiplatelet agents for preventing pre-eclampsia and its complications (rather than just the supportive selective medical literature) be provided in the summary of evidence.
- The RANZCR strongly urged the Government to review the contemporary clinical evidence and to consider any additional funding capabilities for prenatal pregnancy scans to ensure the best clinical outcomes are accessible for all patients.

Cost information for the proposed medical service

- The consultation feedback mostly agreed with the proposed service descriptor.

SOMANZ agreed with the proposed service descriptor but would like to see more detail on assessment of blood pressure, uterine artery pulsatility, and on the appropriate software for calculation of the findings of the proposed intervention.

The ASA suggested that the proposed intervention should be able to be undertaken and co-claimed into the routine 11-14 week anatomy examination, where it is possible to provide the two services in one patient interaction. The ASA considered that the time it takes to perform the proposed medical service should be addressed and noted extending examination times would reduce the number of ultrasound examinations that sonographers could perform.

Additional comments

A number of organisations considered that the implementation of the proposed service should be mindful of workforce shortage, and the cost pressures across credentialling, infrastructure needs, and education and awareness campaigns for consumers and relevant providers.

The RANZCR considered that the Medicare rebate for the first trimester pregnancy ultrasound should be reviewed as it is well below the cost of providing the service. It noted that the role of the first trimester ultrasound in pregnancy care had shifted to risk stratification and includes a number other measurements and assessments to the nuchal translucency (measurement of mean uterine artery pulsatility index, assessment of the fetus for major structural abnormalities, assessment of chronicity in twin pregnancies, dating and viability, assessment of adnexa is included, assessment of placental location, cervical length) with an average time requirement between 30-45 minutes. RANZCR supports a first trimester ultrasound item that incorporates all of the above-mentioned clinical indicators, but acknowledged that this would be beyond the scope of the current MSAC application. Should public funding be provided for a limited indicator of measurement of mean uterine artery pulsatility index, and exclude other indicators, RANZCR considered there would be a medicolegal risk for radiologists as funding would not cover the time required to report on additional issues, such as structural abnormalities.

PASC noted that the application was broadly supported, including recognition of its clinical importance and relevance from the Australian Action on Preeclampsia Inc. (AAPEC), Australian Society for Ultrasound in Medicine, RANZCOG, RCPA, Society of Obstetric Medicine of Australia and NZ (SOMANZ) and individuals.

PASC noted that the Australian Sonographers Association were concerned that the requirement for ultrasound assessment of uterine perfusion would lengthen the current consultation times and given the supply issues of sonographers, would compromise their ability to carry out the work that they are already undertaking. These workforce issues were also highlighted by the Royal Australian and New Zealand College of Radiologists (RANZCR). The RANZCR also considered that the current funding for aneuploidy

screening by ultrasound is insufficient, and an increase in tasks without increasing the Medicare rebate would worsen the situation. This would particularly impact service providers in rural and remote areas and Aboriginal and Torres Strait Islander patients.

PASC noted that SOMANZ stated that it was important that clinics offering the proposed intervention are trained or credentialed.

PASC noted that feedback indicated that UtAPI measurement is not currently a routine component of 1st-trimester ultrasound for anatomical assessment and aneuploidy screening. It is highly unlikely that UtAPI measurement would be done in isolation and it is therefore most appropriate to be included as a component of a revised MBS item #55707.

Next steps

PASC advised that the PICO would require substantial reworking out of session and that the applicant needed to consider the different models and how these would flow through to the item numbers prior to progressing.

PASC noted that the applicant would consider either an ADAR (Applicant Developed Assessment Report) or a DCAR pending outcomes of the ratified PICO and PASC advice.

References

ABS. 2021a. *Births, Australia* [Online]. Available: https://www.abs.gov.au/statistics/people/population/births-australia/latest-release [Accessed].

ABS. 2021b. *Confinements, by nuptiality, by state* [Online]. Available: https://explore.data.abs.gov.au/vis?tm=births&pg=0&df[ds]=ABS_ABS_TOPICS&df[id]=CONFINEMENTS_NUPTIALITY&df[ag]=ABS&df[vs]=1.0.0&pd=2020%2C2020&dq=...A [Accessed].

AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS 2020. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. *Obstet Gynecol,* 135**,** e237-e260.

ARNOTT, C., NELSON, M., ALFARO RAMIREZ, M., HYETT, J., GALE, M., HENRY, A., CELERMAJER, D. S., TAYLOR, L. & WOODWARD, M. 2020. Maternal cardiovascular risk after hypertensive disorder of pregnancy. *Heart,* 106**,** 1927-1933.

