

Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1705 – Structured Prenatal Risk Assessment for Preterm Preeclampsia

Applicant: Professor REDACTED/Roche Diagnostics
Australia Pty Ltd

Date of MSAC consideration: 23-24 November 2023

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of structured prenatal risk assessment for preterm preeclampsia in pregnant women at 11⁺⁰ to 13⁺⁶ weeks gestation was received from Professor REDACTED/Roche by the Department of Health and Aged Care (the Department).

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC did not support the public funding of structured prenatal risk assessment for preterm preeclampsia (PE) in pregnant individuals at 11⁺⁰ to 13⁺⁶ weeks gestation. This was primarily because MSAC considered that the evidence presented was insufficient to show the new risk assessment would improve health outcomes. The direct evidence in the application for comparative effectiveness had a high risk of bias. The linked evidence showed that risk assessment was sensitive in predicting preterm PE and had strong negative predictive value (NPV) in ruling out preterm PE, and separately that aspirin was effective at preventing PE in at-risk pregnancies, but there was insufficient evidence that risk assessment changed management and improved health outcomes. The comparative safety of risk assessment relative to standard of care was also a concern given its high false positive rate with all the attendant costs in terms of patient anxiety and potential harm from the increased use of aspirin. MSAC considered there was substantial uncertainty about the clinical place and need for risk assessment.

MSAC also had concerns with the structure and inputs of the economic model leading to the cost-effectiveness of risk assessment being uncertain and potentially cost-ineffective. There was also considerable uncertainty about the financial impact as the financial estimates included estimates of PE from a study with a high risk of bias, and there was a risk of leakage of the use of the test in later stages of pregnancy. MSAC noted that regulation was not in place, as the Therapeutic Goods Administration (TGA) had advised that the proposed Fetal Medicine Foundation (FMF) risk calculator required regulation in the Australian Register of Therapeutic Goods as 'software as a medical device'.

Consumer summary

This was an application from Professor REDACTED and Roche Diagnostics Australia requesting Medicare Benefits Schedule (MBS) listing of structured prenatal risk assessment for preterm preeclampsia.

Preeclampsia is a complication that can happen during pregnancy. It usually includes high blood pressure in the pregnant person, as well as other signs and symptoms. If it is not managed, preeclampsia can cause serious illness and death in the pregnant person and/or the baby. The only cure for preeclampsia is for the baby to be born and the placenta delivered, so it is often necessary that the baby be born early (preterm). The earlier preeclampsia starts in pregnancy the greater the risk to the pregnant person and baby.

This application was for a set of tests that measure a pregnant person's risk of preeclampsia. The pregnant person's clinical history, and results from blood tests and ultrasound are entered into a risk calculator from the Fetal Medicine Foundation (FMF), a UK-based organisation. The results from the FMF calculator aim to tell if a person has a high risk of preeclampsia early in their pregnancy, before any signs of preeclampsia develop. If the test result shows that a person has a high risk of preeclampsia, the person would be recommended to take aspirin from before 16 weeks gestation and for the rest of their pregnancy to help reduce the onset of preeclampsia and risks from preeclampsia to both the pregnant person and the baby. Currently, the risk for preeclampsia is assessed using clinical history alone.

MSAC found that there was no direct evidence to show that using the FMF calculator leads to an improvement in health outcomes for pregnant persons or babies compared to the current way risk is assessed. There was insufficient data about the risks of pregnant people taking aspirin, and the potential effects of stress and anxiety from having their preeclampsia risk assessed on the person's mental health. The value for money and financial cost of funding risk assessment were also uncertain, and MSAC did not think the risk assessment would be good value for money. There might also be high out-of-pocket costs.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC did not support MBS listing of structured prenatal risk assessment for preterm preeclampsia. This was because there was insufficient evidence that the risk assessment would lead to better health outcomes or be good value for money.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this application was for Medicare Benefits Schedule (MBS) listing of structured prenatal risk assessment for preterm preeclampsia (PE) in pregnant patients at 11⁺⁰ to 13⁺⁶ weeks gestation. The risk assessment involves a series of pathology and ultrasound measurements, with results entered (along with clinical information about the patient) into a risk calculator from the Fetal Medicine Foundation (FMF), a UK-based organisation. A result of 1% or above was proposed to be regarded as indicating high risk for PE, and these patients would be prescribed aspirin from before 16 weeks gestation and for the rest of their pregnancy to reduce the risk of onset of, and complications from, PE. MSAC considered the basis for the 1% threshold had not been made sufficiently clear, and that the choice of threshold would be a trade-off with the risks from aspirin treatment.

MSAC noted that the UK National Institute for Health and Care Excellence (NICE) guidelines recommend placental growth factor (PIGF)-based tests in conjunction with standard clinical assessment, to help rule in or rule out suspected PE (that is, in pregnant patients presenting with signs or symptoms of PE) and help decide on care.

MSAC noted the support for this application in consultation feedback. MSAC considered that people in their first trimester of pregnancy already receive a multitude of information and testing, and was concerned that adding another test would potentially create anxiety and confusion for patients.

MSAC noted the Therapeutic Goods Administration (TGA) had determined that the FMF website that includes the risk calculator meets the definition of software as a medical device (SaMD), and so is required to be regulated through inclusion in the Australian Register of Therapeutic Goods (ARTG). MSAC noted the applicant is in discussions with the TGA and disputes the need for ARTG inclusion of the risk calculator. MSAC considered that appropriate regulation would need to be in place before it could support public funding.

MSAC noted the applicant's proposed amendments to MBS items 55707, 66750 and 66751 to add the tests required for the FMF calculator. MSAC also noted the department's proposed comprehensive new first trimester ultrasound item as an alternative to adding mean uterine artery pulsatility index to an existing item. This item would also encompass nuchal translucency testing as an option for pregnant individuals who want to undertake both this test and prenatal risk assessment for preterm PE. MSAC considered that it was not clear which healthcare provider was proposed to complete the final assessment and calculation of PE risk (for example, the radiologist, pathologist or referrer). MSAC considered that the proposed fee increase to add pathology testing was too high, as it would likely be performed along with other routine bloodwork rather than as a standalone test, so the major incremental cost would be only the test cartridge (around \$15-20). MSAC also considered that there would be a risk of leakage to later in pregnancy, as the FMF website provides two additional risk calculators for use later in pregnancy (testing at 19+0 to 24+6 weeks and 30+0 to 37+6 weeks) and these later gestational ages were not part of this application. MSAC noted concerns from ESC that further MBS-funded consultations would be needed to explain results and manage potential anxiety, and considered this had not been taken into account. MSAC considered that assessing pre-term PE risk was currently optional but widespread, and that public funding would result in widespread use and effectively become a screening tool, although it was not characterised as such.

MSAC noted ESC's estimate that using the current algorithm around 5% of patients are classified as high risk and prescribed aspirin, and with the proposed algorithm this would increase to around 10.5%. The proposed population was all pregnant individuals (around 300,000 per year), which would equate to more than 30,000 people per year being prescribed prophylactic aspirin.

MSAC noted the comparator was standard of care, which involves assessing PE risk based on history and clinical signs using risk algorithms from either NICE or the American College of Obstetrics and Gynaecology (ACOG) guidelines. These guidelines differ in the number and type of risk factors that lead to a recommendation for the patient to take aspirin. MSAC considered that these guidelines are not universally applied and there is significant variation in how they are applied in clinical practice.

MSAC noted that the key clinical evidence cited in the Applicant Developed Assessment Report (ADAR) comprised direct test to health outcomes evidence from Rolnik et al (2022)¹, as well as linked evidence: seven studies on FMF risk assessment test accuracy, two studies on the impact of aspirin on PE-related outcomes, one study on the impact of aspirin in preventing preterm PE and one study on adverse events associated with aspirin.

MSAC considered the direct evidence (Rolnik et al. 2022) was at high risk of selection and confounding bias and uninformative for decision-making, due to the intervention being administered to mainly patients at selected private centres which would result in statistically

¹ Rolnik DL, Selvaratnam RJ, Wertaschnigg D et al. (2022). [Routine first trimester combined screening for preterm preeclampsia in Australia: a multicenter clinical implementation cohort study](#). *Int J Gynaecol Obstet* 158(3):634–42.

significant differences between the intervention and standard of care populations favouring the intervention.

On test accuracy, MSAC noted that the evidence suggested that risk assessment was sensitive in predicting preterm PE and in particular had strong negative predictive value (NPV) in ruling out a pregnant person at risk of preterm PE relative to the comparator. Separately, MSAC considered the evidence showed that aspirin was effective at reducing the risk of PE in at-risk pregnancies, reducing pregnancy-related complications from PE and reducing the need for preterm delivery for those that develop PE despite aspirin use. However MSAC noted that linkages were not demonstrated from the use of the FMF algorithm to uptake of aspirin leading to reduced incidence of PE and improved pregnancy outcomes. MSAC also noted that no evidence was provided on outcomes of those deemed to be low risk by the FMF algorithm. Therefore, while the assumptions underpinning the proposal for funding (that is, that risk assessment leads to treatment, which leads to improved health outcomes) may be reasonable from first principles, they were not demonstrated by the evidence provided given the lack of some of the required linked evidence and the deficiency of the direct evidence.

MSAC agreed with the concerns from ESC regarding the lack of evidence relating to safety considerations as there were potential harms from unnecessary aspirin use during pregnancy (given the approximately 10% false positive rate) such as placental abruption, gastrointestinal bleeding, intracerebral bleeds (for both pregnant person and baby), postpartum haemorrhage and aspirin induced bronchospasm, as well as potential psychological harms and anxiety as a result of testing. In its pre-MSAC response the applicant continued to assert that there were no additional safety concerns from prenatal risk assessment associated with aspirin use, because the application does not seek to introduce the use of aspirin for preterm preeclampsia prophylaxis from a baseline scenario of no use of aspirin and that fewer pregnant patients would be exposed to aspirin when they are actually low risk for preterm preeclampsia using the FMF algorithm than if standard of care was applied. However MSAC considered that no justification or evidence was provided for this claim and that if the test is used in widespread practice as intended, then this would result in a large number of pregnant individuals being potentially adversely affected by the risk of false positives. MSAC considered that it would also result in more patients receiving aspirin treatment, which has risks so is not undertaken lightly. MSAC therefore advised the evidence did not support the clinical claim of non-inferior safety, and had not shown that risk assessment would deliver more benefit than harm. Overall MSAC agreed with the commentary's conclusion that the clinical claim of superior effectiveness and non-inferior safety of prenatal risk assessment was not supported.

MSAC questioned whether there was a clinical place for risk assessment, given the clinical need for additional testing was unclear and it would only add to the multitude of tests that people in early pregnancy already receive, which may not be of value.

MSAC noted the economic evaluation was a cost-utility analysis. MSAC noted that the model was driven by the direct test to health outcomes evidence from Rolnik 2022, which as already discussed was at high risk of bias. Basing the economic model on this study therefore also resulted in the use of questionable transition probabilities as model inputs. MSAC noted that the model used the crude estimates unadjusted for confounders reported by Rolnik 2022 to inform the probability of PE, when adjusted estimates were also available and would have been more appropriate. MSAC noted the sensitivity analyses also relied on these unadjusted estimates.

Given the poor applicability of the direct test to outcomes evidence from Rolnik 2022, MSAC agreed with the commentary and ESC that the economic model was too simplistic. In particular MSAC considered that the model was inappropriately structured because:

- It did not separate the standard of care arm into low-risk and high-risk patients. MSAC noted that all relevant economic models of prenatal risk assessment identified in the

literature search undertaken by the ADAR except one separated standard of care by a high risk and low risk arm.

- It provided limited outcomes beyond PE status. For instance outcomes included in the PICO that were not captured in the model included maternal outcomes, preterm birth/gestational age at birth and neonatal outcomes.

MSAC noted the following deficiencies in the model inputs:

- Safety was not considered in the model including adverse events from test results and treatment and the disutility experienced by all pregnant patients who tested positive (whether true or false positive), such as negative anxiety related psychological effects and the inconvenience of increased frequency of monitoring.
- By implication from the above, disutilities and costs associated with false positive rates were also ignored in the modelling. These omissions favoured the intervention by ignoring factors that tend to reduce utility and therefore reduce the gain in quality adjusted life years (QALYs).
- There were various overestimated costs for the comparator arm in the model such as:
 - o The assumption that the test would result in less aspirin use because prenatal risk assessment was more specific than standard of care, which in turn assumed that all patients currently have their preterm PE risk estimated as part of standard of care.
 - o The assumption that all patients currently receive prenatal testing including nuchal translucency ultrasound and trisomy blood testing, whereas in practice this was approximately 54% of patients (based on MBS data for item 55707 and Australian Bureau of Statistics data for number of pregnancies).
 - o Use of diagnosis-related group (DRG) codes for the costing of preterm and term PE delivery and NICU admissions, which were likely to have overestimated these costs.
- There were also various underestimated costs for the intervention arm in the model such as:
 - o Application of the same monitoring costs to high risk and low risk patients which is inappropriate given that high risk patients are more closely monitored and incur significantly higher costs during the antenatal period than low risk groups.
 - o Omission of further MBS funded consultations to explain results and manage potential anxiety. MSAC disagreed with the applicant's claim that the prenatal risk assessment would not create additional anxiety for patients.
 - o Omission of consideration of the risk of leakage of use of the risk assessment at later stages of pregnancy.

The main drivers of the model were the cost of the intervention when the cost of monitoring is included, and the probability of developing PE. MSAC noted that while the base case incremental cost effectiveness ratio (ICER) was dominant (meaning that the intervention was both more effective and less expensive than standard of care) the dominance of the ICER was highly uncertain given the very small incremental effectiveness of the intervention relative to standard of care (0.002 QALYs). This meant that even small changes in some model inputs could change the ICER from dominant to positive (and potentially large). MSAC therefore considered that the results of the economic evaluation were highly uncertain. For instance, MSAC noted that increasing the probability of pre-term PE if found to be high risk in the intervention arm from the base case assumption of 2.1% to 4.3% shifted the ICER from dominant to \$272,006 per QALY, and increasing the probability of term PE if found to be high risk in the intervention arm from the base assumption of 3.6% to 7% shifted the ICER from dominant to \$30,067 per QALY.

MSAC considered out-of-pocket (OOP) costs to patients would be a significant issue, particularly if the intervention is combined with nuchal translucency screening. MSAC considered that this

would worsen inequity, and also noted it had a large impact on the ICER. MSAC noted that if OOP costs were removed from the base case but it was assumed that 54% of patients in the standard of care arm underwent testing compared to 100% in the intervention arm, the ICER increased to \$163,730 per QALY gained. If OOP costs (of \$150) were included in both arms and an additional antenatal consultation under MBS item 16500 was assumed in the intervention arm, the ICER increased to an ICER of \$746,960 per QALY gained, which MSAC considered was large.

MSAC noted the applicant's claim in the pre-MSAC response that economic modelling was retested for the various concerns expressed about the modelling by ESC (which were reiterated by MSAC) and the intervention remained dominant. However MSAC considered that some of these recalculations needed further evaluation. For instance:

- The assumption of a uniform monitoring cost for both risk groups was retested simply by increasing the base case number of antenatal attendances by 1 and 2 additional visits. It was unclear whether this was clinically sufficient to capture the scenario of different monitoring cost for both groups.
- No justification was provided for the higher use of aspirin assumed in the comparator arm and the pre-MSAC response did not re-test for a higher use of aspirin in the intervention arm.
- The pre-MSAC response retested using hospitalisation costs from application 1706 but it was unclear whether this new value was added to both arms.
- The pre-MSAC response reported on the results of a 'conservative scenario' analysis based on the use of adjusted risk ratios to inform the probability of PE which still found a dominant ICER. However MSAC considered that the premises of the modelling and the recalculation required validation.
- On the lack of false positives in the model, the pre-MSAC response stated that these false positives were already accounted for in the outcomes captured in Rolnik 2022, which was the basis for the economic model. MSAC agreed with this in principle but noted its concerns as above regarding the high risk of bias associated with this study and the use of unadjusted probabilities that rendered questionable the transition probabilities derived from this study.

MSAC noted the financial and budgetary impacts, which estimated net costs to the MBS of \$6-7 million per year but reduced hospitalisation costs, which overall led to a net saving to Government (i.e. combined MBS and State/Territory health expenditure) of approximately \$5 million per year. However, MSAC considered that there was considerable uncertainty in these estimates as they were most sensitive to the assumed clinical utility of prenatal risk assessment in reducing the incidence of PE, which was derived from Rolnik 2022, which had a high risk of bias. MSAC also agreed with ESC that the costs were underestimated, because the average cost of prenatal risk assessment per patient per pregnancy and the average frequency of use of prenatal risk assessment (assumed by the ADAR to only apply to 50% of pregnancies) were underestimated, while additional monitoring costs were not included and provision was not made for use beyond the proposed indication considering that two additional risk calculators are provided for use later in pregnancy. However, as above MSAC also considered that the applicant had over-estimated the cost of adding the required pathology testing. Sensitivity analyses showed that cost savings were likely to be much lower than the base case and, in some cases, resulted in a net cost to combined government budgets rather than a net saving.

Overall, MSAC did not support MBS listing of structured prenatal risk assessment for preterm PE. Significant issues were the lack of TGA regulation of the FMF risk calculator, lack of evidence supporting change in management and improved health outcomes, lack of evidence relating to safety, and the substantial problems with the economic evaluation that also carried over into the financial assessment.

