Australian Government

Department of Health

Application 1705

Structured prenatal risk assessment for preterm preeclampsia

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires to determine whether a proposed medical service is suitable.

Please use this template, along with the associated Application Form Instructions to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted. The separate MSAC Guidelines should be used to guide health technology assessment (HTA) content of the Application Form

Should you require any further assistance, departmental staff are available through the Health Technology Assessment Team (HTA Team) on the email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

Email: hta@health.gov.au

Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant):
Corporation name:
ABN:
Business trading name:

Primary contact name: REDACTED

Primary contact numbers
Business: **REDACTED**
Mobile: **REDACTED**
Email: **REDACTED**

Alternative contact name: REDACTED

Alternative contact numbers
Business: **REDACTED**
Mobile: **REDACTED**
Email: **REDACTED**

2. (a) Are you a lobbyist acting on behalf of an Applicant?

☐ Yes
☒ No

(b) If yes, are you listed on the Register of Lobbyists?

☐ Yes
☐ No

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

3. Application title

Structured Prenatal Risk Assessment for Preterm Preeclampsia

4. Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)

Preeclampsia is a pregnancy specific condition resulting in maternal hypertension and multisystem dysfunction. Once preeclampsia develops it becomes progressively worse until delivery – which is the only effective means of stabilising maternal condition. Preterm preeclampsia is a more severe form of disease with earlier onset that causes more cardiovascular morbidity for mothers in later life.

The preeclamptic fetus is often growth restricted. Iatrogenic prematurity puts the surviving fetus at substantially increased risk of death or lifelong morbidity, including cerebral palsy, cognitive delay, autism and other neuro-developmental, psychomotor, behavioural, or learning disorders. As adolescents or adults these individuals are at increased risk of developing hypertension, diabetes, and obesity.

In Australia, preeclampsia affects 4-5% of pregnancies; 30% of these will be delivered preterm. Preeclampsia leads to 15% of Australian neonatal admissions <32 weeks' gestation. WHO have estimated that preeclampsia is the direct cause of 60,000 maternal deaths and >500,000 preterm births each year.

5. Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

Individualised risks for preterm preeclampsia can be calculated using a multivariate testing algorithm at 11-13^{+6} weeks' gestation. Women identified at high-risk are prescribed aspirin as prophylaxis against preterm preeclampsia. This combination of predictive and preventative strategies has been shown to prevent 62% of deliveries for preterm preeclampsia (<37 weeks' gestation) with 90% effectiveness for preeclampsia leading to delivery <32 weeks. Cost economic analysis in an Australian health setting shows dominance compared to usual care (screening by maternal history), primarily due to the reduction of cost for neonatal admission (Park 2018).

Risk prediction is aligned with current antenatal testing at 11-13^{+6} weeks' gestation. The algorithm includes:

- Clinical measurement of 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).

From the patient's perspective, these parameters can either all be measured at one appointment or alternatively, can be measured separately; each has been validated across the 11-13^{+6} week gestational window. Once all parameters have been measured, they need to be incorporated into a risk algorithm and this risk needs to be described to the patient. The prophylactic intervention (Aspirin) is most effective if started <16 weeks' gestation; so risk calculation should be performed as soon as possible after all components of the test have been assessed.

None of these assessment tools are currently rebated in combined first trimester (11-13^{+6} week) screening.

6. (a) Is this a request for MBS funding?

☒ Yes
☐ No

(b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

☐ Amendment to existing MBS item(s)
☒ New MBS item(s)

(c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service:

Not applicable

(d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?

Not applicable

(e) If a new item(s) is being requested, what is the nature of the change to the MBS being sought?

i. ☐ A new item which also seeks to allow access to the MBS for a specific health practitioner group
ii. ☒ A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)
iii. ☐ A new item for a specific single consultation item
iv. ☐ A new item for a global consultation item(s)

(f) Is the proposed service seeking public funding other than the MBS?