BROWN, M. & LINDHEIMER, M. 2001. de, Swiet, M., Van, Assche, A. & Moutquin, J.-M. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for The Study of Hypertension in Pregnancy (ISSHP). *Hypertens. Pregnancy,* 20.

CHAIWORAPONGSA, T., CHAEMSAITHONG, P., YEO, L. & ROMERO, R. 2014. Pre-eclampsia part 1: current understanding of its pathophysiology. *Nat Rev Nephrol,* 10**,** 466-80.

FETAL MEDICINE FOUNDATION. 2021. *Risk assessment - Risk for preeclampsia* [Online]. Available: https://fetalmedicine.org/research/assess/preeclampsia/first-trimester [Accessed].

GRATACOS, E. 2020. *Prediction and prevention of PE and IUGR* [Online]. Available: http://www.medicinafetalbarcelona.org/docencia2/sites/default/files/pdf/presentaciones/15-04-Pred-PE-IUGR.pdf [Accessed].

HARAM, K., SVENDSEN, E. & ABILDGAARD, U. 2009. The HELLP syndrome: clinical issues and management. A Review. *BMC Pregnancy Childbirth,* 9**,** 8.

HGSA/RANZCOG JOINT COMMITTEE 2015. Prenatal screening and diagnostic testing for fetal chromosomal and genetic conditions. *The Royal Australian and New Zealand College of Obstetricians and Gynaecologists*.

LOWE SA, BOWYER L, LUST K, MCMAHON LP, MORTON M, NORTH RA, PAECH M & JM, S. 2014. Guideline for the Management of Hypertensive Disorders of Pregnancy. *the Society of Obstetric Medicine of Australia and New Zealand*.

LOWE, S. A., BOWYER, L., LUST, K., MCMAHON, L. P., MORTON, M., NORTH, R. A., PAECH, M. & SAID, J. M. 2015. SOMANZ guidelines for the management of hypertensive disorders of pregnancy 2014. *Australian and New Zealand Journal of Obstetrics and Gynaecology,* 55**,** e1-e29.

MARLOW, N., WOLKE, D., BRACEWELL, M. A. & SAMARA, M. 2005. Neurologic and developmental disability at six years of age after extremely preterm birth. *N Engl J Med,* 352**,** 9-19.

NATIONAL COLLABORATING CENTRE FOR WOMEN'S CHILDREN'S HEALTH 2010. Hypertension in pregnancy: the management of hypertensive disorders during pregnancy (updated 2019). *National Institute for Health and Clinical Excellence: Guidance.*

PARK, F., DEEMING, S., BENNETT, N. & HYETT, J. 2021. Cost-effectiveness analysis of a model of first-trimester prediction and prevention of preterm pre-eclampsia compared with usual care. *Ultrasound Obstet Gynecol,* 58**,** 688-697.

PARK, F., RUSSO, K., WILLIAMS, P., PELOSI, M., PUDDEPHATT, R., WALTER, M., LEUNG, C., SAAID, R., RAWASHDEH, H., OGLE, R. & HYETT, J. 2015. Prediction and prevention of early-onset pre-eclampsia: impact of aspirin after first-trimester screening. *Ultrasound Obstet Gynecol,* 46**,** 419-23.

PARK, F. J., LEUNG, C. H. Y., POON, L. C. Y., WILLIAMS, P. F., ROTHWELL, S. J. & HYETT, J. A. 2013. Clinical evaluation of a first trimester algorithm predicting the risk of hypertensive disease of pregnancy. *Australian and New Zealand Journal of Obstetrics and Gynaecology,* 53**,** 532-539.

PERKINELMER. 2015. *Pre-eclampsia Predictor v1.1* [Online]. Available: https://resources.perkinelmer.com/corporate/pdfs/downloads/fly_pre-eclampsia-predictor-1599-9792-01.pdf [Accessed].

POLLOCK, W., PEEK, M. J., WANG, A., LI, Z., ELLWOOD, D., HOMER, C. S. E., JACKSON PULVER, L., MCLINTOCK, C., VAUGHAN, G., KNIGHT, M. & SULLIVAN, E. A. 2020. Eclampsia in Australia and New Zealand: A prospective population-based study. *Aust N Z J Obstet Gynaecol,* 60**,** 533-540.

POON, L. C., SHENNAN, A., HYETT, J. A., KAPUR, A., HADAR, E., DIVAKAR, H., MCAULIFFE, F., DA SILVA COSTA, F., VON DADELSZEN, P., MCINTYRE, H. D., KIHARA, A. B., DI RENZO, G. C., ROMERO, R., D'ALTON, M., BERGHELLA, V., NICOLAIDES, K. H. & HOD, M. 2019. The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: A pragmatic guide for first-trimester screening and prevention. *Int J Gynaecol Obstet,* 145 Suppl 1**,** 1-33.