MSAC considered that its concerns were substantial, and advised that any reconsideration of this application would need to comprehensively address all concerns it raised. MSAC emphasised that a significantly revised economic model would be required to sufficiently demonstrate the cost-effectiveness of structured prenatal risk assessment. MSAC considered that the true positive rate is what drives an improvement in health outcomes (i.e. detecting incrementally more true positive patients at high risk of preterm PE), yet this is not aligned with the greater relative strength of structured prenatal risk assessment, which was in its high NPV relative to the comparator. MSAC therefore considered whether the value of prenatal risk assessment could be better demonstrated as an additional test for those found to be high risk by the comparator i.e. for ruling out those patients found through standard of care risk assessment to be at high risk of preterm PE. MSAC noted that this alternative approach would also better align with the applicant's claim of less rather than more aspirin use in the intervention arm than the comparator arm, but might also suggest that a cost effectiveness analysis was more appropriate than a cost utility analysis.

MSAC noted the applicant had indicated that the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) had advised it is planning to update its guidelines relating to PE (last updated in 2014) to include a recommendation with respect to the FMF risk calculator. MSAC considered that RANZCOG should be contacted to confirm these update plans and the timing of the release of the updated guidelines and noted that these updated guidelines could be potentially relevant to any reconsideration of this application.

4. Background

MSAC has not previously considered structured prenatal risk assessment for preterm preeclampsia in pregnant persons at 11⁺⁰ to 13⁺⁶ weeks gestation.

The proposed intervention is the Fetal Medicine Foundation (FMF) risk assessment algorithm ("FMF risk calculator" or "FMF risk algorithm" henceforth) used to assess risk of preterm preeclampsia in asymptomatic pregnant persons at 11⁺⁰ to 13⁺⁶ gestation. This is before signs and symptoms of preeclampsia develop (typically after 20 weeks).

The proposed FMF risk calculator uses the following inputs to create a risk score:

- Medical history (specific characteristics)
- Maternal Mean Arterial Pressure (MAP)
- Biochemical measurement of maternal serum concentration of Placental Growth Factor (PIGF)
- Ultrasound assessment of uterine perfusion (Doppler measurement of uterine artery pulsatility index (UtA-PI))

An outputted risk score is given as a percentage; a risk of 1 in 100 (1.0%) is considered "high risk" and directs the use of prophylactic aspirin to prevent the onset of preeclampsia².

The current standard of care involves risk assessment through clinical examination and medical history. The applicant has stated that there are currently no formal timelines, but typically assessment is performed between 8- and 20-weeks' gestation. The FMF provides two additional risk calculators for use later in pregnancy (testing at 19⁺⁰ to 24⁺⁶ weeks and 30⁺⁰ to 37⁺⁶ weeks). These later gestational ages were not part of this assessment and may pose a leakage risk for testing PIGF. There are also other risk prediction algorithms which are based predominantly on patient characteristics, medical and obstetric history alone (National Institute for Health and Care

² Rolnik, D.L., Wright, D., Poon, L.C.Y., Syngelaki, A., O'Gorman, N., 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. and Nicolaides, K.H. (2017b), ASPRE trial: performance of screening for preterm pre-eclampsia. *Ultrasound Obstet Gynecol*, 50: 492-495. <https://doi.org/10.1002/uog.18816>

Excellence (NICE) and American College of Obstetrics and Gynaecology (ACOG). These tools are not MBS funded but are usually implemented as part of normal clinical examination during pregnancy care and comprise the comparator.

In a pregnancy where preeclampsia develops the only curative treatment is delivery of the baby. The proposed benefit of prophylactic aspirin is in either obviating preeclampsia onset, or deferring delivery to a later gestation - there are benefits to both the pregnant person and baby in both situations. In the Australian setting for rural and remote patients, timely antenatal transfer to a centre with appropriate neonatal intensive care should be considered in preference to post-natal transfer of a premature infant.

5. Prerequisites to implementation of any funding advice

The structured prenatal risk assessment for preterm preeclampsia requires the use of an in-vitro diagnostic medical device (IVD) for the quantitative determination of serum PAPP-A and/or PIGF. Although, as noted above, the proposed FMF risk calculator recommends use of serum PIGF (because PIGF is considered to be more accurate), either serum PAPP-A or PIGF can be used, although PAPP-A is only suggested to be used in the absence of PIGF. In addition (as noted in Table 1), PAPP-A will typically be undertaken as part of aneuploidy testing. A summary of the regulatory status of PAPP-A and PIGF assays marketed by Roche Diagnostics is provided in Table 1. Ultrasound machines intended for use in Australia must be included in the Australian Register of Therapeutic Goods (ARTG). This registration process involves providing the necessary information about the device, including its intended purpose, technical specifications, and evidence of safety and performance.

The Therapeutic Goods Administration (TGA) has advised that the FMF risk calculator falls within the definition of software as a medical device (SaMD), and so is required to be included in the Australian Register of Therapeutic Goods (ARTG). The TGA also confirmed that the FMF calculator is not currently included in the ARTG.

Table 1 Regulatory details of IVDs that may be used as part prenatal risk assessment for preeclampsia.

Serum biomarker	Assay name	Intended use	ARTG registration
PAPP-A	Elecsys PAPP-A	Immunoassay for the in vitro quantitative determination of pregnancy-associated plasma protein-A in human serum. This assay is intended for use as one component in combination with other parameters to evaluate the risk of trisomy 21 (Down syndrome) during the first trimester of pregnancy. Further testing is required for diagnosis of other chromosomal aberrations	ARTG ID 181221 Both assays included as part of the same ARTG entry under the 'kind of medical device' process. Intended purpose: IVDs that are intended to be used for the qualitative and/or quantitative determination of clinical chemistry hormones in a clinical specimen
PIGF	Elecsys PIGF	Immunoassay for the in vitro quantitative determination of placental growth factor (PIGF) in human serum. The Elecsys PIGF assay is also used in combination with the Elecsys sFit-1 assay to determine the sFit-1/PIGF ratio. The sFit-1/PIGF ratio is intended for use as an aid in the diagnosis of preeclampsia in conjunction with other diagnostic and clinical information. In addition the sFit-1/PIGF ratio is intended for use as an aid in short-term prediction of preeclampsia (rule-out and rule-in) in pregnant persons with suspicion of preeclampsia in conjunction with other diagnostic and clinical information. This assay is intended for the use as one component, in combination with other parameters, to evaluate the risk of early onset preeclampsia during the first trimester of pregnancy.	

Abbreviations: ARTG=Australian Register of Therapeutic Goods; IVD=in vitro diagnostic medical device; PAPP-A=pregnancy-associated plasma protein-A; PIGF=placental growth factor
Source: Table 1, p15 of ADAR.

6. Proposal for public funding

The Applicant-Developed Assessment Report (ADAR) proposed a model for funding FMF risk calculation through the MBS by expansion of existing items to publicly fund the currently non-funded inputs:

- Amending MBS item 55707 to incorporate the assessment of UtA-PI.
 - An increase to the existing fee for MBS item 55707 (\$72.85 to \$91.06) was requested to reflect the increased time and complexity associated with assessing UtA-PI as part of the investigations performed through MBS item 55707.
- Amending MBS item 66750 to incorporate PIGF, with flow-on amendments to 66751.
 - An increase to the existing fee for MBS items 66750 (\$39.75 to \$69.75) and 66751 (\$55.25 to \$85.25) was requested to reflect the addition of the PIGF marker through these items.

Note that the MBS fees have since been updated and the schedule fee is now \$75.45 for MBS item 55707. Modifying existing items was preferred by PASC as an alternative to creation of a series of new MBS items (PICO page 21). The ratified PICO proposed amendments, which were presented in the ADAR, are identified using ~~strikethrough~~ (remove component) and **bold** (add

component) text in Table 2 and Table 3 below. The ADAR added notes to the item descriptors (underlined).

Table 2 Proposed amendments to MBS item 55707 based on the ratified PICO and modified by the applicant.

Category 5 (Diagnostic Imaging Services)
<p>MBS item 55707</p> <p>Pelvis or abdomen, pregnancy related or pregnancy complication, fetal development and anatomy, ultrasound (the current ultrasound) scan of, by any or all approaches, if:</p> <ol style="list-style-type: none"> the pregnancy (as confirmed by the current ultrasound) is dated by a fetal crown-rump length of 45 to 84 mm or 11⁺⁰ to 13⁺⁶ weeks' gestation; and nuchal translucency measurement is performed to assess the risk of fetal abnormality; and/or uterine artery pulsatility index is performed for the assessment of risk of preeclampsia; and the current ultrasound is not performed on the same patient within 24 hours of a service mentioned in another item in this Subgroup (R) <p>(See para IN.0.19 of explanatory notes to this Category)</p> <p>Fee: \$72.85 \$91.06 Benefit: 75% = \$54.65 \$68.30 85% = \$61.95 \$77.40</p> <p><u>Note: Personnel performing uterine artery pulsatility index assessments through this service must have training and certification relating to the conduct of preeclampsia risk assessment.</u></p> <p><u>Providers performing uterine artery pulsatility index assessments through this service must participate in performance audits and Quality Assurance Programs applicable to the preapproved algorithm for the risk of preeclampsia.</u></p>

Source: Table 5, p30 of ADAR.

Table 3 Proposed amendments to MBS items 66750 and 66751 based on the ratified PICO and modified by the applicant.

Category 6 (Pathology Services)
<p>MBS item 66750</p> <p>Quantitation, in pregnancy, of any 2 3 of the following to detect fetal abnormality or 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 (uE3), alpha-fetoprotein (AFP) - including (if performed) a service described in item 73527 or 73529 - Applicable not more than once in a pregnancy</p> <p>Fee: \$39.75 \$69.75 Benefit: 75% = \$29.85 \$52.31 85% = \$33.80 \$59.23</p> <p><u>Note: Providers performing this service for assessment of risk of preeclampsia must participate in performance audits and Quality Assurance Programs applicable to the preapproved algorithm for the risk of preeclampsia</u></p>
<p>MBS item 66751</p> <p>Quantitation, in pregnancy, of any three four or more tests described in 66750</p> <p>Item must not be used for assessment of risk preeclampsia if pregnancy is dated later than 11⁺⁰ to 13⁺⁶ weeks' gestation</p> <p>(Item is subject to rule 25)</p> <p>Fee: \$55.25 \$85.25 Benefit: 75% = \$41.45 \$63.94 85% = \$47.00 \$72.46</p> <p><u>Note: Providers performing this service for assessment of risk of preeclampsia must participate in performance audits and Quality Assurance Programs applicable to the preapproved algorithm for the risk of preeclampsia</u></p>

Source: Table 6, p31 of ADAR.

The amendments to existing MBS items 55707, 66750 and 66751 proposed by the ADAR are as per the Department's recommendations. However, justification for the additional time required for UtA-PI and PIGF to support the increase in MBS fee has not been provided. The commentary also noted that organisations during public consultation were concerned about existing MBS funding for first trimester ultrasounds being well below the cost of service, and this having consequences for bulkbilling.

Restrictions

The proposed FMF risk calculation can be performed in an outpatient setting and does not require inpatient admission. However, the biochemical component of the test (measurement of maternal serum PIGF and/or PAPP-A) would be performed in a laboratory.

The applicant stated that to ensure that each input variable (MABP, UtA-PI and PIGF and/or PAPP-A) is measured to an appropriate standard, it is imperative that the assessments are conducted by trained members of medical staff (e.g., UtA-PI should be assessed by a sonographer or sonologist with training and certification relating to the conduct of preeclampsia testing). Organisational feedback also identified reliance on all the components being done optimally and according to protocol to provide accurate and meaningful results.

The FMF runs training, certification, and audit services for the assessment of MABP, UtA-PI, PIGF and PAPP-A. The proposed MBS items included a note from the applicant outlining that providers must participate in performance audits and Quality Assurance Programs. The intent of this note was to support best standard of care for MABP and UtA-PI assessments funded through the MBS as suggested by PASC. However, no cost or resource requirement details on FMF training were provided as part of the ADAR. How these will be incorporated into the overall cost/public funding requirements should be considered. Key considerations related to training included:

1. What is the current training, certification, and performance auditing requirements? What is the time/opportunity cost in participating?
2. How many sonographers or phlebotomists would need to participate to have the necessary number of trained staff for the population expected to use the proposed technology? Is this feasible/appropriate?
3. What would be the total cost of training and compliance requirements?

7. Population

One population was proposed: all pregnant persons at 11⁺⁰ to 13⁺⁶ weeks gestation. The proposed technology would be used in place of the current clinical risk assessment. The intervention is not currently publicly funded (available, but not funded). The proposed technology would replace the existing SoC in the clinical management algorithm. The SoC is risk assessment for preterm preeclampsia in "early gestation" as part of clinical exam/history (typically done between 8- and 20- weeks' gestation, though there is no formal timeline). If a patient is considered "high risk" (usually based on NICE or ACOG guidelines), they are prescribed aspirin and monitored for preeclampsia.

The ADAR generally addressed the requirements of the ratified PICO. However, the commentary identified some key issues for consideration regarding the proposed clinical management algorithm:

- It was unclear whether assessment of maternal characteristics, medical and obstetric history would be conducted by the GP practice, midwife, or obstetrician, or by sonographers/phlebotomists after referral in the new clinical management algorithm. In the ratified PICO, PASC queried whether a clinician-led model should be used rather than

the proposed sonographer- or phlebotomist-led models of care. Currently, the clinical management algorithm (assessment of maternal characteristics, medical and obstetric history) is clinician or midwife-led. Changing this requirement to a different practitioner may need to consider time/resource burden and how results are interpreted by the patient.

- The ADAR omitted discussion of how aspirin is prescribed in current practice, and how this then translates to use. This has not been included in the clinical management algorithm but is a key consideration. As aspirin is over the counter does this have any impact on prescription and usage?
- Risk-based testing raises issues around eligibility cut-offs and providing risk information to patients because aspirin is over the counter, which means that provision of risk information may lead to self-administration for those not actually considered at high risk for preeclampsia.
- In the ratified PICO, PASC considered that the applicant needed to provide evidence that the protocol prescribed by 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). This point was not discussed in the ADAR.

8. Comparator

The proposed comparator was the standard of care, which consists of collecting maternal characteristics and medical/obstetric history and comparing this with published guidelines (typically NICE or ACOG) to assess risk of preeclampsia. The parameters for each guideline and subsequent treatment recommendations are listed in Table 4.

Table 4 Summary of NICE and ACOG assessment and recommendations for preterm preeclampsia.

Organisation	Moderate risk factors	High risk factors	Recommendations
NICE guidelines	<ul style="list-style-type: none"> • First pregnancy • Age \geq 40 years • BMI \geq35 kg/m² at first visit • Family history of preeclampsia • Pregnancy interval >10 years; • Multiple pregnancy 	<ul style="list-style-type: none"> • Hypertensive disease during previous pregnancy • Chronic kidney disease (>30 mg/mmol or 24-hour urine collection >3000 mg protein threshold for significant proteinuria) • Autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome • Type 1 or Type 2 diabetes • Chronic hypertension 	If \geq 2 moderate risk factors or \geq 1 high risk factor for preeclampsia advise to take aspirin 75 mg/day from 12 weeks until birth.
ACOG guidelines	<ul style="list-style-type: none"> • First pregnancy • Age \geq 35 years • BMI \geq30 kg/m² at first visit • Family history of preeclampsia • Sociodemographic and personal history factors (not specified) 	<ul style="list-style-type: none"> • Previous pregnancy with preeclampsia • Chronic kidney disease • Autoimmune disease • Type 1 or Type 2 diabetes • Chronic hypertension • Multifetal gestation 	If \geq 1 moderate risk factors or any high risk factor for preeclampsia advise to take aspirin 81 mg/day, initiated between 12 and 28 weeks gestation until birth.

Abbreviations: BMI=body mass index
Source: Section 1.5, p22/23 of ADAR.

There are no MBS items specifically for the assessment of risk of preterm preeclampsia. Currently, any assessment of risk of preterm preeclampsia would be provided through generic professional attendance items provided by a GP (MBS items 3, 4, 23, 24, 36, 37, 44 and 47), specialist (MBS items 104, 105, 107, and 108) or obstetrics-related items eligible to be provided by GPs, obstetricians, and allied health workers (MBS items 16400, 16401, 16404 and 16500). These were not considered in the economic or financial impacts as part of the ADAR.

The commentary agreed that the proposed comparator was appropriate. The ADAR stated that the guidelines are “not cohesively applied in clinical practice due to lack of a framework for their application. This has a flow-on consequence of the NICE and ACOG recommendations being suboptimal”, though this was not substantiated. The commentary could not find evidence on the current application of preterm preeclampsia risk assessment and the use of the guidelines in the Australian setting.

9. Summary of public consultation input

Prior to the October ESC Meeting consultation feedback deadline, consultation input was received from eight organisations and eleven individuals, with three consumers, seven medical professionals and one both a consumer and a medical professional. The organisations that submitted input were: Royal Women’s Hospital – Obstetric Medicine Unit; Australia Action on Preeclampsia (AAPEC); 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); The Australian Sonographers Association (ASA); The Royal Australia and New Zealand College of Radiologists (RANZCR); Royal Australian College of General Practitioners (RACGP).

Post ESC deadline feedback was received by two organisations and three individuals all of whom are medical professionals. The organisations that submitted input were Society of Obstetric Medicine Australia and New Zealand (SOMANZ) and The Royal Hospital for Women, Randwick, NSW.