☐ Yes
☒ No

(g) If yes, please advise

Not applicable

7. What is the type of service:

☐ Therapeutic medical service
☒ Investigative medical service
☐ Single consultation medical service
☐ Global consultation medical service
☐ Allied health service
☐ Co-dependent technology
☐ Hybrid health technology

8. For investigative services, advise the specific purpose of performing the service *(which could be one or more of the following)*:

i. ☒ To be used as a screening tool in asymptomatic populations
ii. ☐ Assists in establishing a diagnosis in symptomatic patients
iii. ☒ Provides information about prognosis
iv. ☐ Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
v. ☐ Monitors a patient over time to assess treatment response and guide subsequent treatment decisions

9. Does your service rely on another medical product to achieve or to enhance its intended effect?

☒ Pharmaceutical / Biological
☐ Prosthesis or device
☐ No

10. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?

☐ Yes
☒ No

High risk patients will be prescribed Aspirin 150mg PO nocte day as prophylaxis against preterm preeclampsia. There is currently no suitable PBS listed dosage for this application and patients are advised

to purchase aspirin from a supermarket or chemist (24 days of treatment can be purchased in supermarkets for under $1.00).

(b) If yes, please list the relevant PBS item code(s):
Not applicable

(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?

Not applicable

(d) If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?

Not applicable

11. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?

☐ Yes
☒ No

(b) If yes, please provide the following information (where relevant):

Not applicable

(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)?

☐ Yes
☐ No

(d) Are there any other sponsor(s) and / or manufacturer(s) that have a similar prosthesis or device component in the Australian market place which this application is relevant to?

☐ Yes
☐ No

(e) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):

Not applicable

12. Please identify any single and / or multi-use consumables delivered as part of the service?

Not applicable

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

13. (a) If the proposed medical service involves the use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer or any other type of therapeutic good, please provide the following details:

Type of therapeutic good: in-vitro diagnostic test
Manufacturer's name: This application does not seek patented technologies

(b) Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

☐ Class III
☐ AIMD
☒ N/A

14. (a) Is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?

☐ Yes (If yes, please provide supporting documentation as an attachment to this application form)
☒ No

(b) If no, has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?

☒ Yes (if yes, please provide details below)
☐ No

ARTG listing, registration or inclusion number: 181221
TGA approved indication(s), if applicable: n/a
TGA approved purpose(s), if applicable: IVDs that are intended to be used for the qualitative and/or quantitative determination of clinical chemistry hormones in a clinical specimen

15. If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?

Not applicable

16. If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the TGA being prepared?

Not applicable

PART 4 – SUMMARY OF EVIDENCE

17. **Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only).** ***Please do not attach full text articles, this is just intended to be a summary.***

	Type of study design	**Title of journal article or research project**	**Short description of research**	**Website link to journal article or research**	**Date of publication**
1.	Retrospective cohort study of 7797 singleton pregnancies including 34 with early onset (delivery <34 weeks) preeclampsia (ePE).	First trimester prediction of hypertensive disorders in pregnancy. Poon L *et al*. Hypertension 2009; 53: 812-818	First study demonstrating value of multivariate first algorithm for early onset preeclampsia. Algorithm: Maternal history Mean arterial pressure (MAP) Mean uterine artery PI PaPP-A and PlGF Showed sensitivity 93.1% at 95% specificity with PPV of 20%.	doi: 10.1161/HYPERTENSIONAHA.108.127977	May 2009
2.	Retrospective cohort study of 57,458 singleton pregnancies including 214 that developed ePE (<34 weeks GA) and 568 that developed preterm (<37 weeks GA) preeclampsia.	Competing risks model in early screening for preeclampsia by biophysical and biochemical markers. Akolekar R et al. Fetal Diagn Ther 2013; 33: 8-15.	This paper describes the current risk algorithm that is used internationally (including Australia) to predict early onset preeclampsia. Algorithm: Maternal history Mean arterial pressure (MAP) Mean uterine artery PI PaPP-A and PlGF Showed sensitivity 96% at 90% specificity.	doi: 10.1159/000341264.	Jan 2013

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
3.	Retrospective cohort of 3,099 singleton pregnancies including 12 with ePE (<34 weeks GA).	Clinical evaluation of a first trimester algorithm predicting the risk of hypertensive disease of pregnancy Park et al. Aust NZ J Obstet Gynaecol 2013; 53: 532-539.	An Australian cohort validating the predictive algorithm described in the previous two papers. Sensitivity: 91.7% Specificity: 90.0%	doi: 10.1111/ajo.12126	June 2013
4.	Prospective cohort of 35,948 singleton pregnancies including 292 with preterm PE (<37 weeks GA).	Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks gestation. O'Gorman N et al. Am J Obstet Gynecol 2016; 214: 103.e1-103.e12	A prospective cohort validating the algorithm described in the second paper listed in this table and making comparison to use of maternal history (usual care). Shows a 26% increase (from 49% to 75%) in sensitivity.	doi: 10.1016/j.ajog.2015.08.034.	Jan 2016