RAYMOND, D. & PETERSON, E. 2011. A critical review of early-onset and late-onset preeclampsia. *Obstet Gynecol Surv,* 66**,** 497-506.

ROLNIK, D. L., WRIGHT, D., POON, L., SYNGELAKI, A., O'GORMAN, N., DE PACO MATALLANA, C., AKOLEKAR, R., CICERO, S., JANGA, D. & SINGH, M. 2017a. ASPRE trial: performance of screening for preterm pre-eclampsia. *Ultrasound in obstetrics & gynecology,* 50**,** 492-495.

ROLNIK, D. L., WRIGHT, D., POON, L. C., O'GORMAN, N., SYNGELAKI, A., DE PACO MATALLANA, C., AKOLEKAR, R., CICERO, S., JANGA, D., SINGH, M., MOLINA, F. S., PERSICO, N., JANI, J. C., PLASENCIA, W., PAPAIOANNOU, G., TENENBAUM-GAVISH, K., MEIRI, H., GIZURARSON, S., MACLAGAN, K. & NICOLAIDES, K. H. 2017b. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. *New England Journal of Medicine,* 377**,** 613-622.

THORNTON, C., DAHLEN, H., KORDA, A. & HENNESSY, A. 2013. The incidence of preeclampsia and eclampsia and associated maternal mortality in Australia from population-linked datasets: 2000-2008. *Am J Obstet Gynecol,* 208**,** 476 e1-5.

VISINTIN, C., MUGGLESTONE, M. A., ALMERIE, M. Q., NHERERA, L. M., JAMES, D. & WALKINSHAW, S. 2010. Management of hypertensive disorders during pregnancy: summary of NICE guidance. *BMJ,* 341**,** c2207.

VON DADELSZEN, P., MAGEE, L. A. & ROBERTS, J. M. 2003. Subclassification of preeclampsia. *Hypertension in pregnancy,* 22**,** 143-148.

WALD, N. J., BESTWICK, J. P., GEORGE, L. M., WU, T. & MORRIS, J. K. 2012. Screening for pre-eclampsia using serum placental growth factor and endoglin with Down's syndrome Quadruple test markers. *J Med Screen,* 19**,** 60-7.

Appendix 1: Existing MBS items

Existing MBS items that could be modified to accommodate preterm PE

Category 5 – Diagnostic Imaging Services	
55704	Pelvis or abdomen, pregnancy related or pregnancy complication, fetal development and anatomy, ultrasound scan of, by any or all approaches, for determining the structure, gestation, location, viability or number of fetuses, if the dating of the pregnancy (as confirmed by ultrasound) is 12 to 16 weeks of gestation (R) Fee: $71.70 Benefit: 75% = $53.80 85% = $60.95 (See para IN.0.19 of explanatory notes to this Category)
55707	Pelvis or abdomen, pregnancy related or pregnancy complication, fetal development and anatomy, ultrasound scan of, by any or all approaches, if: (a) the pregnancy (as confirmed by ultrasound) is dated by a fetal crown rump length of 45 to 84 mm; and (b) nuchal translucency measurement is performed to assess the risk of fetal abnormality; and (c) the service is not performed with item 55700, 55703, 55704 or 55705 on the same patient within 24 hours (R) Fee: $71.70 Benefit: 75% = $53.80 85% = $60.95 (See para IN.0.19 of explanatory notes to this Category)
Category 6 – Pathology Services	
66750	Quantitation, in pregnancy, of any 2 of the following to detect fetal abnormality - total human chorionic gonadotrophin (total HCG), free alpha human chorionic gonadotrophin (free alpha HCG), free beta human chorionic gonadotrophin (free beta HCG), pregnancy associated plasma protein A (PAPP-A), unconjugated oestriol (uE_3), alpha-fetoprotein (AFP) - including (if performed) a service described in item 73527 or 73529 - Applicable not more than once in a pregnancy Fee: $39.75 Benefit: 75% = $29.85 85% = $33.80
66751	Quantitation, in pregnancy, of any three or more tests described in 66750 (Item is subject to rule 25) Fee: $55.25 Benefit: 75% = $41.45 85% = $47.00
Category 3 - THERAPEUTIC PROCEDURES	
16400	ANTENATAL CARE Antenatal service provided by a midwife, nurse or an Aboriginal and Torres Strait Islander health practitionerif: (a) the service is provided on behalf of, and under the supervision of, a medical practitioner; (b) the service is provided at, or from, a practice location in a regional, rural or remote area; (c) the service is not performed in conjunction with another antenatal attendance item (same patient, same practitioner on the same day); (d) the service is not provided for an admitted patient of a hospital; and to a maximum of 10 service per pregnancy Fee: $28.35 Benefit: 85% = $24.10 (See para TN.4.1, TN.4.15 of explanatory notes to this Category)
16401	Professional attendance at consulting rooms or a hospital by a specialist in the practice of his or her specialty of obstetrics, after referral of the patient to him or her - each attendance, other than a second or subsequent attendance in a single course of treatment Fee: $89.00 Benefit: 75% = $66.75 85% = $75.65 (See para TN.4.2 of explanatory notes to this Category)
16404	Professional attendance at consulting rooms or a hospital by a specialist in the practice of his or her specialty of obstetrics after referral of the patient to him or her - each attendance SUBSEQUENT to the first attendance in a single course of treatment. Fee: $44.75 Benefit: 75% = $33.60 85% = $38.05