All consultation comments received indicated support for the proposal.

Benefits

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

- Early identification of women at increased risk for developing preeclampsia and the severity
- Allows early implementation of appropriate prophylactic management, including targeted commencement of aspirin
- Allows identification for when higher level surveillance is required
- Improved screening efficacy beyond clinical judgement
- Reduction in maternal and fetal mortality and morbidity
- Cost savings to the health system with decreased incidence of preeclampsia
- Reduction of preeclampsia may also help reduce long-term cardiovascular risk in pregnant persons and their babies
- Outside metropolitan areas, this will assist in triaging patients to higher acuity hospitals when appropriate.

Disadvantages

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

- Potential for falsely alarming women in early pregnancy
- May cause increased stress and worry for women with a 'high risk' result
- Time in getting the testing performed.

Other issues received in the consultation feedback included:

- Ideally this structured prenatal risk assessment would be part of a coordinated antenatal care pathway.
- One organisation noted that the women most likely to be severely adversely affected by preeclampsia are vulnerable women who present to public hospitals.
- One organisation noted that women will need counselling prior to and after having the test, regarding the results and the implications for the pregnancy.

10. Characteristics of the evidence base

The clinical analysis presented in the application was based on 5 published reports from the ASPRE (Combined Multimarker Testing and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention) trial^{3,4,5,6,7}. The ASPRE trial was a high quality randomised controlled trial (RCT) directly comparing prescription of 150mg of aspirin from 11-14 weeks of gestation until 36 weeks to SoC for patients identified as high risk for preeclampsia using the FMF risk calculator, at maternity hospitals in the UK, Spain, Italy, Belgium, Greece, and Israel. A systematic review was conducted by the applicant as part of the ADAR to identify additional evidence relevant to the PICO. A summary of the included evidence is presented in Table 5.

3 O'Gorman, N., Wright, D., Poon, L. C., Rolnik, D. L., Syngelaki, A., de Alvarado, M., Carbone, I. F., Dutemeyer, V., Fiolna, M., Frick, A., Karagiotis, N., Mastrodima, S., de Paco Matallana, C., Papaioannou, G., Pazos, A., Plasencia, W., & Nicolaides, K. H. (2017). Multicenter for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation: comparison with NICE guidelines and ACOG recommendations. *Ultrasound Obstet Gynecol*, 49(6), 756-760. <https://doi.org/10.1002/uog.17455>

4 Poon, L. C., Rolnik, D. L., Tan, M. Y., Delgado, J. L., Tsokaki, T., Akolekar, R., Singh, M., Andrade, W., Efeturk, T., Jani, J. C., Plasencia, W., Papaioannou, G., Blazquez, A. R., Carbone, I. F., Wright, D., & Nicolaides, K. H. (2018). ASPRE trial: incidence of preterm pre-eclampsia in patients fulfilling ACOG and NICE criteria according to risk by FMF algorithm. *Ultrasound Obstet Gynecol*, 51(6), 738-742. <https://doi.org/10.1002/uog.19019>

5 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. (2017a). Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. *New England Journal of Medicine*, 377(7), 613-622. <https://doi.org/10.1056/NEJMoa1704559>

6 Wright, D., Poon, L. C., Rolnik, D. L., Syngelaki, A., Delgado, J. L., Vojtassakova, D., de Alvarado, M., Kapeti, E., Rehal, A., Pazos, A., Carbone, I. F., Dutemeyer, V., Plasencia, W., Papantoniou, N., & Nicolaides, K. H. (2017). Aspirin for Evidence-Based Preeclampsia Prevention trial: influence of compliance on beneficial effect of aspirin in prevention of preterm preeclampsia. *American Journal of Obstetrics and Gynecology*, 217(6), 685.e681-685.e685. <https://doi.org/https://doi.org/10.1016/j.ajog.2017.08.110>

7 Rolnik, D. L., Wright, D., Poon, L. C. Y., et al. (2017b). ASPRE trial: performance of screening for preterm pre-eclampsia [<https://doi.org/10.1002/uog.18816>]. *Ultrasound in Obstetrics & Gynecology*, 50(4), 492-495. 6

Table 5 Key features of the included evidence.

Criterion	Context	Study [^]	Type of evidence supplied
1. Direct from test to health outcomes evidence	Direct evidence of the use of FMF risk algorithm [versus SoC] on health outcomes.	Rolnik et al., 2021	One study reported on pregnancy outcomes in those who underwent preeclampsia assessment using the FMF risk calculator [versus SoC].
2. Test accuracy	Evidence of the test accuracy of FMF risk algorithm for diagnosis of preterm preeclampsia [versus SoC].	O'Gorman et al., 2017 Poon et al., 2018	Two studies from the ASPRE program compared the performance of the FMF risk calculator with ACOG and NICE criteria.
		Rolnik et al., 2017b	One study from the ASPRE program reported on the performance of the FMF risk calculator in the whole population tested in the ASPRE trial.
		Tan et al., 2017	One study examined the performance of the FMF risk calculator [versus NICE guidelines].
		Rolnik et al., 2021 Boutin et al., 2021 Chen et al., 2021	Three studies validated the FMF risk calculator in different populations (Australia, Canada, Taiwan).
3. Change in diagnosis/ treatment/ management	Evidence of the impact of risk score calculated by FMF on prescription of aspirin [versus SoC].	-	There was no evidence provided for the incremental impact of the FMF risk calculator on prescription of aspirin.
4. Influence of the change in management on health outcomes	Evidence of the impact of aspirin [versus no aspirin] on preeclampsia-related health outcomes.	Rolnik et al., 2017a	One study reported the primary and secondary outcomes of the ASPRE trial (prescription of aspirin on health outcomes).
		Roberge et al., 2018a	A meta-analysis on the effect of aspirin use for prevention of preeclampsia was provided.
5. Influence of the change in management on intermediate outcomes	Evidence of the impact of aspirin [versus no aspirin] on incidence of pre-term preeclampsia.	Wright et al., 2017	One study from the ASPRE trial reported a secondary analysis examining the influence of treatment compliance on the beneficial effect of aspirin in preventing preterm preeclampsia.
6. Association of intermediate outcomes with health outcomes	Evidence of the impact of incidence of preterm preeclampsia on preeclampsia-related health outcomes.	-	There was no evidence provided for the impact of incidence of preterm preeclampsia on preeclampsia-related health outcomes.
7. Adverse events due to testing	Evidence for adverse events associated with use of FMF risk calculator [versus SoC].	-	There was no evidence provided for adverse events associated with testing.
8. Adverse events due to treatment	Evidence for adverse events associated with aspirin [versus no aspirin].	Rolnik et al., 2017a	One study reported the adverse events associated with aspirin recorded as part of the ASPRE trial.

[^]Underlined studies represent those reporting results from the ASPRE trial. Pale grey shading indicates criteria for which no evidence was provided by the ADAR.

Source: Table C1, p35 of ADAR.

Supporting evidence was provided for some outcomes, but not others. If broader literature is being used to support the clinical claim for test accuracy (e.g., Boutin et al., 2021⁸ or Chen et al., 2021⁹) or treatment effectiveness (Roberge et al., 2018a¹⁰), the commentary considered it was also necessary to conduct a similar systematic review related to safety outcomes of the treatment.

While evidence to support both a direct and linked evidence approach was provided, the distinction was not identified in the ADAR. A summary of the evidence, interpretation and key uncertainties is provided below.

Table 6 Summary table of key uncertainties in investigative evidence – direct evidence.

Evidence component of the assessment	Interpretation and key uncertainties
Health outcomes	The only study that provided direct to test evidence was a large retrospective cohort study in Australia ¹ . There were significant selection bias concerns with this study. All but one of the sites that the patients who underwent FMF risk calculation were recruited from were part of selected private fetal medicine practices. By contrast the comparator patients for standard of care (SOC) were drawn from the general Australian patient population, making it likely that the ‘intervention’ group is not representative of the general population. Whilst adjustment was performed on relevant covariates, there were still inherent risks of the outcomes being reflective of the special characteristics of the ‘intervention’ group (including socioeconomic status and whether they held private health insurance) or related variables, rather than the test alone.

Source: developed by the commentary.

8 Boutin, A., et al. (2021). Pregnancy outcomes in nulliparous women with positive first-trimester preterm preeclampsia screening test: the Great Obstetrical Syndromes cohort study. *Am J Obstet Gynecol*, 224(2), 204 e201-204 e207. <https://doi.org/10.1016/j.ajog.2020.08.008>

9 Chen, Y. T., et al. (2021). Taiwanese new direction in prediction of early pregnancy preeclampsia. *Taiwan J Obstet Gynecol*, 60(1), 66-69. <https://doi.org/10.1016/j.tjog.2020.11.009>

10 Roberge, S., et al. (2018a). Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. *Am J Obstet Gynecol*, 218(3), 287-293 e281. <https://doi.org/10.1016/j.ajog.2017.11.561>

Table 7 Summary table of key uncertainties in investigative evidence – linked evidence.

Evidence component of the assessment	Interpretation and key uncertainties
Test accuracy	The clinical claim for superior test accuracy of the test compared to SoC was supported by the evidence, though there was significant variation in test accuracy outcome results across studies (e.g., FMF risk calculator sensitivity from 50.0% to 82.4%), with some risk of bias concerns.
Change in management	There was no evidence provided for the incremental impact of the test on change in management (i.e., prescription of aspirin in practice). International literature indicated that in the absence of the FMF calculation up to 40% of women are not offered aspirin despite being at high risk of preeclampsia ^{11,12} , as well as practicality-related treatment delays experienced by approximately 20% of women. ¹⁵
Health outcomes	The evidence supported superior health outcomes in high-risk patients due to treatment with aspirin compared to SoC. Evidence presented demonstrated that aspirin prescription for those deemed “high risk” by the test was effective at (a) reducing incidence of preterm preeclampsia, and (b) reducing pregnancy-related complications. However these findings only apply to patients identified as high-risk and the superiority of the FMF risk-calculator compared to current practice for management of women identified as low-risk (including impact on false negatives) cannot be assumed.
Safety of the test	<p>The ADAR did not provide evidence to support the clinical claim for non-inferior safety of the test. The assessment team conducted an independent scoping search of relevant literature and concluded that the clinical claim for non-inferior safety of testing was not supported. Key safety issues related to the test are:</p> <ul style="list-style-type: none"> • Psychological harm associated with risk-based testing and results (this outcome was included in the PICO but not discussed in the ADAR). • Safety outcomes related to comparative psychological harms of having delivery at a non-viable gestation or a preterm infant, with or without the proposed intervention were not described. • Safety outcomes related to comparative physical harms to (a) the pregnant person and (b) the baby once delivered, with or without the proposed intervention were not described. • Safety consequences of unnecessary aspirin treatment in false positive cases and missed aspirin treatment in false negative cases were mentioned, though the impact was not explored. The evidence found that the false negative rate was minimal, however, the false positive rate (estimated at around 10%) was practically significant due to the number of people who will be tested (estimated by the applicant at almost 260,000 per year in the PICO). The clinical impacts of false positive cases are dependent on the clinical claim for the safety of the treatment (discussed below).
Safety of the treatment	The clinical claim for non-inferior safety related to treatment was not supported. While the ASPRE trial found that adverse events were no more common or more serious in the aspirin versus placebo treatment group, the applicant stated that the trial was not powered for a definitive assessment. In addition, literature from outside the ASPRE trial is inconclusive. For most complications, additional literature indicated no additional risk from aspirin. However, for some safety outcomes (such as placental abruption and postpartum haemorrhage and blood loss), results varied.

Source: developed by the commentary.

11 Lailier, G., Grave, C., Gabet, A., Regnault, N., Deneux-Tharoux, C., Kretz, S., Tsatsaris, V., Plu-Bureau, G., Blacher, J., & Olie, V. (2023). Aspirin for the Prevention of Early and Severe Pre-Eclampsia Recurrence: A Real-World Population-Based Study. *Drugs*, 83(5), 429-437. <https://doi.org/10.1007/s40265-023-01842-3>

12 Olson, D. N., Russell, T., & Ranzini, A. C. (2022). Assessment of adherence to aspirin for preeclampsia prophylaxis and reasons for nonadherence. *Am J Obstet Gynecol MFM*, 4(5), 100663. <https://doi.org/10.1016/j.ajogmf.2022.100663>

11. Comparative safety

The commentary considered that overall, the clinical claim for non-inferior safety of the intervention compared to SoC was **not supported**. No evidence was provided in the ADAR for the adverse impacts of testing (first bullet point under the “Safety outcomes” heading in the PICO). However, the commentary determined that there were key safety issues for MSAC consideration, which are discussed below.

Safety of test procedures

The commentary considered the evidence **supported** the clinical claim for non-inferior safety related to direct harm of testing procedures required for the FMF risk calculator, compared to SoC. For the required inputs into the risk calculator, all tests are part of general prenatal care and are already, or can be, implemented into the normal pregnancy care pathway. UtA-PI would be performed as part of the routine first trimester ultrasound scan; PIGF would be an additional measurement in the general biochemical testing of pregnant persons, together with PAPP-A testing performed as part of the routine first trimester testing. Similarly, assessment of the maternal MAP, while requiring adherence to a protocol of blood pressure measurement, is universally carried out as part of routine pregnancy care. The FMF risk algorithm is proposed to be used in all pregnant persons, which is the same population as the current comparator.

Psychological harm from testing

The commentary considered that there was **insufficient evidence provided to support** the clinical claim for non-inferior safety related to psychological impacts of the proposed intervention compared to SoC. The PICO included “Anxiety associated with the finding of increased risk of PE” as a safety outcome, but this was not addressed in the ADAR. Public consultation from organisational stakeholders identified this outcome as a key issue. Other testing programs show that testing-induced distress is common¹³; there was no discussion of this safety impact or the implications of managing this burden. Importantly, managing distress would likely be done by additional consultation time with clinicians. This would have impacts on time burden to healthcare providers and increased cost. The pre-ESC response argued that the potential for psychological harm associated with preeclampsia screening should be considered in the context of the potential psychological harms from preterm births and other preeclampsia-related outcomes at term; and the improved diagnostic performance of the FMF algorithm compared with SoC increases the precision with which women at high risk for preterm preeclampsia are identified and the subsequent use of low-dose aspirin in high risk pregnancies significantly reduces the incidence of preterm preeclampsia. As such, the pre-ESC response argued that the ability to better identify women at risk of developing preterm preeclampsia and recommended prophylactic treatment with low-dose aspirin using the FMF algorithm compared with SoC is expected to reduce rather than exacerbate psychological harm and stress associated with screening and downstream maternal and fetal outcomes.

The commentary also noted that there is an absence of evidence presented by the ADAR on the incidence of preeclampsia in the low-risk pregnancies (i.e. there is no evidence to ascertain the impact of false negatives made by FMF compared to current risk-assessment). However the pre-ESC response argued that as the test sensitivity of the FMF algorithm has been shown to be higher than that of SoC, it is unlikely that the FMF algorithm will systematically miss a true high risk pregnancy that would otherwise be picked up by SoC.

13 Kim Tam, B., et al. (2021). Scanxiety: a scoping review about scan-associated anxiety. *BMJ Open*, 11(5), e043215. <https://doi.org/10.1136/bmjopen-2020-043215>

Safety related to clinical utility of FMF risk calculator

The commentary considered there was **insufficient evidence provided to support** the clinical claim for non-inferior safety related to the clinical utility of the proposed intervention compared to SoC. The applicant mentioned the possibility of downstream safety consequences, including unnecessary aspirin treatment in women falsely deemed high risk (false positive testing result) and missed aspirin treatment in women with a false negative testing test result. However, no supporting evidence or modelling of these harms was provided in the ADAR.

The false positive and negative rates of the FMF risk calculator are discussed below. Evidence suggested that the false negative rate was minimal. However, the false positive rate (estimated at around 10%) was operationally significant due to the volume of people who will be tested (estimated by the applicant at almost 260,000 per year in the PICO). The clinical impacts of false positive cases are dependent on the clinical claim for the safety of the treatment (discussed below).

The ADAR described the use of the current risk assessment guidelines in practice as being “not routine”. If this is the case, standardised use of the FMF risk algorithm as proposed may increase the actual volume of false positives compared to the SoC.

Safety of consequent treatment

The commentary considered there was **insufficient evidence provided to support** the clinical claim for non-inferior safety of consequent aspirin treatment arising from the proposed intervention. The ADAR presented evidence from the ASPRE trial only; key results are presented in Table 8 below. There was no evidence that adverse events were more common or more serious in the aspirin (n=798) versus placebo treatment group (n=822). On balance, the commentary considered that outcomes from the ASPRE trial suggested non-inferior safety of aspirin use compared to placebo, though the ADAR identified that the trial was not powered for a definitive assessment. The incidence of adverse effects occurring at a frequency of less than 1:798 would not be expected to be identified from this study.

Table 8 Serious and non-serious adverse events reported in the ASPRE trial.