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
5.	Prospective screening study testing the predictive algorithm (above) in seven NHS hospital populations and comparing to usual care (as per NICE guidelines). Cohort included 16747 pregnancies, 142 with preterm (<37 weeks GA) preeclampsia. Gives breakdown of different screening combinations	Comparison of diagnostic accuracy of early screening for pre-eclampsia by NICE guidelines and a method combining maternal factors and biomarkers: results of SPREE Tan et al. Ultrasound Obstet Gynecol 2018; 51: 743-750.	Screening by NICE guideline detected 40.8% of preterm preeclampsia at 10.3% screen positive rate. Only 23% of women high risk by NICE guidelines were treated (appropriately) with aspirin. In comparison, the new algorithm identifies 82.4% of preterm PE. Inclusion of PaPP-A was of no added benefit.	doi: 10.1002/uog.19039	June 2018
6.	Prospective prediction and prevention RCT recruiting 25,797 singleton pregnancies including 180 cases of preterm preeclampsia (<37 weeks GA)	ASPRE trial: performance of screening for preterm preeclampsia. Rolnik et al. Ultrasound Obstet Gynecol 2017; 50: 492-495.	Reports the screening data (all women were screened). Multicentre / pan-European study. Includes modelling to account for effect of aspirin treatment. Sensitivity 76.7%; Specificity 89.5%.	doi: 10.1002/uog.18816	October 2017

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
7.	Prospective prediction and prevention RCT recruiting 25,797 singleton pregnancies including 180 cases of preterm preeclampsia (<37 weeks GA)	Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. (ASPRE) Rolnik et al. N Engl J Med 2017; 377: 613-622.	Reports the outcome of Aspirin as a preventative therapy after first trimester identification of a high-risk group. Aspirin 150mg PO nocte 89%, 82% and 62% reductions in prevalence of preeclampsia before 32, 34 and 37 weeks respectively.	10.1056/NEJMoa1704559	August 2017
8.	Prospective cohort study comparing observational and interventional datasets. Observational cohort (n=3,066) were screened. Interventional cohort (n=2,717) screened and high-risk subgroup treated with aspirin 150mg PO nocte.	Prediction and prevention of early-onset pre-eclampsia: impact of aspirin after first-trimester screening. Park et al. Ultrasound Obstet Gynecol 2015; 46: 419-423.	Australian dataset demonstrating the impact of first trimester prediction AND prevention with a 90% reduction in rate of preterm (<34 weeks' gestation) preeclampsia (from 0.4% to 0.04%)	doi: 10.1002/uog.14819	October 2015.

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
9.	Retrospective cohort study comparing 'usual care' and interventional (FMF based) datasets. Observational cohort n=7,720. Interventional cohort n=4,841.	Implementation of routine first trimester combined screening for pre-eclampsia: a clinical effectiveness study. Guy et al. BJOG 2021; 128: 149-156.	'NICE' standard of care compared to 'FMF' model. FMF model involving PaPP-A rather than PlGF. 50% reduction in screen positive rate (16.1 vs. 8.2%) Increase in targeted aspirin use (28.9% vs. 99%) Aspirin effect: 89% reduction in prevalence of early preterm preeclampsia and 80% reduction in preterm preeclampsia.	doi: 10.1111/1471-0528.16361	July 2020.
10.	Decision analytic model comparing usual care (history based screening / prophylaxis) vs. formal first trimester risk assessment for screening. Uses two years of data from HNELDH (n=6,822 pregnancies) with disease prevalence and costs grounded on Australian Health Care System.	Cost effective analysis of a model of first trimester prediction and prevention for preterm preeclampsia against usual care. Park et al. Ultrasound Obstet Gynecol 2020; ePub ahead of print	The new, first trimester based approach to screening would both reduce the number of cases of preeclampsia (31 less) and reduce aggregate health service costs (by $1,431,186) over a two year period. The intervention dominates usual care.	doi: 10.1002/uog.22193	August 2020.