	(See para AN.0.70, TN.4.2 of explanatory notes to this Category)
16500	ANTENATAL ATTENDANCE Fee: $49.05 Benefit: 75% = $36.80 85% = $41.70 (See para TN.4.3, TN.4.15 of explanatory notes to this Category)
91850	Antenatal telehealth service provided by a midwife, nurse or an Aboriginal and Torres Strait Islander health practitioner, to a maximum of 10 services per pregnancy, if: (a) the service is provided on behalf of, and under the supervision of, a medical practitioner; and (b) the service is provided at, or from, a practice location in a regional, rural or remote area; and (c) the service is not performed in conjunction with another antenatal attendance item in Group T4 for the same patient on the same day by the same practitioner. Fee: $28.35 Benefit: 85% = $24.10
91853	Antenatal telehealth attendance. Fee: $49.05 Benefit: 85% = $41.70
91855	Antenatal phone service provided by a midwife, nurse or an Aboriginal and Torres Strait Islander health practitioner, to a maximum of 10 services per pregnancy, if: (a) the service is provided on behalf of, and under the supervision of, a medical practitioner; and (b) the service is provided at, or from, a practice location in a regional, rural or remote area; and (c) the service is not performed in conjunction with another antenatal attendance item in Group T4 for the same patient on the same day by the same practitioner. Fee: $28.35 Benefit: 85% = $24.10
91858	Antenatal phone attendance. Fee: $49.05 Benefit: 85% = $41.70
Category 8 - MISCELLANEOUS SERVICES	
82100	Initial antenatal professional attendance by a participating midwife, lasting at least 40 minutes, including all of the following: (a) taking a detailed patient history; (b) performing a comprehensive examination; (c) performing a risk assessment; (d) based on the risk assessment - arranging referral or transfer of the patient's care to an obstetrician; (e) requesting pathology and diagnostic imaging services, when necessary; (f) discussing with the patient the collaborative arrangements for her maternity care and recording the arrangements in the midwife's written records in accordance with section 6 of the Health Insurance Regulations 2018. Payable once only for any pregnancy.

	Fee: $55.55 Benefit: 85% = $47.25 (See para MN.13.15, MN.13.16, MN.13.17, MN.13.18 of explanatory notes to this Category)
82105	Short antenatal professional attendance by a participating midwife, lasting up to 40 minutes. Fee: $33.60 Benefit: 75% = $25.20 85% = $28.60 (See para MN.13.15, MN.13.16, MN.13.17, MN.13.18 of explanatory notes to this Category)
82110	Long antenatal professional attendance by a participating midwife, lasting at least 40 minutes. Fee: $55.55 Benefit: 75% = $41.70 85% = $47.25 (See para MN.13.15, MN.13.16, MN.13.17, MN.13.18 of explanatory notes to this Category)
91211	Short antenatal telehealth attendance by a participating midwife, lasting up to 40 minutes. Fee: $33.60 Benefit: 85% = $28.60 (See para MN.13.15, MN.13.16, MN.13.17, MN.13.18 of explanatory notes to this Category)
91212	Long antenatal telehealth attendance by a participating midwife, lasting at least 40 minutes. Fee: $55.55 Benefit: 85% = $47.25 (See para MN.13.15, MN.13.16, MN.13.17, MN.13.18 of explanatory notes to this Category)
91218	Short antenatal phone attendance by a participating midwife, lasting up to 40 minutes. Fee: $33.60 Benefit: 85% = $28.60 (See para MN.13.15, MN.13.16, MN.13.17, MN.13.18 of explanatory notes to this Category)
91219	Long antenatal phone attendance by a participating midwife, lasting at least 40 minutes. Fee: $55.55 Benefit: 75% = $41.70 85% = $47.25 (See para MN.13.15, MN.13.16, MN.13.17, MN.13.18 of explanatory notes to this Category)