Outcome	Intervention (Aspirin)	SoC (Placebo)	Difference between groups
Number of participants experiencing at least 1 serious adverse events, including: <ul style="list-style-type: none"> maternal appendicitis requiring surgery fetal chromosomal abnormalities fetal structural defects (congenital diaphragmatic hernia hypoplastic left heart syndrome, etc.). 	1.6% (13/798)	3.2% (26/822)	Not significant
Number of participants experiencing at least 1 non-serious adverse events, including:	25.9% (207/798)	25.5% (210/822)	Not significant
Headache/dizziness	9.6%	8.8%	
Nausea/vomiting	5.0%	4.4%	
Abdominal and/or pelvic pain	3.3%	4.0%	
Dyspepsia/heartburn	2.4%	2.7%	

Source: Table S4, Rolnik et al., 2017a

However, the ADAR did not conduct a review for additional evidence related to safety outcomes of aspirin use in pregnancy. The commentary completed a scoping search of the literature for relevant supporting evidence related to this PICO (Table 9). External literature pointed to possible

safety risks of aspirin use in pregnancy¹⁴. For most treatment-related complications, the literature indicates no additional risk from aspirin. However, for some safety outcomes results vary – most saliently for placental abruption (where results across meta-analyses are conflicting^{15,16,17}, and postpartum haemorrhage and blood loss – where results from the most recent meta-analysis point to increased risk from aspirin use¹⁸. Therefore the evidence uncovered by the scoping search was inconclusive on this point.

The pre-ESC response noted that many studies included in the meta-analysis identified in the scoping search did not enrol women assessed as being high risk for preeclampsia and, thus, have different baseline risk profiles compared with women taken low-dose aspirin specifically for prophylaxis of preterm preeclampsia. The pre-ESC response argued that the independent scoping review did not identify any compelling new evidence to conclude that low-dose aspirin is unsafe to use for the purpose of preterm preeclampsia prophylaxis.

Table 9 Key supporting evidence and results identified by a scoping search undertaken by the commentary.

Study	Description	Outcome, Population	Key results
Jiang et al., 2023	Systematic review and meta-analysis of studies comparing pregnancy outcomes that covered the incidence of postpartum haemorrhage or the amount of postpartum blood loss in pregnancies with aspirin vs placebo (or no aspirin) were included.	Postpartum haemorrhage (21 studies, N=373,926)	Results suggested that aspirin (dose 60-150mg a day) use during pregnancy was associated with an increased incidence of postpartum haemorrhage (OR 1.20; 95% CI: 1.07-1.34).
		Postpartum blood loss (7 studies, N=10,163)	Results suggested that aspirin use during pregnancy was associated with slightly higher postpartum blood loss (MD=12.85 mL; 95% CI: 3.28–22.42) than placebo or no treatment.
Roberge et al., 2018b	Meta-analysis to estimate the effect of aspirin on the risk of placental abruption or antepartum haemorrhage in relation to gestational age at onset of therapy and the dosage of the drug.	Antepartum haemorrhage, placental abruption (20 studies, N=12,585)	Aspirin (<100 mg per day) had no impact on the risk of placental abruption or antepartum haemorrhage (initiated at ≤16 weeks of gestation=RR 1.11; 95% CI: 0.52–2.36; at >16 weeks of gestation=RR 1.32; 95% CI 0.73–2.39). Aspirin (≥100 mg per day) was not associated with a significant change on the risk of placental abruption or antepartum haemorrhage (initiated at ≤16 weeks of gestation=RR 95% CI: 0.31–1.26; at >16 weeks of gestation=RR 2.08; 95% CI 0.86–5.06), but the difference between the subgroups was significant (p=.04).
Turner et al., 2020	Meta-analysis and meta-regression of RCTs to evaluate the impact of low dose aspirin (LDA) on perinatal outcomes.	Placental abruption, low 5-min Apgar score, neonatal acidosis, neonatal intensive care unit admission, periventricular	LDA was not associated with any significant increase in adverse events if commenced ≤16 weeks gestation. If commenced >16 weeks' gestation, low dose aspirin was associated with a significant reduction in 5-min Apgar score <7 (RR 0.75;

14 Tousty, P., et al. (2023). Low-Dose Aspirin after ASPRE-More Questions Than Answers? Current International Approach after PE Screening in the First Trimester. *Biomedicines*, 11(6). <https://doi.org/10.3390/biomedicines11061495>

15 Roberge, S., et al. (2018b). Meta-analysis on the effect of aspirin use for prevention of preeclampsia on placental abruption and antepartum hemorrhage. *Am J Obstet Gynecol*, 218(5), 483-489. <https://doi.org/10.1016/j.ajog.2017.12.238>

16 Turner, J. M., et al. (2020). Impact of low-dose aspirin on adverse perinatal outcome: meta-analysis and meta-regression. *Ultrasound Obstet Gynecol*, 55(2), 157-169. <https://doi.org/10.1002/uog.20859>

17 Xu, T. T., et al. (2015). Low-Dose Aspirin for Preventing Preeclampsia and Its Complications: A Meta-Analysis. *J Clin Hypertens (Greenwich)*, 17(7), 567-573. <https://doi.org/10.1111/jch.12541>

18 Jiang, Y., et al. (2023). Low-dose aspirin use during pregnancy may be a potential risk for postpartum hemorrhage and increased blood loss: a systematic review and meta-analysis. *Am J Obstet Gynecol MFM*, 5(4), 100878. <https://doi.org/10.1016/j.ajogmf.2023.100878>

		haemorrhage and perinatal death (40 studies, N=34,807)	95% CI 0.58–0.96) and periventricular haemorrhage (RR 0.68; 95% CI 0.47–0.99), but a trend towards an increase in the risk of placental abruption (RR 1.20; 95% CI 1.00–1.46; p=0.06) was also noted.
Xu et al., 2015	Meta-analysis of RCTs to evaluate low dose aspirin for preventing preeclampsia and its complications.	Preterm delivery, postpartum haemorrhage, placental abruption, antepartum haemorrhage, caesarean birth, perinatal death, IUGR, spontaneous abortion, NIH, low Apgar score (5-minute score <7), transfer to NICU (29 studies)	Low dose aspirin increases the incidence of placental abruption (OR 1.35; 95% CI: 1.05–1.73), but not other major complications.

Abbreviations: CI=Confidence interval; IGUR=intrauterine growth restriction (IUGR); MD=mean difference; NICU=neonatal intensive care unit; NIH=neonatal intraventricular haemorrhage; LDA=low dose aspirin; OR=odds ratio; RR=relative risk; RCT=randomised controlled trial; IGUR=intrauterine growth restriction
Source: Table C2, p46-47 of ADAR.

12. Comparative effectiveness

Direct from test to health outcomes evidence

One study reported direct from test to health outcomes evidence, that is, reporting of pregnancy outcomes for those who underwent preeclampsia testing using the FMF risk calculator versus SoC¹. After adjustment for potential confounders, women who were tested with FMF risk calculator versus not tested were significantly less likely to have preeclampsia, preterm birth, and neonates with low birthweight. Key results from the study are presented in Table 10 and Table 11 below.

The commentary considered that there were significant selection bias concerns with this study that limited the reliability of results presented. Specifically, all but one of the sites that the patients who underwent FMF risk calculation were recruited from were part of selected private fetal medicine practices. By contrast the comparator patients for standard of care (SOC) were drawn from the general Australian patient population, making it likely that the ‘intervention’ group is not representative of the general population. Whilst adjustment was performed on relevant covariates, there were still inherent risks of the outcomes being reflective of the special characteristics of the ‘intervention’ group (including socioeconomic status and whether they held private health insurance) or related variables, rather than the test alone.

In addition the study did not report on the incremental proportion of pregnancies identified as at high-risk when using FMF versus current assessment.

However the pre-ESC response argued that while differences in baseline demographic and clinical characteristics were statistically significant, this can partly be explained by the very large sample sizes and the magnitude of the differences is not clinically meaningful. The pre-ESC response argued that there is no evidence that the selection of patients was systematically favouring either cohort as the imbalances in baseline risk across cohorts (albeit negligible) did not systematically favour the FMF algorithm or SoC cohorts.

Table 10 Direct from test to health outcomes from Rolnik et al., 2021.

Outcome	FMF (n=29,618)	SoC (N=301,566)	Crude RR (95% CI)		Adjusted RR (95% CI)	
				p<0.001		p<0.001
Preterm preeclampsia	132 (0.4)	2096 (0.7)	0.64 (0.54–0.76)	p<0.001	0.70 (0.58–0.84)	p<0.001
All preeclampsia	455 (1.5)	7340 (2.4)	0.63 (0.57–0.89)	p<0.001	0.69 (0.63–0.76)	p<0.001
Birth <32 weeks	278 (0.9)	4435 (1.5)	0.64 (0.57–0.72)	p<0.001	0.83 (0.74–0.95)	p=0.004
Birth <37 weeks	1736 (5.9)	21,283 (7.1)	0.83 (0.79–0.87)	p<0.001	0.92 (0.88–0.97)	p=0.001
Birthweight <2500g	1354 (4.6)	17,295 (5.7)	0.80 (0.76–0.84)	p<0.001	0.89 (0.85–0.94)	p<0.001

Source: Rolnik et al., 2021, Table 2.

Risk ratios adjusted with modified Poisson models for age, body mass index, parity, socioeconomic status as given by IRSD (Index of Relative Socioeconomic Disadvantage), smoking, chronic hypertension, systemic lupus erythematosus, antiphospholipid syndrome, and pre-existing diabetes.

Table 11 Direct from test to health outcomes from Rolnik et al., 2021 (risk subgroup).

Outcome	High risk (≥ 1 in 100) (n=4,068)	Risk ratio (95% CI) p<0.001	Low risk (<1 in 100) (n=25,550)	Risk ratio (95% CI) p<0.001	SoC (n=301,566)
Preterm preeclampsia	86 (2.1)	3.04 (2.46–3.77) p<0.001	46 (0.2)	0.26 (0.19–0.35) p<0.001	2,096 (0.7)
Birth <37 weeks	466 (11.5)	1.62 (1.49–1.77) p<0.001	1270 (5.0)	0.70 (0.67–0.74) p<0.001	21,283 (7.1)
Birthweight <3 rd percentile	183 (4.5)	2.10 (1.82–2.42) p<0.001	379 (1.5)	0.70 (0.62–0.77) p<0.001	6,466 (2.1)
Neonatal death	8 (2.0 per 1,000)	1.76 (0.88–3.55) p=0.11	16 (0.6 per 1000)	0.56 (0.34–0.92) p=0.02	336 (1.1 per 1,000)

Source: Rolnik et al., 2021, Table 3.

The ADAR did not provide evidence for the following direct to test health outcomes as indicated in the PICO:

- Reduction 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)

However on the lack of evidence that use of the FMF algorithm would reduce downstream preeclampsia-related complications, the pre-ESC response argued that very large studies would be required to estimate the impacts of testing on the downstream rates of these very rare events and as such comparative clinical evidence for these outcomes is unlikely to be forthcoming.

Test accuracy

Test accuracy of the FMF risk calculator was examined in seven studies. Key reported results are displayed in Table 12. The commentary completed independent calculations of test accuracy outcomes based on confusion matrices from studies where available.

Based on assessment of risk of bias and applicability, the ASPRE trial provided the best evidence for test accuracy of the FMF risk calculator for the Australian population. Detection rate (i.e., sensitivity) of the FMF risk algorithm was reported as 76.7%; the false positive rate was 9.2%.

Table 12 Summary of key results from studies reporting test accuracy of FMF algorithm.

Study	Population (trial/country, N)	Risk cut-off	% (95% CI)				
			Sensitivity	Specificity	PPV	NPV	Accuracy
<u>Rolnik et al., 2017</u>	ASPRE N=25,797	1 in 100	76.7% (69.8-82.6)	90.0% (89.6- 90.3)	5.1% (4.3-6.0)	99.8% (99.8-99.9)	89.9% (89.5-90.2)
<u>O’Gorman et al., 2017</u>	ASPRE N=8,775	NR	75.0%	NR	10.0%	NR	NR
<u>Poon et al., 2018</u>	ASPRE N=34,573	1+ ACOG risk factor N=22,287	78.8% (72.8-84.0)	84.6% (84.1-85.1)	4.8% (4.1-5.5)	99.8% (99.7-99.8)	84.6 (84.1-85.0)
		1+ NICE high risk factor N=1,392	94.4% (86.4-98.5)	46.0% (43.3-48.7)	8.7% (6.8-10.9)	99.3% (98.3- 99.8)	48.5% (45.8-51.2)
		2+ NICE moderate risk factor N=2,360	82.9% (67.9-92.8)	71.6% (69.7-73.5)	4.9% (3.4-6.8)	99.6% (99.1-99.8)	71.8% (70-73.6)
Rolnik et al., 2021*	Australia N= 29,618	Assuming 10% of high risk women treated with aspirin	66.7% (58.1-74.5)	86.5% (86.1-86.9)	2.3% (1.8-2.8)	99.8% (99.8-99.9)	NR
		Assuming 90% of high risk women treated with aspirin	80.9% (75.4-85.7)	86.8% (86.4-87.2)	4.8% (4.2-5.5)	99.8% (99.8-99.9)	NR
Tan et al., 2017	UK N=16,747	1 in 100	82.4% (76.1-88.7)	NR	NR	NR	NR
Boutin et al., 2021	Canada N=4,575	1 in 100	69.0%	84.4%	15.6%	2.7%	99.8%
Chen et al., 2021	Taiwan N=700	1 in 98	50.0% (21.5-78.5)	90.0%	10%	NR	NR

Abbreviations: FPR=False positive rate; NPV=Negative predictive value; NR=Not Reported; ACOG=American College of Obstetricians and Gynecologists; FMF=Fetal Medicine Foundation; NICE=National Institute for Health and Excellence; PE=preeclampsia.

Italicised=results calculated by the commentary from confusion matrix where available; Underline=ASPRE trial

Source: Table 7, p38 of the ADAR

FMF risk calculator versus SoC

Test accuracy of the FMF risk calculator in comparison to SoC (NICE or ACOG guidelines/criteria) was examined in three studies^{4,5,19} each is summarised below.

Poon et al., 2018

The commentary completed independent calculations of test accuracy outcomes based on confusion matrices from the study, presented in Table 13 below. This study only used the entire sample (N=34,573) for testing the diagnostic performance of the comparator. From those who met the comparator criteria of “high risk”, the FMF risk algorithm was then applied. This may represent a possible clinical management pathway – i.e., initial risk testing via guidelines without invasive testing, followed by use of the FMF risk calculator (as suggested by RANZGP in consultation). However, it limits the ability to compare diagnostic performance across the FMF risk calculator and comparator.

19 Tan, M. Y., Wright, D., Syngelaki, A., Akolekar, R., Cicero, S., Janga, D., Singh, M., Greco, E., Wright, A., Maclagan, K., Poon, L. C., & Nicolaides, K. H. (2018). Comparison of diagnostic accuracy of early for pre-eclampsia by NICE guidelines and a method combining maternal factors and biomarkers: results of SPREE. *Ultrasound Obstet Gynecol*, 51(6), 743-750. <https://doi.org/10.1002/uog.19039>

Table 13 Performance of FMF algorithm vs NICE and ACOG criteria from Poon et al., 2018.

Population	Risk-cut off	% (95% CI)				
		Sensitivity	Specificity	PPV	NPV	Accuracy
FMF risk calculator						
Those with any one high risk factor in NICE guidelines N=22,287	1 in 100	78.8% (72.8-84.0)	84.6% (84.1-85.1)	4.8% (4.1-5.5)	99.8% (99.7-99.8)	84.6% (84.1-85.0)
Those with any two moderate risk factors in NICE guidelines N=1,392	1 in 100	94.4% (86.4-98.5)	46% (43.3-48.7)	8.7% (6.8- 10.9)	99.3% (98.3-99.8)	48.5% (45.8-51.2)
Those with any one risk factor in ACOG guidelines N=2,360	1 in 100	82.9% (67.9-92.8)	71.6% (69.7-73.5)	4.9% (3.4-6.8)	99.6% (99.1-99.8)	71.8 (70.0-73.6)
Comparators						
Full study sample N=34,573	Any one high risk factor in NICE guidelines	30.1% (24.4- 36.4)	96.2% (95.9-96.4)	5.2% (4.1- 6.5)	99.5% (99.4-99.6)	95.7% (95.5-95.9)
Full study sample N=34,573	Any two moderate risk factors in NICE guidelines	17.2% (12.6-22.5)	93.2% (93-93.5)	1.7% (1.2-2.0)	99.4% (99.3-99.5)	92.7% (92.4-93.0)
Full study sample N=34,573	Any one risk factor in ACOG guidelines	90.8% (86.4-94.1)	35.7% (35.2-36.2)	1.0% (0.8- 1.1)	99.8% (99.7-99.9)	36.1% (35.6-36.6)

Abbreviations: FPR=False positive rate; NPV=Negative predictive value; NR=Not Reported; ACOG = American College of Obstetricians and Gynecologists; FMF: Fetal Medicine Foundation; NICE: National Institute for Health and Excellence; PE: preeclampsia.

Source: Table C3, p51-52 of the ADAR

O’Gorman et al., 2017

The commentary was unable to independently calculate diagnostic performance outcomes from confusion matrices generated from data in the study. Diagnostic accuracy outcomes as reported in the study are displayed in Table 14. The risk cut-off used for the FMF algorithm was not reported in this study, therefore, it is unclear if this is the same threshold used in practice and if test accuracy is applicable to the proposed intervention.

Table 14 Performance of FMF algorithm vs NICE and ACOG criteria from O’Gorman et al., 2017.