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
11.	Secondary analysis of neonatal outcomes in ASPRE trial (reference 7 in this table).	Aspirin for evidence-based preeclampsia prevention trial: effect of aspirin on length of stay in the neonatal intensive care unit. Wright et al. Am J Obstet Gynecol 2018; 218: 612.e1-612.e6.	Confirms that: >80% of NICU admissions are for women delivering with PE <32 wks. First trimester prediction and prevention of preeclampsia results in a 68% reduction in length of neonatal stay. This is where the cost savings are.	doi: 10.1016/j.ajog.2018.02.014	June 2018.

18. Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only). ***Please do not attach full text articles, this is just intended to be a summary.***

	Type of study design*	Title of research (including any trial identifier if relevant)	Short description of research (max 50 words)**	Website link to research (if available)	Date***
1.	Retrospective cohort review: 29,618 women who had first trimester screening for preeclampsia and 301,566 who did not. Examines impact on range of adverse pregnancy outcomes	Multicentre clinical implementation of routine first trimester combined screening for preterm preeclampsia in Australia. Rolnik et al. Submitted to BJOG June 2021	High prev ePE (0.7% vs. 0.2%) High prev PE (2.1% vs. 0.7%) High prev PTL (11.5% vs. 7.1%) High prev FGR (<3rd) (4.5% vs. 2.1%) Modelled DR 83.1%	-	June 2021.

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

19. List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a statement of clinical relevance from each group nominated):

- Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)
- The Royal College of Pathologists of Australasia (RCPA)
- Royal Australian and New Zealand College of Radiologists (RANZCR)
- Society of Obstetric Medicine of Australia and New Zealand (SOMANZ)
- Australasian Society for Ultrasound in Medicine (ASUM)
- The Royal Australian College of General Practitioners (RACGP)

20. List any professional bodies/organisations that may be impacted by this medical service (i.e. those who provide the comparator service):

Nil

21. List the consumer organisations relevant to the proposed medical service (please attach a letter of support for each consumer organisation nominated):

- Australian Action on Preeclampsia Inc. (AAPEC)

22. List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:

- Roche Diagnostics
- Thermo Fisher
- PerkinElmer

23. Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):

Name of expert 1: **REDACTED**

Name of expert 2: **REDACTED**

PART 6 – POPULATION (AND PRIOR TESTS), INTERVENTION, COMPARATOR, OUTCOME (PICO)

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

24. Define the medical condition, including providing information on the natural history of the condition and a high level summary of associated burden of disease in terms of both morbidity and mortality:

Definition:

Preeclampsia is a pregnancy specific condition that affects multiple organ systems. It is most typically defined as a condition with increased blood pressure (above 140mmHg systolic and/or 90mmHg diastolic) combined with functional anomalies in at least one of renal, hepatic, haematological, neurological or respiratory systems or alternatively with evidence of placental insufficiency and fetal growth restriction.

A more extended description of the systemic anomalies associated with preeclampsia is reported in the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) guideline (2014).[1]

Preeclampsia has been identified as being severe (blood pressure >160/110mmHg) or mild and as early (delivery <34 weeks) or preterm (delivery <37 weeks) or late (delivery >37 weeks' gestation) in onset.

Natural history:

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.[2] 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.[3] 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 pregnancy is delivered – which includes delivery of the placenta.

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 becomes symptomatic.

Burden of disease:

Preeclampsia causes significant maternal and fetal mortality and morbidity. Mothers that develop preeclampsia may have an eclamptic fit and/ or other neurological sequelae (such as a cerebrovascular accident), renal and hepatic impairment.[4,5] Significant uncontrolled hypertension is also associated with placental abruption and haematological dysfunction can lead to postpartum haemorrhage.

The disease is the one of the commonest causes of maternal death in pregnancy and approximately 60,000 mothers die from the morbidities of preeclampsia each year. Whilst maternal deaths are rare in Australia, this is part due to clinical supervision and the decision to deliver women affected by severe preeclampsia to break the pathological cycle of disease (by removing the placenta). Preterm delivery has a very significant impact on the fetus and is associated with 500,000 deaths worldwide.[6] Approximately 15% of admissions in Australian neonatal intensive care units are the result of severe early onset preeclampsia. Approximately 1,200 infants are born prematurely (<34 weeks) in Australia because of maternal preeclampsia each year. We have the potential to reduce this by 80%.[7]

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.[1,8] Often only two of the three components are recognisable. 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.[9] The risk is most significant in those women who have early onset / severe disease. Severe early onset preeclampsia carries a similar ongoing risk for cardiovascular disease as smoking.

Preterm birth is also associated with increased risks of neurodevelopmental disability, increased special educational needs and ongoing cardiovascular and metabolic disease.[10]

25. Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed medical service, including any details of how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the service:

Eligibility:

Current systems of risk assessment for preeclampsia are based on clinical assessment of maternal characteristics and medical history. This process has poor sensitivity and specificity and there is good data to show that this approach has been ineffective in modifying the prevalence of this disease.

All pregnant women will be eligible for this proposed service, with risk assessment being performed at $11\text{-}13^{+6}$ weeks' gestation (this is the same time at which it is already recommended that all pregnant women receive an aneuploidy screen).

Patient journey:

The risk assessment algorithm combines factors ascertained from maternal history, assessment of maternal blood pressure and the investigative results of ultrasound assessment of uterine artery blood flow (the uterine artery pulsatility index) and of the maternal serum concentration of the biomarker placental growth factor (PlGF).

We propose that this screening test is carried out in conjunction with the current early pregnancy screening test for common forms of chromosomal abnormality. This process is well established and involves identification of pregnancy by GPs or obstetricians/gynaecologists, 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, although reinforcement of the value of the intervention likely improves compliance and the impact of treatment.

26. Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point):

Women are currently identified as being high risk for preeclampsia by assessment of maternal characteristic, medical and obstetric history. This is traditionally done within GP practice or by a midwife of obstetrician after referral, at the time of the booking visit. There is no formal timeline for this process, which normally happens 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 preeclampsia include:

Previous preeclampsia
Chronic hypertension
Chronic renal disease
Diabetes Mellitus
Maternal SLE or antiphospholipid syndrome

Moderate risk factors include:

- First ongoing pregnancy
- Maternal age >35 years
- Maternal BMI >30kg/m^2
- Interpregnancy interval >10years
- Family history of preeclampsia
- Non-Caucasian | 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.

Aspirin is recognised as being of value in reducing the risk or preeclampsia. Aspirin has been shown to be most effective if prescribed <16 weeks' gestation and is most effective at preventing severe early onset disease leading to delivery <34 weeks.

This screening process is recognised as being poorly applied and/or applied at too late a gestation to allow maximal effect of intervention. Several studies have shown that, in current practice, only 25% of women who should be deemed high risk are prescribed aspirin.

This pathway is demonstrated in Appendix 1.

PART 6b – INFORMATION ABOUT THE INTERVENTION

27. Describe the key components and clinical steps involved in delivering the proposed medical service:

Key components:

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.

Maternal mean arterial pressure: Maternal blood pressure is measured using a prescribed standardised protocol (positioning the rested patient appropriately and measuring blood pressure with an electronic BP machine, recognised to be suitable for pregnancy). Two measurements are made in each arm. The mean value of these measures of mean arterial pressure is recorded.

Ultrasound assessment of 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. The mean uterine artery pulsatility index is recorded.

Measurement of maternal serum PlGF: The maternal serum concentration of placental growth factor (PlGF) is measured using a standard biochemical assay.

Risk computation: These 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.

Clinical steps:

Gestation: This test formalises risk assessment to the 11-13^{+6} week gestational window so all women are screened whilst the intervention is most useful.

Blood pressure: Assessment of mean arterial pressure is a clinical process that is not normally completed in a radiology or biochemical laboratory setting and specific resources have to be dedicated to do this in a standardised, quality assured fashion.

Ultrasound assessment of uterine artery PI: This is a clinical assessment as it occurs during transabdominal/ transvaginal ultrasound assessment of pregnancy. Measurement of these Doppler indices uses a standardised technique by appropriately trained sonographers and needs to be reported by an appropriately trained radiologist / sonologist (Rolnik 2018).

Maternal serum PlGF: Using an established assay. This involves collection of a maternal blood sample that is then managed through a biochemical laboratory to produce a quality assured result.

Practical and Pragmatic Implementation:

Preeclampsia screening will have maximal effect when used across the whole population of pregnant women. 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, we would recommend a pragmatic approach to the introduction of this screening program that would enable women to access components of the test and their risk result in an easy manner.