Testing method	Specificity	Sensitivity (95% CI)		
		<32 weeks of pregnancy	<37 weeks of pregnancy	≥37 weeks of pregnancy
FMF algorithm	90%	100% (80–100)	75% (62–85)	43% (35–50)
NICE guidelines	89.8%	41% (18–67)	39% (27–53)	34% (27–41)
ACOG recommendations	35.8%	94% (71–100)	90% (79–96)	89% (84–94)

Abbreviations: ACOG= American College of Obstetricians and Gynecologists; FMF=Fetal Medicine Foundation; NICE=National Institute for Health and Excellence; CI=confidence interval

Source: Table 14, p50 of the ADAR.

Tan et al., 2017

The commentary was unable to independently calculate diagnostic performance outcomes from confusion matrices generated from data in the study. Diagnostic accuracy outcomes as reported in the study are displayed in Table 15.

Table 15 Performance of FMF risk calculator versus NICE criteria from Tan et al., 2017.

Testing method	Sensitivity (95% CI)	No adjustment for effect of aspirin (95% CI)	Adjustment for effect of aspirin* (95% CI)
FMF algorithm	82.4 (76.1–88.7)		
NICE guidelines	40.8 (32.8–48.9)		
Difference in detection rates between methods (% (95% CI))		41.6 (33.2–49.9)	35.1 (25.1–45.0)

Abbreviations: FMF=Fetal Medicine Foundation risk calculator; NICE=National Institute for Health and Excellence; CI=confidence interval; PE=preeclampsia

*Assumes that aspirin reduces risk of preterm pre-eclampsia by 60%.

Source: Table C4, p54 of the ADAR.

Summary

The evidence suggested that the FMF risk calculator and ACOG guidelines have superior sensitivity compared to the NICE criteria, but the FMF risk calculator and NICE criteria had superior specificity. Low levels of sensitivity (as seen in NICE) suggest many cases will be missed. Low levels of specificity (as seen in ACOG) indicate a high false positive rate (reported as 62.4% in Poon et al., 2017). Both present potential risks for implementation.

Some limitations of the test accuracy studies included no reporting of the risk cut off used, no justification for sample size or power, no adjustment for treatment (aspirin), and low incidences of outcomes results in wide confidence intervals obtained for performance of testing.

Treatment effectiveness

The commentary considered the evidence from the ASPRE trial supported the claim that aspirin reduced the risk of adverse health outcomes arising from preeclampsia, compared to placebo, in women identified at high-risk. The incidence of preterm preeclampsia was 13 of 798 participants (1.6%) in the aspirin group, as compared with 35 of 822 (4.3%) in the placebo group (Table 16). The incidence of preterm preeclampsia was 62% lower in the aspirin group compared with the placebo group. However there is an important caveat - given that these findings only apply to women identified as high-risk by the FMF risk-calculator the superiority of the FMF risk-calculator compared to current practice for management of women identified as low-risk (including impact on false negatives) cannot be assumed.

Table 16 ASPRE trial: preterm preeclampsia in aspirin and placebo groups.

Outcome	Aspirin group (n=798) (%)	Placebo group (n=822) (%)	Odd ratio (95% CI)	NNT (95% CI)
Preterm PE at <37 weeks of gestation	13 (1.6)	35 (4.3)	0.38 (0.20–0.74)	38 (23-100)
Preterm PE at < 34 weeks gestation	3 (0.04)	15 (1.8)	0.18 (0.05 -0.71))	70 (40-227)

Abbreviations: CI=confidence interval; PE=preeclampsia; NNT=number needed to treat; OR=odds ratio

Source: Rolnik et al., 2017

Prespecified subgroup analysis showed consistent treatment effects across estimated testing risk groups (test for interaction between treatment and risk group: p=0.86) and obstetrical history (interaction between treatment and obstetric history: p=0.39), see Figure 1.

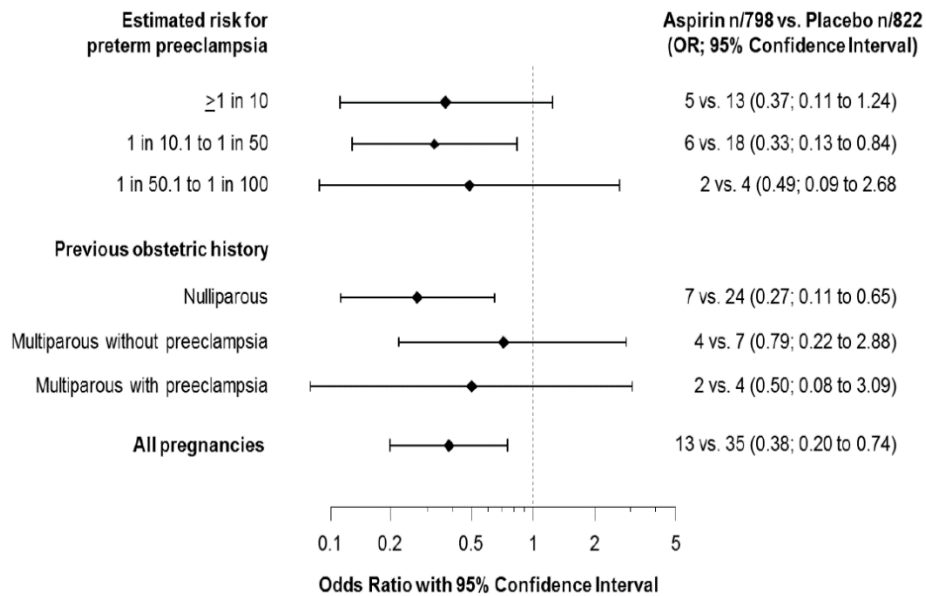


Figure 1 ASPRE trial subgroup analysis: different risk groups and obstetric history

Source: Rolnik et al., 2017a, Figure S1 in Supplementary Appendix

Secondary outcomes reported in the ASPRE trial included adverse outcomes of pregnancy before 34 weeks of gestation, before 37 weeks of gestation, and at or after 37 weeks of gestation; stillbirth or neonatal death; death and neonatal complications; neonatal therapy; and poor fetal growth. No significant between group difference in the incidence of any of these outcomes was observed. The outcomes relevant for this submission are tabulated in Table 17. However again the caveat applies that these findings are for women identified as high-risk by the FMF risk-calculator. The superiority of the FMF risk-calculator compared to current practice for management of women identified as low-risk (including impact on false negatives) cannot be assumed.

Table 17 ASPRE trial: secondary outcome results.

Outcome	Aspirin group (N=798)	Placebo group (N=822)	Odds ratio (99% CI)
Adverse outcomes at <34 weeks gestation			
Preeclampsia	3 (0.4)	15 (1.8)	0.18 (0.03–1.03)
Gestational hypertension	2 (0.3)	2 (0.2)	1.02 (0.08–13.49)
Abruption without preeclampsia	1 (0.1)	3 (0.4)	0.36 (0.02–7.14)
Spontaneous delivery without preeclampsia	12 (1.5)	12 (1.5)	1.07 (0.37–3.10)
Adverse outcomes at <37 weeks gestation			
Gestational hypertension	8 (1.0)	7 (0.9)	1.19 (0.31–4.56)
Abruption without preeclampsia	2 (0.3)	4 (0.5)	0.52 (0.06–4.91)
Spontaneous delivery without preeclampsia	40 (5.0)	49 (6.0)	0.83 (0.47–1.47)
Adverse outcomes at ≥37 weeks gestation			
Preeclampsia	53 (6.6)	59 (7.2)	0.95 (0.57–1.57)
Gestational hypertension	72 (9.0)	62 (7.5)	1.24 (0.78–1.98)

Abruption without preeclampsia	2 (0.3)	2 (0.2)	1.01 (0.08–13.40)
Neonatal outcomes			
Stillbirth or death with preeclampsia or status of SGA	5 (0.6)	8 (1.0)	0.65 (0.15–2.90)
Stillbirth or death without PE or status of SGA	3 (0.4)	6 (0.7)	0.51 (0.08–3.19)
Admission to intensive care unit	48 (6.0)	54 (6.6)	0.93 (0.55–1.59)

Abbreviations: CI=confidence interval; PE=preeclampsia; SGA=small for gestational age
Source: Table 13, p49 of ADAR

Influence of treatment compliance

A secondary analysis showed that the beneficial effect of aspirin in the prevention of preterm preeclampsia appears to be associated with treatment adherence (Wright et al., 2017). While the ASPRE trial reported generally high levels of compliance (>90% in 85% of women) in the aspirin arm, true compliance is likely to be significantly lower. This is because patient interviews, diaries, and counts of returned, untaken doses have been shown by both marker and electronic monitoring methods to consistently and substantially to overestimate compliance^{20,21}. These measurement issues were identified in the risk of bias assessment by the ADAR. Further, as this was a trial, aspirin compliance was likely to be substantially higher than would be seen in a real-world setting. Recent studies investigating compliance of low-dose aspirin among women with increased preeclampsia risk have consistently demonstrated adherence rates well below 90%, with one study reporting adherence as low as 29%²².

In the ASPRE analysis, compliance was also positively associated with family history of preeclampsia and negatively associated with smoking, maternal age <25 years, Afro-Caribbean and South Asian ancestry, and history of preeclampsia in a previous pregnancy (Wright et al., 2017). This suggested disparities in adherence underpinned by certain sociodemographic or health literacy levels.

Clinical claim

The commentary considered that overall, the clinical claim for superior health outcomes of structured prenatal risk assessment (“FMF risk calculator”) in asymptomatic pregnancies at 11⁺⁰ to 13⁺⁶ weeks’ gestation for identification of preterm preeclampsia compared to the standard of care (risk assessment through clinical examination and medical history) was not supported. This conclusion was made based on the commentary’s weighing of the direct evidence showing improved health outcomes (both maternal and neonatal), and the linked evidence demonstrating superior test accuracy and superior health outcomes in high-risk patients, against the strength of selection and confounding bias concerns with the direct evidence and the lack of evidence provided for the incremental impact of the test on change in management (i.e., prescription of aspirin in practice).

The commentary considered that overall, the clinical claim for non-inferior safety of structured prenatal risk assessment (“FMF risk calculator”) in asymptomatic pregnancies at 11⁺⁰ to 13⁺⁶ weeks’ gestation for identification of preterm preeclampsia compared to the standard of care (risk assessment through clinical examination and medical history) was not supported.

20 Urquhart, J. (1994). Role of patient compliance in clinical pharmacokinetics. A review of recent research. *Clin Pharmacokinet*, 27(3), 202-215. <https://doi.org/10.2165/00003088-199427030-00004>

21 Blaschke, T. F., Osterberg, L., Vrijens, B., & Urquhart, J. (2012). Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories. *Annu Rev Pharmacol Toxicol*, 52, 275-301. <https://doi.org/10.1146/annurev-pharmtox-011711-113247>

22 van Montfort, P., Scheepers, H. C. J., van Dooren, I. M. A., Meertens, L. J. E., Zelis, M., Zwaan, I. M., Spaanderman, M. E. A., & Smits, L. J. M. (2020). Low-dose-aspirin usage among women with an increased preeclampsia risk: A prospective cohort study. *Acta Obstet Gynecol Scand*, 99(7), 875-883. <https://doi.org/10.1111/aogs.13808>

13. Economic evaluation

Overview and rationale of the economic evaluation

Based on the ADAR's clinical claim that testing asymptomatic pregnant persons at 11⁺⁰ to 13⁺⁶ weeks' gestation using the FMF risk calculator for predicting preterm preeclampsia resulted in superior health outcomes compared to current SoC, the commentary determined that a cost-utility analysis was appropriate.

The ADAR presented the results of a cost-utility analysis of structured risk assessment for preterm preeclampsia using the FMF risk calculator versus the current SoC.

The economic evaluation used outcomes for the result of structured prenatal risk assessment (high risk vs low risk) and clinical outcomes (preterm preeclampsia and term preeclampsia) reported in the Australian clinical implementation study reported by Rolnik et al., 2021 without extrapolation or transformation.

A summary of the key characteristics of the economic evaluation are detailed below.

Table 8 Summary of the economic evaluation.

Component	Description
Perspective	Health care system perspective.
Population	Pregnant persons 11+0 to 13+6 weeks gestation presenting for first trimester risk-based testing.
Prior testing	None required
Comparator	Standard care (risk assessment for preeclampsia through clinical examination and medical history).
Type of analysis	Cost-utility analysis
Outcomes	Preterm preeclampsia, term preeclampsia, no preeclampsia, quality-adjusted life years.
Costs	Costs associated with risk-based testing, monitoring, aspirin treatment and hospitalisation due to preeclampsia were included in the model.
Time horizon	Up to 28 weeks (from risk-based testing at 11+0 weeks gestation to term delivery at 39 weeks) in the model <ul style="list-style-type: none"> The time horizon used in the model aligns with the time horizon of the key trial.
Computational method	Cohort expected value. Results are reported at the individual (per patient) level. An alternate analysis based on a cohort of 100,000 pregnant persons undergoing preterm preeclampsia risk assessment is presented to provide for broader clinical context relevant for a population-based testing program.
Generation of the base case	Trial based. Results of an Australian clinical implementation study (Rolnik et al., 2021) are used to generate the base case
Health states	Preterm preeclampsia, term preeclampsia, no preeclampsia (decision tree used)
Cycle length	Not applicable
Transition probabilities	Transition probabilities allocating patients to 'High risk' and 'Low risk' branches of the decision tree were obtained from an Australian clinical validation study (Rolnik et al., 2021) and applied without transformation. Transition probabilities allocating patients to the 'Preterm preeclampsia', 'Term preeclampsia' health outcomes obtained from an Australian clinical validation study (Rolnik et al., 2021) and applied without transformation
Discount rate	Not applied. All costs and consequences accrued in less than 1 year.
Software	TreeAge Pro (Healthcare Version)

Source: Table 25, p69 of ADAR.

The commentary considered the use of a decision tree model was appropriate.

The commentary considered the model structure was oversimplified. Specifically, it considered that the standard care population should have been separated into low risk and high risk cohorts, rather than applying a uniform risk of preeclampsia. Current testing practice guidelines in Australia recommend assessment of the risk of preeclampsia using of a combination of maternal characteristics and history such as those contained in the NICE, ACOG and SOMANZ clinical risk assessment for preeclampsia guidelines. All models in relevant cost-effectiveness analysis studies identified during a search of the literature²³ were structured so that the SoC arm was separated into groups assessed high and low risk^{28,24,25}.

As the key study was conducted in Australia, the population in the economic evaluation matches the population in the PICO. The internal validity of the pivotal study depends largely on whether the characteristics of the population of private patients is sufficiently similar to those of the population of public patients. The commentary considered this was an unreasonable assumption as the clinical implementation study itself demonstrated that these populations are significantly different. It would have been more appropriate to use the data from the ASPRE cohorts to drive the identification of risk of preeclampsia in both arms, and then use the Australian study to provide the clinical outcomes based on the risk of developing preeclampsia in the structured cohort.

The ADAR argues that the use of preeclampsia outcomes at delivery reported in the clinical implementation study accounts for recommended (per guidelines) and actual changes in management for women being tested for preeclampsia (i.e., the proportion of women offered aspirin) and this negates the need to incorporate transition probabilities for the aspirin uptake. The underlying assumption of the economic evaluation is that all women who are tested as high risk of preeclampsia by structured risk assessment will be offered aspirin and the uptake in this population will be 100%. During evaluation, it was noted that the uptake of aspirin in women undergoing testing may be much less than 100%.

The ADAR acknowledged that transition probabilities related to test accuracy and changes in clinical management should be included for investigative technologies but argued that the application of transition probabilities derived from a clinical implementation study negated this requirement. Regarding test accuracy, the ADAR argued the use of preeclampsia outcomes at delivery already reflected the potential for variation in health outcomes due to false positive or false negative prenatal testing. Similarly, the ADAR argued that the use of preeclampsia outcomes at delivery accounted for recommended and actual changes in management (i.e., the uptake in aspirin treatment) and incorporating transition probabilities for aspirin uptake to the 'High risk' and 'Low risk' arms in the economic model would result in 'double counting' changes in management.

The commentary agreed with these arguments in principle, but only where the relevant evidence is available. However, the significant differences in the population characteristics and settings in which testing was undertaken, and the lack of understanding of what testing for preeclampsia actually existed in the control cohort resulted in considerable uncertainty about the evidence used in the economic model.

23 Mewes, J. C., Lindenberg, M., & Vrijhoef, H. J. M. (2022). Cost-effectiveness analysis of implementing on preterm pre-eclampsia at first trimester of pregnancy in Germany and Switzerland. *PLoS One*, 17(6), e0270490. <https://doi.org/10.1371/journal.pone.0270490>

24 Dubon Garcia, A., Devlieger, R., Redekop, K., Vandeweyer, K., Verlohren, S., & Poon, L. C. (2021). Cost-utility of a first-trimester strategy versus the standard of care for nulliparous women to prevent pre-term pre-eclampsia in Belgium. *Pregnancy Hypertension*, 25, 219-224.

25 Nzelu, D., Palmer, T., Stott, D., Pandya, P., Napolitano, R., Casagrandi, D., Ammari, C., & Hillman, S. (2023). First trimester for pre-eclampsia and targeted aspirin prophylaxis: a cost-effectiveness cohort study. *BJOG: An International Journal of Obstetrics & Gynaecology*, n/a(n/a). <https://doi.org/https://doi.org/10.1111/1471-0528.17598>

Safety outcomes

The following outcomes included in the PICO were not reported:

- Safety outcomes – adverse events associated with the test, anxiety associated with the finding of increased risk of preeclampsia and adverse events associated with treatment.
- Disutility in test-positive women associated with a) negative psychological effects due to increased anxiety resulting from the knowledge they are at high risk of preeclampsia; b) inconvenience associated with increased frequency of monitoring appointments/investigations.