Combined first trimester screening for aneuploidy provides a framework for this approach – as it has been introduced across Australia with different approaches, some based around imaging practices, others based around pathology laboratory services. Two potential models for implementation are described below.

Both models:

GP or maternity service clinician refers patient for (i) BP assessment and fetal CRL / uterine artery Doppler assessment and (ii) for maternal blood draw for PlGF test. In public services, all 11-13+6 week referrals are made by GPs as this predates the hospital booking visit and allocation to maternity service model of care.

Model I: Ultrasound service risk calculation:

The PlGF blood test result is reported to the GP / maternity service and the ultrasound service provider. The ultrasound service provider collects maternal demographics, a series of BP measures, and completes the ultrasound scan (measurement of CRL and uterine artery Doppler). The ultrasound service then collates these data in the risk algorithm and reports these to the GP / maternity service and the patient. The patient returns to the GP / maternity service who are responsible for ongoing pregnancy management.

This reflects, for example, the service model for 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, a series of BP measures, 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. The patient returns to the GP / maternity service who are responsible for discussing risk and for ongoing pregnancy management.

This reflects, for example, the service model for cFTS for aneuploidy in Victoria and SA.

We recommend centralised collection of blood pressure measurements in order to standardise the approach to measurement and allow ongoing quality assurance of these data. Ongoing monitoring of the quality of data (BP measures, uterine artery Doppler measures and PlGF assay) is important to ensure test accuracy.

Risk algorithm(s):

The commonest algorithm used to predict risk of early onset preeclampsia is that published by the Fetal Medicine Foundation (FMF), a charity based in the UK. This group have produced risk algorithms for a number of adverse pregnancy outcomes and the risk algorithm used by most Australian centres that offer combined first trimester screening was described by the FMF. The FMF risk algorithm for preeclampsia has been validated in an Australian population and is currently used by a number of public and private providers across the country. Limited introduction has been supported by the Nuchal Translucency Ultrasound Education and Monitoring Committee (NTUEMP) of RANZCOG. 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 Australia to generate risks for first trimester screening for aneuploidy. The algorithm is also freely available as an online risk calculator through the FMF website. This is not proprietary software.

The FMF early onset preeclampsia algorithm has been validated in an Australian population and has been shown to have sensitivity and specificity of 90% and 90%. Other algorithms have been published such as those from the Wolfson Institute of Preventative Screening (UK) and of Medicine Fetal Barcelona.

A variety of algorithms have been used to screen for aneuploidy and the RANZCOG statement for aneuploidy accepts all tests that have been demonstrated to perform above a level of screening efficacy (70% detection for a 5% screen positive rate). We would suggest that a similar stance be taken in regard to preeclampsia screening and that a variety of algorithms can be used provided their performance has been validated in an Australian population.

For transparency the primary applicant would like to make it clear that he is a trustee of FMF (UK) and is currently chair of NTUEMP within RANZCOG.

28. Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?

No trademarked components are involved.

29. If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?

Not applicable.

30. If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e. accessibility, dosage, quantity, duration or frequency):

Each pregnant woman need only be assessed once in any pregnancy.

31. If applicable, identify any healthcare resources or other medical services that would need to be delivered <u>at the same time</u> as the proposed medical service:

The test is best performed in tandem with first trimester screening for common forms of chromosomal abnormality.

32. If applicable, advise which health professionals will primarily deliver the proposed service:

Different models have been used to provide this service:

The first approach involves referral by the GP/obstetrician to a recognised ultrasound practice. The radiologist / sonologist collects relevant maternal characteristics, arranges measurement of blood pressure within their practice and measurement of uterine artery PI. They collate these data with the PlGF measurement, made in a biochemical laboratory and complete the risk assessment, which is reported back to the referring GP/obstetrician.

The second approach centralises risk assessment to the laboratory who measure PlGF. They then collate this with data about maternal characteristics, mean arterial pressure and uterine artery PI provided by the radiologist / sonologist. They report the risk data either back to the radiologist / sonologist (for inclusion in their final report) or directly to the referring GP/obstetrician.

These two approaches are the same as those currently used to report risks from first trimester screening for chromosomal abnormality.

33. If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:

Each investigational component needs to be performed in a standardised and quality assured manner in order to maximise screening performance.