Utility weights

No clinical studies presented in the ADAR's clinical assessment reported health-related quality of life (HRQoL) outcomes. The commentary considered the utilities identified by a targeted literature review by the ADAR were suitable to incorporate into the economic evaluation. The utility for preterm preeclampsia was calculated as the average weighted utility (by patient numbers) of women with late preterm preeclampsia assigned to planned delivery (0.761) or expectant management (0.746). The commentary was unable to verify if this was a valid method to calculate the overall utility in women with preterm preeclampsia. The commentary considered it was unclear how the utility for term preeclampsia was derived. Specifically, the utility decrement that was applied to the utility for no preeclampsia was unable to be identified in either Hunter et al., 2022 or Regan et al., 2023. The utility value for no preeclampsia was derived from a US population, and the commentary considered was reflective of the population outlined in the PICO.

Costs

Overall, the resource items and unit costs were current and have mostly been retrieved from the appropriate sources.

The following costs outlined in the PICO were not applied in the model:

- Costs associated with adverse events associated with aspirin treatment.
- Additional costs associated with pre-test counselling and post-test follow-up.

The ADAR applied the same antenatal monitoring costs to women who were tested and found to be at high risk and low risk by structured risk assessment. The commentary considered this to be inappropriate as women assessed at high risk of developing preeclampsia are more closely monitored and incur significantly higher costs during the antenatal period than women assessed as low risk of preeclampsia. However the pre-ESC response noted that during the model validation process the monitoring schedule and resources applied to both the SoC and FMF algorithm arms of the model were reviewed by an obstetrician and advised as being reflective of broader clinical practice.

The commentary considered that the Diagnostic Related Groups (DRGs) assigned for the costing of preterm and term preeclampsia delivery are likely to overestimate the true cost of delivery for each.

Whilst early-onset preeclampsia (onset before 34 weeks of gestation) is much more likely to be severe than preeclampsia that begins later in gestation, the onset of preterm preeclampsia (<37 weeks) is heavily skewed with the incidence of late onset (≥ 34 weeks) 6 times that of early onset (<34 weeks)²⁶. Additionally, less than 20% of nulliparous women with severe preeclampsia

26 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(4), 419-423. <https://doi.org/10.1002/uog.14819>.

deliver before 34 weeks gestational age²⁷. Since a significant proportion of women with preterm preeclampsia have uncomplicated deliveries, the commentary considered applying costs for DRGs O01A (Caesarean Delivery, Major Complexity) and O60A (Vaginal Delivery, Major Complexity) for all births in women with preterm preeclampsia likely to overestimate the costs associated with these deliveries. Similarly, given a significant proportion of births in women with term preeclampsia are without complication the commentary considered the application of intermediate complexity DRGs (i.e., O01B Caesarean Delivery, Intermediate Complexity and O60A Vaginal Delivery, Intermediate Complexity) likely to overestimate the costs associated with these deliveries.

The commentary also had concerns about the costs applied to neonatal intensive care unit (NICU) admissions. Whilst acknowledging the imperfect correlation between birth weight and the need for and complexity of NICU admission, the commentary considered the application of the cost for DRG P66B (Neonate, Admission Weight 2000-2499 grams without Significant General Interventions or Ventilation ≥ 96 hrs, Major Complexity) for all neonates born to pregnant persons with preterm preeclampsia likely to overestimate associated cost for the following reasons:

- The occurrence of birth weights less <2500 grams is only 37.0% and 11.1% in women with severe and mild preeclampsia.³²
- The mean birth weight in this study was >2500 grams for both mild (3282 grams) and severe (2714 grams) preeclampsia, respectively.³²
- A large, population-based study conducted in California (n~ 543,000) demonstrated the proportion of neonates with abnormal DRGs is 68% and 36% for births weights 2000-2249 grams and 2250-2499 grams, respectively²⁸.
- Whilst 73% neonates from very early deliveries (<32 weeks) have abnormal DRGs this proportion decreases at an increasing rate with only 30% assigned an abnormal DRG when delivered at 37 weeks gestational age³³.

However the pre-ESC response supplied a comparison (Table 19) of the health care resources incurred for preeclamptic outcomes applied in the ADAR with those applied in a peer-reviewed economic evaluation in an Australian context (Park et al. 2021) obtained from eMaternity electronic medical records at the Hunter New England Local Health District (NSW). The pre-ESC response argued that the comparison does not suggest that the ADAR likely overestimated cost associated with hospitalisations and NICU admissions.

Table 19: Costs for delivery with preeclampsia applied in ADAR and publish Australian economic evaluation

Health outcome in ADAR model	Health care resource costs: ADAR (FMF algorithm arm)	Health care resource costs: (Park et al. 2021)
Preterm preeclampsia	\$21,230	\$34,883 (34-36 ⁺⁶ weeks) \$86,966 (<34 weeks)
Term preeclampsia (>37 weeks)	\$12,217	\$17,680

Source: Table 35 (91) of the ADAR and Table 4 (p. 693) of (Park et al. 2021)

Quality assessment is a requirement for the use of FMF structured risk assessment. MAP and UtA-PI are susceptible to considerable variability in their measurements, mainly due to poor adherence to defined protocols. Quality control of biomarkers needs to be performed regularly for

27 Hauth, J. C., Ewell, M. G., Levine, R. J., Esterlitz, J. R., Sibai, B., Curet, L. B., Catalano, P. M., & Morris, C. D. (2000). Pregnancy outcomes in healthy nulliparas who developed hypertension. *Obstetrics & Gynecology*, 95(1), 24-28. [https://doi.org/https://doi.org/10.1016/S0029-7844\(99\)00462-7](https://doi.org/https://doi.org/10.1016/S0029-7844(99)00462-7)

28 Gilbert, W. M., Nesbitt, T. S., & Danielsen, B. (2003). The cost of prematurity: quantification by gestational age and birth weight. *Obstet Gynecol*, 102(3), 488-492. [https://doi.org/10.1016/s0029-7844\(03\)00617-3](https://doi.org/10.1016/s0029-7844(03)00617-3)

data standardization, reliability, and accuracy and retraining is indicated if deviations are noted. As noted in the clinical assessment, no cost or resource requirement details on FMF training have been provided in the ADAR. The Fetal Medicine Group stipulates the implementation of quality control regimens, specifically continuous audit of uterine artery pulsatility index measurements with regular feedback to sonographers to ensure reliability and accuracy. How these will be incorporated into the overall cost/public funding requirements should be considered and could be applied in the economic model.

Results of the economic evaluation

The ADAR did not present a stepped economic evaluation. The results of the ADAR's economic evaluation presented are outlined in Table 20.

Table 20 Results of base analysis presented by the ADAR

	Structured risk assessment	Standard care	Increment
Costs	\$7,898.10	\$7,914.06	-\$15.96
Effectiveness: Preterm preeclampsia	0.005	0.007	-0.002
Effectiveness: Term preeclampsia	0.011	0.017	-0.006
Effectiveness: QALYs	0.3996	0.3993	0.002
ICER (Cost/QALY)	-	-	Dominant

Abbreviations: ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year

Source: Table 38, p91 of the ADAR

The results of the sensitivity analysis characterising the uncertainty around the ICER as presented by the ADAR are summarised in Table 21 below.

Table 21 Results of the sensitivity analysis characterising uncertainty around the ICER as presented by the ADAR.

Variable	Input value			ICER (\$/QALY)		
	Base case	Alternative value (lower bound)	Alternative value (upper bound)	Base case	Alternative value (lower bound)	Alternative value (upper bound)
pPreTerm_PE_High Risk_Structured ¹	2.1%	1.6%	2.3%	-\$66,397	-\$91,514 (↓38%)	-\$54,226 (↑18%)
pPreTerm_PE_Low Risk_Structured ²	0.2%	0.1%	-	-\$66,397	-\$97,047 (↓46%)	-
pHighRisk_Structured ³	13.7%	10.5%	-	-\$66,397	-\$103,966 (↓57%)	-
pAspirin_Standard ⁴	23.2%	0%	24.3%	-\$66,397	-\$69,141 (↓4%)	-\$8,540 (↑87%)

Abbreviations: ICER=incremental cost effectiveness ratio; QALY=quality adjusted life years

1. Probability of developing preterm preeclampsia if assessed as high risk by structured risk assessment 2. Probability of developing preterm preeclampsia if assessed as low risk by structured risk assessment 3. Probability of being assessed as high risk (>1 in 100) by structured risk assessment 4. Probability of being prescribed aspirin if assessed with Standard care

Source: Table 41, p97 of the ADAR

The key drivers in the model presented by the ADAR were probability of developing preterm preeclampsia if assessed as high risk by structured care, the probability of developing preterm preeclampsia if assessed as low risk by structured care, the probability of being assessed as high risk by structured care and the probability of being prescribed aspirin in standard care.

Uncertainty analysis: model inputs and assumptions

Additional sensitivity analyses were performed during evaluation using alternate lower and upper bounds identified by targeted literature search to reflect the significant uncertainty of the results from the clinical implementation study. The ADAR assumed that all patients received translucency ultrasound and trisomy blood testing. This was likely to overestimate the costs of the standard care arm as in practice approximately 54% of patients (based on MBS data for item 55707 and ABS for number of pregnancies) would have received these treatments. Additionally, it may be inappropriate to include these costs in the cost-effectiveness analysis as they are not associated with pre-eclampsia testing. During evaluation, sensitivity analyses around the proportion of patients receiving ultrasound and blood testing was performed. The requirement for a follow up appointment after structured risk testing for risk of preeclampsia to discuss the test results and management options was considered reasonable and the cost of an additional practitioner consultation (MBS item 16500 at \$49.85) was also included into the total cost of FMF testing.

The key results of the sensitivity analyses performed during evaluation are outlined in Table 22 and Table 23.

Table 22 Key results of one-way sensitivity analyses performed during evaluation

Analyses	Incremental cost	Incremental QALY	ICER
Base case	-\$15.96	0.0002	Dominant -\$66,397.35
Cost of SoC (base case \$179.81) ¹			
\$124.49 (No OOP)	\$39.36	0.0002	\$163,730
\$205.49 (\$150 OOP)	-\$41.64	0.0002	Dominant -\$173,224
\$332.85 (\$385.50 OOP)	-\$169.00	0.0002	Dominant -\$703,029
Cost of structured risk assessment testing (base case \$228.02) ²			
\$277.87 (No OOP + 1 consultation \$49.85)	\$33.89	0.0002	\$140,974
\$427.87 (\$150 OOP + 1 consultation \$49.85)	\$183.89	0.0002	\$764,960
\$663.72 (\$385.50 OOP + 1 consultation \$49.85)	\$419.74	0.0002	\$1,746,074
Probability of developing preterm PE if high risk by structured risk testing (base case 0.021; Rolnik et al 2017))			
Low (0.016) (Tan et al., 2017)	-\$25.13	0.0003	Dominant -\$91,514
High (0.043) (Rolinik et al.,2017)	\$24.40	0.0001	\$272,006
Probability of taking aspirin if tested in SoC (base case 0.232; Rolnik et al., 2021)			
Low (0.0)	-\$2.05	0.0002	Dominant -\$8,540
High (0.645) This was considered a more reasonable value corresponding to the proportion of women assessed as being at high risk using ACOG criteria) (Poon et al, 2017).	-\$40.72	0.0002	Dominant -\$169,394
Probability of being assessed as high (>1 in 100) by structured risk assessment testing (base case 0.137; Rolnik et al. 2021)			
Low 0.105 (Rolinik et al., 2017a)	-\$30.08	0.0003	Dominant -\$103,966
High 0.18 ²⁹	\$3.01	0.0002	\$17,264

29 Guy, G. P., Leslie, K., Diaz Gomez, D., Forenc, K., Buck, E., Khalil, A., & Thilaganathan, B. (2021). Implementation of routine first trimester combined screening for pre-eclampsia: a clinical effectiveness study. BJOG, 128(2), 149-156. <https://doi.org/10.1111/1471-0528.16361>

Analyses	Incremental cost	Incremental QALY	ICER
Probability of developing term PE if assessed high risk by structure risk assessment (base case 0.036 Rolnik et al., 2021)			
High 0.070 (Rolnik et al., 2017a)	\$4.43	0.0001	\$30,067

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year; ACOG= American College of Obstetricians and Gynaecologists; PE=preeclampsia; OOP=out of pocket expense; SoC=standard of care

1 This cost assumes that 54% of patients are tested in the standard of care arm. 2. This cost assumes that 100% of patients are tested in the intervention arm.

Source: Table C7, p97 of the ADAR

Table 23 Key results of two-way sensitivity analyses of costs of SoC and structured risk assessment testing preformed during evaluation

Analyses	Incr. cost	Incr. QALY	ICER
Base case	-\$15.96	0.0002	Dominant -\$66,397.35
SoC cost \$124.49 and FMF testing cost \$277.87	\$89.21	0.0002	\$371,100
SoC cost \$205.49 and FMF testing cost \$427.87	\$158.21	0.0002	\$658,134
SoC cost \$332.85 and FMF testing cost \$663.72	\$266.70	0.0002	\$1,109,442

Abbreviations: SoC=standard of care; Incr=Incremental; QALY=quality adjusted life years; FMF=Fetal Medicine Foundation

Source: Table C8, p97 of the ADAR

Key drivers of the model were the cost of the structured testing intervention, the probability of developing preterm preeclampsia if high risk by structured risk assessment, the probability of being assessed as high risk by structured risk assessment, the probability of developing term preeclampsia if assessed low risk by structured testing and the probability of taking aspirin if tested with standard care and the likelihood of pre-term delivery if assessed as high risk by structured risk assessment. The sensitivity analysis showed the dominance of structured prenatal risk assessment for preterm preeclampsia reported by the ADAR was maintained. However, during evaluation it was demonstrated that the ICER was sensitive to changes to the cost of structured testing such that the technology was no longer dominant and may not be cost effective if its cost was increased. Additionally, increasing the probability of developing preterm preeclampsia also led to the technology having similar effects on the model (in terms of shifting the cost effectiveness result away from dominance) and given the issues with the key study underpinning the model, the commentary considered that this could be a real concern and mean that the cost utility analysis was unreliable.

14. Financial/budgetary impacts

Justification of the approach and data sources

A market share approach was used to estimate the uptake of the proposed technology in the ADAR. The market share was based on utilisation of the currently listed items proposed to be changed (items 55707, 66750 and 66751), assuming a 10% increase driven by the addition of preeclampsia testing. The commentary considered this was appropriate, although an epidemiological approach based on the number of pregnant persons opting to uptake the testing could also have been used for validation.

Key assumptions

The following key cost assumptions/drivers were used for the budgetary impact analysis:

- The ADAR estimated that there would be an increase in use of the items due to some women currently not using the items due to choosing not to be tested for chromosomal or anatomic abnormalities.
 - This increase in use (10%) was based on expert opinion of one clinician, who is one of the ADAR applicants.
- No patients would take up testing for chromosomal or anatomic abnormalities and not take up structured prenatal risk assessment for preterm preeclampsia.
- The estimates of preeclampsia are based on the cohort study by Rolnik et al., 2021, and not on the trial data, which incorporated the biases noted above.

Results

The financial implications to the MBS resulting from the proposed listing of structured prenatal risk assessment for preterm preeclampsia are summarised in Table 24. The ADAR estimated that the modification of MBS items 55707, 66750 and 66751 and increased use with the addition of preeclampsia testing would lead to a cost of just under \$7 million in the first year of listing, with an estimated cost of \$39 million over the first six years of listing.

Table 24 Net financial implications of structured prenatal risk assessment for preterm preeclampsia to the MBS presented in the ADAR.

Parameter	Year 2024	Year 2025	Year 2026	Year 2027	Year 2028	Year 2029
Estimated use and cost of MBS items proposed to be amended to include structured prenatal risk assessment						
<i>Number of people eligible for risk assessment (Evaluation estimates based on ABS Births Series B predictions)</i>	353,848	358,184	362,105	365,620	368,746	371,583
Number of services (amended MBS Item 55707; 85% = \$77.40)	175,476	176,139	176,802	177,465	178,129	178,792
Number of services (amended MBS Item 66750; 85% = \$59.23)	42,425	33,006	23,587	14,168	4,750	4,750
Number of services (amended MBS Item 66751; 85% = \$72.46)	67,662	70,167	72,671	75,176	77,681	80,186
<i>Total cost to the MBS (with appropriate copayments excluded)</i>	\$21,000,212	\$20,674,634	\$20,349,055	\$20,023,477	\$19,697,899	\$19,930,735
Change in use and cost of unamended MBS items currently delivering standard of care						
Number of unamended MBS Item 55707 replaced (85% = \$61.95)	159,524	160,127	160,729	161,332	161,935	162,538
<i>Change in number of 55707 services</i>	15,952	16,013	16,073	16,133	16,194	16,254
Number of unamended MBS Item 66750 replaced (85% = 33.80)	38,568	30,005	21,443	12,880	4,318	4,318
<i>Change in number of 66750 services</i>	3,857	3,001	2,144	1,288	432	432

Parameter	Year 2024	Year 2025	Year 2026	Year 2027	Year 2028	Year 2029
Number of unamended MBS Item 66751 replaced (85% = 47.00)	61,511	63,788	66,065	68,342	70,619	72,897
<i>Change in number of 66751 services</i>	<i>6,151</i>	<i>6,379</i>	<i>6,606</i>	<i>6,834</i>	<i>7,062</i>	<i>7,290</i>
Total costs of unamended MBS items	\$14,069,914	\$13,924,878	\$13,779,842	\$13,634,807	\$13,489,771	\$13,634,041
Net financial impact to the MBS (total costs to MBS with pre-eclampsia testing, minus total costs without pre-eclampsia testing)	\$6,930,299	\$6,749,756	\$6,569,213	\$6,388,670	\$6,208,128	\$6,296,694

Abbreviations: ABS=Australian Bureau of Statistics; MBS=Medicare Benefits Scheme

Italics indicate calculated during evaluation from spreadsheet "MSAC Application 1705 and 1706 Section 4 Workbook.xlsx".

Source: Based on Tables 44 and 44; p90-91 of the ADAR and spreadsheet "MSAC Application 1705 and 1706 Section 4 Workbook.xlsx"

Key drivers of the financial cost analysis included:

- The average cost of the proposed technology per patient per pregnancy was \$120 in the ADAR, though this is likely to be underestimated.
- The average frequency of use of the proposed technology is once per pregnancy, but the ADAR estimated that only 50% of pregnancies would receive the test.
- The out-of-pocket cost per patient could be in the range of \$380 per pregnancy based on out-of-pocket costs for a standard anatomy scan based on commercial pricing.³⁰
- It is likely that the Extended Medicare Safety Net will not be affected for this service but may cause later services to be covered under the EMSN. This was explored using MBS data for 2022/23 and only MBS item 66751 was paid out higher than the 85% benefit (\$1).

The ADAR's analysis included cost offsets for state and territory hospitals due to a reduction in hospitalisation costs from pre-eclampsia avoided (Table 25). It was estimated by the ADAR that the addition of structured testing for pre-eclampsia would lead to a net saving to Government (i.e. MBS plus state and territory health budgets) of just under \$5 million in the first year of listing with an estimated saving of \$31.5 million over the first six years of listing.

³⁰ Sydney Ultrasound for Women, (2023). Ultrasound costs. Retrieved from: <https://www.sufw.com.au/ultrasound-costs/>

Table25 Net financial implications of structured prenatal risk assessment for preterm preeclampsia to the Government (MBS + states and territory health budgets).

Parameter	Year 2024	Year 2025	Year 2026	Year 2027	Year 2028	Year 2029
Incremental hospital admissions: preeclampsia <37 weeks	-526	-528	-530	-532	-534	-536
Incremental hospital admissions: preeclampsia ≥37 weeks	-1,053	-1,057	-1,061	-1,065	-1,069	-1,073
Incremental hospital admissions: for preeclampsia management	-1,579	-1,585	-1,591	-1,597	-1,603	-1,609
Hospital costs: Standard care	\$1,251,988,480	\$1,256,719,427	\$1,261,450,374	\$1,266,181,321	\$1,270,912,268	\$1,275,643,215
Hospital costs: Structured prenatal risk assessment	\$1,240,330,366	\$1,245,017,260	\$1,249,704,154	\$1,254,391,048	\$1,259,077,943	\$1,263,764,837
Net financial impact to state and territory governments (Incremental hospital costs)	-\$11,658,113	-\$11,702,166	-\$11,746,219	-\$11,790,273	-\$11,834,326	-\$11,878,379
Net financial impact to the MBS	\$6,930,299	\$6,749,756	\$6,569,213	\$6,388,670	\$6,208,128	\$6,296,694
Net financial impact to the Government (MBS + State and Territory)	-\$4,727,815	-\$4,952,411	-\$5,177,006	-\$5,401,602	-\$5,626,198	-\$5,581,685

Abbreviations: MBS=Medicare Benefits Scheme
Source: Tables 46 to 48, p92-94 of the ADAR.

Out of pocket costs

During evaluation it was determined that there is likely to be substantial out of pocket costs associated with the proposed technologies especially ultrasound for UtA-PI as there already exists substantial out of pocket costs for anatomy ultrasound; however, the true out of pocket costs are unclear. Commercially available pricing presented an out-of-pocket cost of \$385.85 and the Department of Health Medical cost finder estimating an expected out of pocket cost of \$150.³¹ The out-of-pocket calculations included the \$12.79 (for Item 66750) and \$10.46 (for item 66751). The financial implications to the patients are outlined in Table 26 below. It was estimated that the out-of-pocket cost to the Australian population could be between \$27.5 million and \$69 million in the first year of listing with an estimated cost of between \$166 million and \$416 million over the first six years of listing.

³¹ Medical Costs Finder. (2023). *MBS item 55707*. Retrieved online: <https://medicalcostsfinder.health.gov.au/services/Q55707/oh?specialty=021901>

Table 26 Financial implications of structured prenatal risk assessment for preterm preeclampsia to the Australian population due to co-payments.

Parameter	Year 2024	Year 2025	Year 2026	Year 2027	Year 2028	Year 2029
<i>Out of pocket costs based on the ADAR base case and a \$385.85 co pay.</i>	\$68,957,898	\$69,119,513	\$69,281,128	\$69,442,743	\$69,604,358	\$69,886,415
Out of pocket costs based on the ADAR base case and a \$150 co pay.	\$27,571,841	\$27,577,069	\$27,582,296	\$27,587,524	\$27,592,751	\$27,718,421

Abbreviations: ADAR=Applicant developed assessment report.

Italics indicate calculated during evaluation using spreadsheet "MSAC Application 1705 and 1706 Section 4 Workbook.xlsx".

Sensitivity analyses

The ADAR provided sensitivity analyses of the net financial implication, with further additions from the evaluation group (Table 27). The lower and upper bounds for the parameters and alternate value tested in sensitivity analysis presented by the ADAR were limited. Anatomy ultrasound testing and parental history factors are often used in the assessment for aneuploidy without the use of blood tests. It is unlikely the number of persons taking up preeclampsia testing will be less than the anatomy ultrasound numbers. Additional analysis was required to test the scenario where most pregnant persons who undergo first trimester testing take up the services (Table 26). There was considerable uncertainty about the clinical utility of FMF compared to standard care (i.e. no difference in term preeclampsia and likely overestimate of efficacy using the comparative cohorts). The preeclampsia related outcomes were based on data from an Australian clinical implementation study of preeclampsia risk assessment (Rolnik et al., 2021). The commentary considered the use of this data was inappropriate as the comparison between the populations was biased. The use of this data demonstrated that there was a difference in the clinical utility of preventing preterm and term pre-eclampsia (a benefit of 0.3% and 0.6% respectively). The clinical evidence demonstrated that there was no difference in the diagnostic accuracy of term pre-eclampsia and there was no robust evidence that demonstrated that the use of FMF structured testing leads to an improvement in pre-term pre-eclampsia. These were also tested during evaluation.

Table27 Variables chosen for sensitivity analysis and justification of values.

Variable	Base case	Sensitivity values	Justification
Growth in MBS item use driven by preeclampsia testing	10%	5%, 15%	The base case value was an assumption based on an estimate from a clinician with extensive experience in the use of structured prenatal risk assessment for preeclampsia. Given the uncertainty in this assumption, alternate values based on a 50% (relative) change in the base value were applied
MBS rebate	85%	75%, 100%	The lower bound and upper bound MBS rebates represent the minimum and maximum government contributions to MBS items
Number of women tested for preeclampsia risk used as basis for calculation of hospital admissions and costs	Based on projected number of items claimed for MBS item 55707 (UtA-PI assessment)	Sum of the number of items claimed for MBS items 66750 and 66751 (PIGF assessment)	It is possible to estimate the number of women tested for preeclampsia risk based on the number of ultrasound items claimed for UtA-PI assessment (item 55707) or pathology items claimed for PIGF assessment items 66750 and 66751)
<i>Proportion of pregnant persons taking up the technology</i>	80%	70%, 90%	<i>75% appears to be a proxy for “most”, testing upper and lower limits</i>
<i>Clinical utility: proportion of women developing term preeclampsia incidence</i>	<i>FMF 1.7% SoC 1.1%</i>	<i>Both set at 1.1%</i>	<i>The comparative diagnostic studies demonstrated that there was no difference in the rate of term preeclampsia between SoC and FMF</i>
<i>Clinical utility: proportion of women developing preterm preeclampsia</i>	<i>FMF 0.4% SoC 0.7%</i>	<i>SoC set at 0.6%</i>	<i>The comparative diagnostic studies demonstrated that there was no difference in the rate of preterm preeclampsia between SoC and FMF</i>

Abbreviations: FMF=Fetal Medicine Foundation risk calculator; MBS=Medicare Benefits Schedule; PIGF=Placental Growth Factor; SoC=Standard of care; UtA-PI=Uterine artery pulsatility index

Source: Table 49; p 95 of the ADAR and italics indicate compiled during evaluation.

The commentary considered there was considerable uncertainty in the financial estimates presented by the ADAR and tested this during evaluation. The ADAR’s base case estimated that structured prenatal risk assessment would save the Government (MBS and State and Territory health budgets) an estimated \$5 million per year.

However, during evaluation it was considered this estimate was not robust. Sensitivity analysis demonstrated that listing the modified MBS items could lead to a net cost to the combined MBS, State, and territory health budgets (Table 28). This was based on varying the number of pregnant persons tested and the proportion of patients that developed term and preterm preeclampsia, the ADAR’s values for which were not well supported by the evidence.

Table28 Results of sensitivity analysis for net budget impact of structured prenatal risk assessment for preeclampsia to the Government (MBS + state and territory health budgets).

Summary	2024 (Year 1)	2025 (Year 2)	2026 (Year 3)	2027 (Year 4)	2028 (Year 5)	2029 (Year 6)
Base case	-\$4,727,815	-\$4,952,411	-\$5,177,006	-\$5,401,602	-\$5,626,198	-\$5,581,685
Growth in MBS item use driven by preeclampsia testing (base case = 10%)						
5%	-\$5,152,456	-\$5,360,250	-\$5,568,044	-\$5,775,839	-\$5,983,633	-\$5,947,701
15%	-\$4,303,174	-\$4,544,571	-\$4,785,968	-\$5,027,366	-\$5,268,763	-\$5,215,669
MBS rebate (base case = 85%)						
75%	-\$5,543,144	-\$5,746,500	-\$5,949,855	-\$6,153,210	-\$6,356,566	-\$6,322,473
100%	-\$3,504,821	-\$3,761,277	-\$4,017,734	-\$4,274,190	-\$4,530,646	-\$4,470,504
Number of women tested for preeclampsia (base case = items claimed for MBS item 55707)						
Services claimed for MBS items 66750 and 66751	-\$383,502	-\$104,711	\$174,080	\$452,872	\$731,663	\$653,810
<i>75% of all pregnant persons</i>	-\$201,081	-\$119,827	-\$49,922	\$8,879	\$57,042	\$97,301
<i>Clinical utility - proportion of persons developing preeclampsia (base case = preeclampsia ≥37 weeks standard = 1.7%; FMF = 1.1%)</i>						
<i>Preeclampsia: ≥37 weeks standard = 1.1%</i>	-\$118,625	-\$325,804	-\$532,983	-\$740,162	-\$947,341	-\$885,411
<i>Clinical utility - proportion of women developing preeclampsia (base case = preeclampsia <37 weeks standard = 0.7%; FMF = 0.4%)</i>						
<i>Preeclampsia: <37 weeks standard = 0.6%</i>	\$2,231,016	\$2,032,716	\$1,834,416	\$1,636,116	\$1,437,816	\$1,508,624

Abbreviations: FMF=Fetal Medicine Foundation risk calculator; MBS=Medicare Benefits Schedule.

Source: Table 51 to 53; p96-98 of the ADAR and italics indicate compiled during evaluation.

15. Other relevant information

There were some important considerations related to the proposed structured prenatal assessment tool, primarily related to demand and implementation, which were not discussed in this ADAR.

Equity of access

The ADAR did not provide any information on access to services for underserved populations, such as: Aboriginal and Torres Strait Islander people, people in rural and remote communities, or culturally and linguistically diverse groups. This was identified as an issue in consultation by multiple organisations, but was not discussed in the ADAR.

Workforce considerations

The components of the risk algorithm must be completed by appropriately trained staff (this was identified as a key issue from organisational stakeholders). Consideration of the individual training, certification, and performance auditing requirements is needed, as well as the number of staff required to meet demand for services and the consequential costs.

Education and support

Both (1) pre-intervention education regarding availability of the test for preeclampsia, and (2) post-intervention counselling regarding interpretation of test results were identified as necessary in public consultation. Both will assist in managing psychological burden associated with testing, as well as self-administration of aspirin. Consideration of the cost and resource requirements for this is required, as this has not been incorporated into this ADAR.

Data collection and privacy

Data collection and privacy implications may need to be considered given the FMF risk calculator hosted online.

Managing risk information and related self-administration

Risk-based testing has issues around risk perception and eligibility cut-offs which were not addressed in this application. Participants who receive risk information may conceptualise this in different ways. For example, those who are “close to” the risk threshold for treatment may perceive themselves as high risk. Equally, those who are deemed low risk but have certain concerns or personal biases, may also perceive themselves as high risk. In either case, receiving risk information can trigger people to consider their risk, and based on their perceptions, may want treatment. For this proposal, this is a particular concern given that aspirin is over the counter and readily accessible. Self-administration and its impacts should be considered, particularly in the context of the possible safety concerns of treatment raised above.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- The TGA recently advised that the FMF risk calculator requires regulation as a medical device. An application for TGA regulation must be in train before public funding can be supported, and therefore MSAC is requested to consider the context of any uncertainty regarding TGA registration.
- Additional MBS-funded consultations may be needed to explain the results of structured prenatal risk assessment for preterm preeclampsia and manage potential anxiety.
- The evidence on how well the FMF algorithm predicted risk of preeclampsia and, separately, how effective aspirin was at preventing preeclampsia in at-risk pregnancies was strong. However, linkages from the use of the FMF algorithm to uptake of aspirin leading to reduced incidence of preeclampsia and improved pregnancy outcomes were not demonstrated. Therefore, while the assumptions underpinning the proposal for funding (that is, that risk assessment leads to treatment, which leads to improved health outcomes) may be reasonable from first principles, they were not demonstrated by the evidence provided.

- The safety outcomes of the use of aspirin in the proposed pregnant population were based on a study which reported aspirin use in a population of 789 at-risk individuals, and therefore this limits the ability to account for adverse events occurring at low frequency.
- Given the evidence regarding false positive rates from testing using the FMF algorithm, and therefore potentially high uptake rates of prophylactic aspirin and the lack of evidence on incremental psychological harm associated with this testing compared to standard of care, the safety implications of the structured prenatal risk assessment for preterm preeclampsia (both in terms of direct testing and consequent treatment) are uncertain.
- The only study to provide evidence for the direct link between use of the FMF risk calculator and health outcomes had a high risk of bias (in particular, selection and confounding bias) due to the intervention being administered to mainly patients at selected private centres who may not be representative of the general Australian patient population, while the standard of care population was drawn from the general Australian population, leading to significant differences between the two populations.
- Risk assessment may impact access to existing ultrasound services, particularly given the uncertainties regarding training/certification for the radiology item.

Economic issues:

- The economic model was based on the clinical validation study investigating the direct link between use of the FMF risk calculator and health outcomes, which as discussed previously, had a high risk of selection and confounding bias.
- The economic model had the following discrepancies and omissions - the model structure was oversimplified as there was a lack of separation of the standard of care (SoC) arm into low-risk and high-risk cohorts and the impacts of this oversimplification are unclear though the assumption of a uniform monitoring cost for both risk groups is potentially more favourable to the risk assessment arm; the percentage of patients receiving aspirin was assumed to be higher in the SoC arm than the risk assessment arm; assumed hospitalisation costs were lower than those used in the economic model for MSAC application 1706 by the same applicant; the false positive rate of testing was not taken into account. the base case assumptions regarding probability of pre-term preeclampsia under SoC and in the risk assessment arm (if assessed as low risk and high risk) were all based on the unadjusted risk ratio in the clinical validation study rather than the adjusted risk ratio.

Financial issues:

- There was considerable uncertainty in the financial estimates, and some of the assumptions used to calculate financial impact were questionable, especially assumptions regarding the diagnostic yield of the test in preventing pre-term and term preeclampsia.
- There may be significant out-of-pocket costs associated with the FMF risk calculator that were not considered by the ADAR. This would increase the overall societal costs of listing the structured risk assessment.

ESC discussion

ESC noted that this was a new application requesting Medicare Benefits Schedule (MBS) listing of structured prenatal risk assessment for preterm preeclampsia in pregnant individuals at 11+0 to 13+6 weeks gestation.

ESC noted that in preeclampsia there is impaired trophoblastic invasion, which can cause placental thromboses and infarcts, and that early preeclampsia (before 34 weeks gestation) tends to be more severe and is associated with intrauterine growth restriction (IUGR) and low birth weight. ESC noted preeclampsia is associated with maternal hypertension, and can result in proteinuria, thrombocytopenia and increased risk of miscarriage or stillbirth. There is also a risk of preterm delivery as the ultimate therapeutic option for preeclampsia management, and

consequent risk of gestation-dependent neonatal morbidity and mortality. ESC noted that preeclampsia is antecedent in 10-15% of direct maternal deaths (approximately 1 per year in Australia), and in one third of pre-term births (approximately 2700 infants) and in approximately 200 neonatal or infant deaths per year in Australia. The management of preeclampsia is informed by the gestation at which it occurs, and may include administration of steroids for fetal lung maturation, intravenous magnesium, stabilisation of haemodynamic or haematological instability, prior to delivery.