Whilst BP measurement, phlebotomy and ultrasound assessment could be delegated to another part (a nurse / midwife, phlebotomist or sonographer respectively) the test findings and responsibility for quality assurance should remain with the radiologist / sonologist / clinical pathologist reporting the findings.

34. If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:

Not applicable

35. If applicable, advise what type of training or qualifications would be required to perform the proposed service, as well as any accreditation requirements to support service delivery:

Each measured variable (mean arterial pressure, uterine artery PI and biomarker PlGF) needs to be measured to an appropriate standard.

Mean arterial pressure is assessable by a trained member of medical staff.

Uterine artery PI is assessable by a trained sonographer / sonologist. The appropriate training standard is currently available through the RANZCOG NTUEMP program.

PlGF is a routine biomarker measured in a number of biochemistry laboratories, and is already widely available in Australia.

36. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select <u>ALL</u> relevant settings):

- ☐ Inpatient private hospital (admitted patient)
- ☐ Inpatient public hospital (admitted patient)
- ☒ Private outpatient clinic
- ☒ Public outpatient clinic
- ☐ Emergency Department
- ☐ Private consulting rooms - GP
- ☒ Private consulting rooms – specialist
- ☐ Private consulting rooms – other health practitioner (nurse or allied health)
- ☐ Private day surgery clinic (admitted patient)
- ☐ Private day surgery clinic (non-admitted patient)
- ☐ Public day surgery clinic (admitted patient)
- ☐ Public day surgery clinic (non-admitted patient)
- ☐ Residential aged care facility
- ☐ Patient's home
- ☒ Laboratory
- ☐ Other – please specify below

(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:

This is a population-based screening test that can be performed in an outpatient setting and does not require inpatient admission.

The test needs to be available to both public and private patients.

The biochemical component of the test needs to be performed in a laboratory.

37. Is the proposed medical service intended to be entirely rendered in Australia?

- ☒ Yes
- ☐ No – please specify below

<u>PART 6c – INFORMATION ABOUT THE COMPARATOR(S)</u>

38. Nominate the appropriate comparator(s) for the proposed medical service, i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system (including identifying health care resources that are needed to be delivered at the same time as the comparator service):

The current standard of care involves assessment of risk for preeclampsia through taking a medical history.

39. Does the medical service (that has been nominated as the comparator) have an existing MBS item number(s)?

☐ Yes (please list all relevant MBS item numbers below)
☒ No

40. Define and summarise the current clinical management pathway/s that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards, including health care resources):

The management pathway is the same for high-risk patients generated through either approach to screening.

High risk patients will be prescribed Aspirin 150mg PO nocte.

The main difference is that the comparator has poorer sensitivity and specificity, 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.

41. (a) Will the proposed medical service be used in addition to, or instead of, the nominated comparator(s)?

☐ In addition to (i.e. it is an add-on service)
☒ Instead of (i.e. it is a replacement or alternative)

As screening efficacy is superior it should be used as the sole screening tool.

(b) If instead of (i.e. alternative service), please outline the extent to which the current service/comparator is expected to be substituted:

The new test would become standard of care for all pregnant women.

42. Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service, including variation in health care resources (Refer to Question 39 as baseline):

Use of this new screening tool would:

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

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

43. Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):

Performance of comparator:
Recent studies have shown that the comparator:
Identifies 40% of affected pregnancies as being high-risk (at a 10% false positive rate)
Provides effective prophylactic therapy to 25% of high-risk cases
Provides an intervention at a wide GA range (>50% more than 16 weeks), limiting effectiveness of the intervention to 10% reduction in prevalence of preterm preeclampsia in women given the intervention.
These three figures combine to give a 1% reduction in absolute prevalence of disease

Performance of proposed service:

Recent studies have shown that the new screening test:

Identifies 82% of affected pregnancies as being high-risk (at a 10% false positive rate)

Provides effective prophylactic therapy to 90% of high-risk cases

Provides intervention before 16 weeks' gestation; improving effectiveness of the intervention to 62% reduction in prevalence of preterm preeclampsia in women given the intervention.

These three figures combine to give a 46% reduction in absolute prevalence of disease

This is calculated for all preterm deliveries <37 weeks' gestation.

Predictive performance AND prophylactic intervention are in fact both better at identifying and preventing early (<34 weeks) cases of preeclampsia; these are also the cases that carry the biggest cost burden (due to costs of neonatal care).