ESC noted that the proposed intervention was the Fetal Medicine Foundation (FMF) risk assessment algorithm (“FMF risk calculator” or “FMF risk algorithm”), used to assess risk of preterm preeclampsia in asymptomatic pregnant individuals at 11+0 to 13+6 weeks gestation, before signs and symptoms of preeclampsia develop (typically after 20 weeks). The proposed FMF risk calculator uses the following inputs to create a risk score:

- medical history (specific characteristics)
- maternal mean arterial pressure (MAP)
- biochemical measurement of maternal serum concentration of placental growth factor (PIGF)
- ultrasound assessment of uterine perfusion (Doppler measurement of uterine artery pulsatility index [UtA-PI]).

The risk score is given as a percentage: 1 in 100 (1.0%) is considered “high risk” and directs the use of prophylactic aspirin to prevent the onset of preeclampsia.

ESC noted that the Therapeutic Goods Administration (TGA) had been assessing whether the FMF risk calculator was required to be registered as a medical device, and that this application had therefore been permitted to enter the MSAC process given the TGA’s uncertainty. ESC noted that on the day of ESC proceedings the TGA had advised that the FMF risk calculator falls within the definition of software as a medical device (SaMD), and so is required to be included in the Australian Register of Therapeutic Goods (ARTG). The TGA also confirmed that the FMF calculator is not currently included in the ARTG. ESC considered that as TGA regulation must be in place before public funding can be supported, MSAC should consider the context of any uncertainty regarding TGA registration.

ESC noted that the applicant developed assessment report (ADAR) proposed amending MBS item 55707 to incorporate the assessment of UtA-PI to align with current timing around aneuploidy screening, and amending MBS item 66750 to incorporate quantitation of PIGF (with flow-on amendments to MBS item 66751), at small fee increases. ESC noted that the descriptors align with the population. ESC noted that the proposed amendments to item 55707 and 66750 specify that providers must participate in performance audits and Quality Assurance Programs applicable to the FMF risk algorithm. However, further MBS-funded consultations may be needed to explain results and manage potential anxiety, and it is not clear whether this has been taken into account in the ADAR. ESC noted the Department’s preference to create a new first trimester ultrasound item instead of adding mean uterine artery pulsatility index to item 55707 in light of advice from the Royal Australian and New Zealand College of Radiologists (RANZCR) that first trimester ultrasound scans are not routinely available for all patients, which raises concerns around access and equity.

ESC noted that consultation feedback broadly supported public funding. Consumers considered that counselling and dietary advice should be available to women when they are found to be at high risk of preeclampsia. ESC noted disadvantages of testing raised in consultation included the potential for falsely alarming women in early pregnancy, including stress and worry for those with a high-risk result. ESC considered that were pregnant women to be fully informed of the levels of uncertainty about results of testing, the stress this may induce in some women may be significant such that it may outweigh any benefits. ESC also noted the high rate and number of false positives associated with testing and the difficulties that identified high-risk patients may

face with aspirin adherence. One organisation commented that the women most likely to be severely affected by preeclampsia were the vulnerable women presenting to public hospitals. ESC considered that hospitalisation for preeclampsia may also have access and equity issues for women in more remote areas (due to costs of travel, need to arrange care for other children, and the potential need for transfer if local hospitals did not have capacity to admit). ESC also considered that a systematic review had shown the risk of postpartum depression was higher in people with preeclampsia than people without preeclampsia, and considered that the risks of postpartum depression should be considered in patients with preeclampsia.

ESC noted that the clinical management algorithm as described is consistent with the proposed modifications to the two MBS descriptors and, as mentioned above, there is the potential for additional downstream MBS funded consultations. However, ESC noted that the ADAR left unresolved which healthcare provider should undertake the computation of the FMF algorithm (which is currently publicly accessible) based on the clinical indicators provided and which provider should communicate the results to the patient. Related to this, the ADAR left unresolved whether the amended MBS items should specify a particular service model for structured prenatal risk assessment for preterm preeclampsia (i.e. determine in all settings in which medical service providers should coordinate and report the testing) or whether this can be determined by the service provider (as per current aneuploidy testing where it differs from State to State whether this is the ultrasound service provider or the pathology service provider). ESC expressed a preference for the latter.

ESC noted that current practices regarding prescription and use of aspirin are also unspecified in the ADAR.

ESC noted that the proposed comparator was standard of care (SoC), which consisted of collecting maternal characteristics and medical/obstetric history and comparing this with published guidelines (typically from the UK National Institute for Health and Care Excellence [NICE] or American College of Obstetrics and Gynaecology [ACOG]) to assess risk of preeclampsia. ESC noted that there was significant variability in how the SoC of clinician-based assessment (with or without the NICE/ACOG algorithm) is applied and therefore many pregnant people with two or more moderate risk factors or with high risk factors may not be offered aspirin at a time when it might influence outcomes. Alternatively, they may be offered aspirin but not accept it. ESC considered that given the variation in current clinical practice this application essentially sought to change clinical practice rather than reflect it, which may not be appropriate. ESC noted that the National Health and Medical Research Council's website recommends that all patients should have clinical screening for preeclampsia risk in early pregnancy but that this recommendation expired in 2022 and is "under review" and does not recommend the use of any risk algorithm. ESC estimated that taking these uncertainties into account less than 5% of pregnant patients would be identified as being at high risk and prescribed aspirin as an intervention while under the proposed algorithm, roughly 10.5% of pregnant patients would be identified as high risk, which amounts to over 30,000 people a year treated with aspirin.

ESC noted that the evidence provided seemed to support both a direct and a linked evidence approach but this was not clearly or explicitly stated. In particular, ESC noted that:

- evidence on whether the FMF algorithm accurately predicted pre-eclampsia came from three studies associated with the ASPRE trial (Combined Multimarker Testing and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention), a large, high-quality randomised controlled trial (RCT) conducted in the UK, Europe and Israel and four other datasets. ESC noted that although some of the included studies were at risk of bias, overall the evidence was assessed to be of high quality;
- no evidence was provided on whether use of the FMF algorithm led to changes in treatment and management of patients (in particular uptake of aspirin);
- evidence was provided on the impact of aspirin on pre-term preeclampsia incidence from one study associated with the ASPRE trial;

- evidence on the effect of aspirin on preeclampsia related outcomes came from one study associated with the ASPRE trial and from a meta-analysis looking at the effect of aspirin and prevention of preeclampsia from randomised controlled trials (RCTs) by Roberge³²;
- evidence on adverse events from aspirin was provided from one small study (associated with the ASPRE trial).

ESC considered that the evidence on how well the FMF algorithm predicted risk of pre-eclampsia and, separately, how effective aspirin was at preventing preeclampsia in at-risk pregnancies was strong. However, linkages from the use of the FMF algorithm to uptake of aspirin leading to reduced incidence of preeclampsia and improved pregnancy outcomes were not demonstrated. Therefore, while the assumptions underpinning the proposal for funding (that is, that risk assessment leads to treatment, which leads to improved pregnancy outcomes) may be reasonable from first principles, they were not demonstrated by the evidence provided.

ESC noted that the ADAR did not provide sufficient evidence to support the clinical claim for non-inferior safety. The ADAR did not discuss psychological harm associated with risk-based testing and results (particularly for the population determined high risk by the FMF risk algorithm) nor did it provide as a basis for comparison to safety outcomes related to comparative psychological harms of having delivery at a non-viable gestation or a preterm infant owing to preeclampsia. Safety outcomes related to comparative physical harms to the gestational parent and the baby once delivered, with or without the proposed intervention, were also not described.

ESC also noted that the safety consequences of unnecessary aspirin treatment in false positive cases and missed aspirin treatment in false negative cases were mentioned. However, ESC considered the evidence on this impact was not sufficiently explored in the ADAR. In particular, ESC noted that the evidence for safety of use of aspirin in the proposed pregnant population cited in the ADAR only reported aspirin use in a population of 789 at-risk individuals, which limits the ability to account for adverse events occurring at low frequency. ESC considered the potential disutility of risk assessment was uncertain. ESC considered that the claim of non-inferior safety could not be supported in the absence of sufficient evidence, and that the evidence on safety associated with risk assessment and consequent treatment needed further investigation given that the estimated false positive rate of testing is approximately 10% and up to 300,000 patients a year would be tested under the proposal. ESC noted that the commentary conducted an independent scoping search of relevant literature and had also concluded that the clinical claim for non-inferior safety of testing was not supported due to the insufficient evidence.

In terms of effectiveness, ESC noted that the use of structured prenatal risk assessment for predicting preterm preeclampsia as a screening tool in asymptomatic pregnancies at 11+0 to 13+6 weeks gestation had superior effectiveness compared with standard practice that involved the assessment of risk for preterm preeclampsia through taking a medical history. ESC noted that most of the evidence supported the superiority of the FMF over the NICE (which have good specificity but low sensitivity) and ACOG (which have good sensitivity but low specificity) guidelines.

ESC accepted the evidence presented for the effectiveness of aspirin to prevent pre-term preeclampsia in identified high-risk individuals, and noted that the evidence suggested a reduction in the incidence of pre-term preeclampsia of 62% in this high risk group from being treated with aspirin. ESC noted that the meta-analysis by Roberge estimated the number needed to treat for aspirin to prevent one case of pre-eclampsia was 38. However it was unclear what impact aspirin treatment had on women identified as low risk by the FMF risk calculator compared with standard of care. ESC noted that there was no difference in secondary health outcomes for the mother and baby (e.g. neonatal death, stillbirth, underweight etc) but that the relevant ASPRE trial was underpowered to detect these impacts. ESC noted that the pre-ESC

³² Roberge, S., et al. (2018a). Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. *Am J Obstet Gynecol*, 218(3), 287-293 e281. <https://doi.org/10.1016/j.ajog.2017.11.561>

response acknowledged the absence of evidence to support the effect of screening using the intervention on reduction in downstream adverse outcomes secondary to preeclampsia.

ESC noted that only one study (Rolnik 2022)³³ provided evidence for the direct link between use of the FMF risk calculator and health outcomes (e.g. incidence of pre-term preeclampsia, delivery <32 weeks, low birth weight, stillbirth/neonatal death, APGAR<4). However the study had a high risk of bias (in particular, selection and confounding bias) due to the intervention being administered to mainly patients at selected private centres who may not be representative of the general Australian patient population, while the SoC population were drawn from the general Australian population. This led to significant differences in the study populations (e.g. the intervention group was older, had lower BMI, lower rates of diabetes, etc). ESC noted that it was unknown from the study what the rates of treatment uptake and compliance were. ESC also noted the commentary's concerns that the study omitted data on ancestry for the two populations even though ancestry is one of the inputs into the FMF risk algorithm. In the pre-ESC response, the applicant acknowledged the statistically significant differences between the intervention and SoC patients but stated that this was due to the very large sample sizes of the control and intervention groups and stated that the differences are unlikely to be clinically significant (i.e. whatever statistically significant differences there were did not systematically favour better outcomes for one group over another).

ESC noted that as the study by Rolnik was used to drive the economic model, given the high risk of bias of that study (as discussed above), this also created considerable uncertainty in the economic evaluation.

ESC noted that the commentary considered the model structure to be oversimplified including the lack of separation of the SoC arm into low-risk and high-risk cohorts. ESC agreed and considered this limited comparability, although the impact was unclear. Current testing practice guidelines in Australia recommend assessment of the risk of preeclampsia using a combination of maternal characteristics and history. As the prevalence of preeclampsia outcomes vary significantly between risk groups as does the cost of aspirin treatment, it was difficult to make an unbiased estimate of the effect of the introduction of structured risk testing in the SoC population if a uniform risk of preeclampsia was applied. ESC also noted that not differentiating between high and low risk cohorts in the SoC arm meant that a uniform monitoring cost applied to both groups, which was an assumption potentially favourable to the FMF risk algorithm. ESC noted that the percentage of patients receiving aspirin was higher in the SoC arm than the risk assessment arm, and queried the reason for the difference. ESC considered it may arise from overtreatment or that the data for each arm came from different sources.

ESC noted that hospitalisation costs were lower than those used in MSAC application 1706, lodged by the same applicant for sFit-1/PIGF ratio testing for the identification and management of preeclampsia. For example, the cost of \$585.20 assumed for cost of monitoring in 1705 was different from the weighted cost of \$987 in 1706. ESC considered that the hospital delivery costs, including maternal costs and neonatal intensive care costs were lower in 1705 than in 1706 – and considered that it was unclear why the applicant had used different cost estimates in the two applications. ESC recommended that a sensitivity analysis be undertaken based on the alternative higher estimates from 1706, which should also distinguish between the costs of monitoring high-risk versus low-risk cohorts.

ESC noted that the model also did not take into account the false positive rate of testing of 13.4% (95% CI 13.1–13.8%).

³³ Rolnik, D. L., Selvaratnam, R. J., Wertaschnigg, D., et al. (2022). Routine first trimester combined screening for preterm preeclampsia in Australia: A multicenter clinical implementation cohort study. *Int J Gynaecol Obstet*, 158(3), 634-642. <https://doi.org/10.1002/ijgo.14049>

ESC noted that the model was most sensitive to changes in the cost of the intervention, the probability of being assessed as at high risk for preterm preeclampsia by the FMF algorithm, and the probability of treatment with aspirin.

ESC noted that the ICER shifted from dominant to \$272,006 per QALY when the probability of developing pre-term PE if determined to be high risk by structured prenatal risk assessment increased from the base case of 2.1% to 4.3%. ESC noted that the ICER shifted from dominant to \$30,067 per QALY when the probability of developing term PE if determined to be high risk by structured prenatal risk assessment increased from the base case of 3.6% to 7%.

ESC noted that the base case assumptions made regarding the probability of pre-term preeclampsia under SoC (0.007) and the probabilities of pre-term pre-eclampsia if assessed at high risk by the FMF algorithm (0.0021) and if assessed as low risk (0.002) were premised on the crude or unadjusted risk ratio of 0.64 in Rolnik 2022 (i.e. the total percentage share of patients with pre-term preeclampsia implied by the latter two assumptions divided by the total percentage share of patients with pre-term preeclampsia implied by the first assumption equals the crude risk ratio) rather than the adjusted risk ratio of 0.7. ESC noted the two differed by 10%, and considered that the applicant should rerun the model based on assumptions consistent with the adjusted risk ratio of 0.7.

ESC noted that the applicant acknowledged in the pre-ESC response that there is the potential for patients to incur out-of-pocket costs for ultrasound assessments provided as part of antenatal care, as well as for people assessed as being high risk for preeclampsia to benefit from a follow-up antenatal attendance. ESC considered that the implications of these additional out-of-pocket costs should be presented to MSAC in the financial analyses (as they are sufficiently prominent to warrant consideration in the financial estimates even though these typically only include government payer costs).

ESC noted that a market share approach was used for the utilisation estimates, which assumed that there would be a 10% increase in utilisation of the MBS item proposed to be amended, driven by increased demand from the addition of preeclampsia testing. ESC noted that the commentary considered this a reasonable assumption, but considered that an epidemiological approach based on the number of pregnant women opting to uptake the testing could have been used for validation of these estimates.

ESC noted that there was considerable uncertainty in the financial estimates. The base case provided estimates that the intervention would cost the MBS \$6–7 million per year but due to reduced hospitalisations would overall reduce government health spending (that is, MBS and state and territory hospital spending combined) by \$5 million per year.

ESC considered that some questionable assumptions were used to calculate the financial impact: that the increased diagnostic yield from adopting the test would lead to increased prevention of term and preterm preeclampsia even though the evidence this was derived from was at high risk of bias; and that the average cost of the proposed test per patient per pregnancy was assumed to be \$120 which was likely an underestimate. ESC also noted that the out-of-pocket cost per patient could be in the range of \$380 per pregnancy based on out-of-pocket costs for a standard anatomy scan based on commercial pricing (or more than \$69 million a year in OOP costs) and the applicant should clarify the range of these estimates.

ESC noted that the FMF provides two additional risk calculators for use later in pregnancy (testing at 19+0 to 24+6 weeks and 30+0 to 37+6 weeks) and these later gestational ages were not part of this assessment, which ESC considered may pose a leakage risk for testing PIGF.

ESC noted that sensitivity analysis demonstrated that cost savings were likely to be much lower and, in some cases (depending on the variation in the number of pregnant individuals tested and the clinical utility of the tests in preventing preeclampsia), resulted in a net cost to combined

government budgets rather than a net saving, although most sensitivity analyses remained cost saving.

ESC noted that the decision on whether to fund structured prenatal risk assessment for preterm preeclampsia will need to take into account the potential impacts of this funding on access to existing ultrasound services particularly given the uncertainties regarding training for the radiology item and existing constraints on access to first trimester ultrasound testing.

ESC noted the potential impact on MSAC Application 1706 would need to be considered if MBS funding of structured prenatal risk assessment for preterm preeclampsia is supported.

17. Applicant comments on MSAC's Public Summary Document

Roche wishes to thank the Medical Services Advisory Committee (MSAC) for reviewing and considering our application. While the outcome was disappointing, we respectfully accept the committee's findings.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)