Comparison of costs associated between the proposed service and the comparator have been completed in an Australian public health service setting. These show that the proposed service dominates usual care, providing cost savings to the health system, and preventing cases of early onset preeclampsia.

Safety of Low Dose Aspirin

Low dose aspirin (LDA) is currently recommended for prophylaxis against preeclampsia in women deemed high risk (see the comparator above). The recent cost economic analysis completed at John Hunter Hospital found that using this approach, 2% of women are currently been treated with aspirin during pregnancy.

The intervention would lead to prescription of aspirin to 10% of women – a five-fold increase in prescription of aspirin during pregnancy.

The American College of Obstetricians and Gynaecologists have reviewed the potential risks associated with LDA use in pregnancy.[11] They concluded:

> There is no evidence in increase in haemorrhagic complications including placental abruption, postpartum haemorrhage or mean blood loss.
>
> Long term (>5 year use in non-pregnant [older] adults had been associated with an increased risk of major gastrointestinal and cerebral bleeding.
>
> There is no increased risk of congenital abnormality.
>
> There is no association between use of LDA in the third trimester and ductal closure.
>
> There is no increased risk of neonatal intracranial haemorrhage.

44. Please advise if the overall clinical claim is for:

☒ Superiority
☐ Non-inferiority

45. Below, list the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:

Safety Outcomes:

Structured prenatal risk assessment for preterm preeclampsia facilitates early recognition of developing preeclampsia, thereby reducing the incidence of maternal adverse events such as;

- eclamptic fit and/ or other neurological sequelae (such as a cerebrovascular accident)
- renal and hepatic impairment
- haematological dysfunction and postpartum haemorrhage
- HELLP syndrome
- placental abruption

Preeclampsia is also associated with preterm birth which increases risks of neurodevelopmental disability, increased special educational needs and ongoing cardiovascular and metabolic disease to the child. 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.

Clinical Effectiveness Outcomes:
Structured prenatal risk assessment for preterm preeclampsia facilitates improved clinical management of pregnancies identified as high-risk, or symptomatic of preeclampsia.

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

46. Estimate the prevalence and/or incidence of the proposed population:

Latest release from the Australian Bureau of Statistics stated that there were 305,832 registered births in 2019, a decrease of 3.0% from 2018.
https://www.abs.gov.au/statistics/people/population/births-australia/latest-release

47. Estimate the number of times the proposed medical service(s) would be delivered to a patient per year:

One risk assessment per pregnancy

48. How many years would the proposed medical service(s) be required for the patient?

One risk assessment per pregnancy

49. Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:

One risk assessment per pregnancy

50. Estimate the anticipated uptake of the proposed medical service over the next three years factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors) as well as provide commentary on risk of 'leakage' to populations not targeted by the service:

Data within the Hunter New England Local Health District (HNELHD) patient database found 89.26% of pregnant women had visited a GP prior to 14 weeks gestation.[12] This proportion is believed to be a reasonable estimate of uptake of a structured prenatal risk assessment for preterm preeclampsia.

Three year estimates for utilisation	**Year 1**	**Year 2**	**Year 3**
Births per year (ABS)	305,832	305,832	305,832
Uptake	89.26%	89.26%	89.26%
Risk assessment utilisation per year	272,986	272,986	272,986
Cumulative utilisation	272,986	545,971	818,957

There is no foreseen risk of leakage beyond target population.

PART 8 – COST INFORMATION

51. Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:

Applicant is in the process of consultation with relevant service providers

52. Specify how long the proposed medical service typically takes to perform:

53. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and medical service usage characteristics that would define eligibility for MBS funding.

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, we would recommend individual item numbers for each step of the assessment in order to best facilitate the implementation and utilisation of the risk assessment.

Mean arterial pressure

Item no 1

Category 1 - PROFESSIONAL ATTENDENCES
Standardised assessment of mean arterial pressure to predict preeclampsia in pregnancies 11-13+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

Uterine artery PI

Item no 2

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 11-13+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

PlGF

Item no 3

Category 6 - PATHOLOGY SERVICES
Quantitative determination of maternal serum placental growth factor (PlGF) to predict preeclampsia in pregnancies 11-13+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

Collation and communication

Item no 4

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.