National Institute for Health and Care Excellence

Draft for consultation

Hypertension in pregnancy

[C] Evidence review for prediction of complications in pre-eclampsia

NICE guideline CG107 (update)

Evidence reviews

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Draft for Consultation

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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Contents

1

Review question HiP3. Which tests or clinical prediction models are accurate in identifying or predicting women at risk of severe complications of pre-eclampsia?

Introduction

Women with pre-eclampsia can have varying clinical courses of disease, with some women being monitored successfully as outpatients, while other women will require urgent admission for their condition to be managed in a critical care setting. The identification of women at increased risk of developing severe complications (either themselves, or complications for their babies) from pre-eclampsia is therefore important in order to manage women in appropriate settings. However, it remains difficult for healthcare providers to differentiate between women at increased risk of severe complications and women at low risk.

The aim of this review is to determine which investigations or risk prediction models are useful in identifying women (and babies) at risk of severe complications from pre-eclampsia, in order to guide stratified surveillance and target interventions for those at higher risk.

Summary of the protocol

Please see Table 1 for a summary of the population, intervention (clinical prediction tools), comparator, outcome, timing and setting (PICOTS) of this review.

Table 1: Summary of the protocol (PICOTS table)

Population	Pregnant women with pre-eclampsia
Intervention	• Externally validated clinical prediction model studies • Prognostic test accuracy studies
Comparator	Not applicable - alternative predictive models/prognostic test accuracy studies were not considered in this review

Outcome	• Maternal adverse outcomes
	  ○ Severe pre-eclampsia
	  ○ Eclampsia
	  ○ Maternal mortality
	  ○ Maternal morbidity, including serious CNS, cardiorespiratory, hepatic, renal or haematological morbidity
	  ○ Placental abruption
	  ○ Need for delivery (any delivery/delivery for pre-eclampsia)
	• Perinatal adverse outcomes
	  ○ Preterm delivery (<34 weeks)
	  ○ Perinatal mortality (stillbirths and death during first 7 days of life)
	  ○ Stillbirth
	  ○ Neonatal death (during first 28 days of life)
	  ○ Serious neonatal morbidity e.g. respiratory, gastrointestinal or CNS complications

Timing	• Up to 48 hours • Up to 7 days • Over 7 days
Setting	Risk stratification of women at high risk of severe complications who may require admission to hospital or specific interventions

CNS: central nervous system

For full details see the review protocol in appendix A

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual 2014. Methods specific to this review question are described in the review protocol in appendix A.

Declaration of interests were recorded according to NICE's 2018 conflicts of interest policy (see Register of interests).

Clinical evidence

The aim of this review was to assess which clinical prediction model or prognostic test was most helpful at predicting adverse maternal and/or fetal outcomes in women with suspected or confirmed pre-eclampsia (PE).

For a study to be included, it had to report at least one type of clinical predictive performance measure (or sufficient data for this to be calculated) to predict composite maternal and/or fetal adverse outcomes.

Included studies

Two different types of studies were included, namely externally validated clinical prediction model studies and prognostic test accuracy studies (and systematic reviews of these studies). For a study to be considered as externally validated, the performance of the prediction model should have been assessed in a sample of patients that were not used for the development of the tool, as described by Debray 2017.

Externally validated clinical prediction model studies

Eight publications providing external validation of 4 prediction models (fullPIERS, miniPIERS, PREP-L and PREP-S) were included (Agrawal 2014, Akkermans 2014, Almeida 2017, Payne 2014, Payne 2015, Thangaratinam 2017, Ukah 2017a, and Ukah 2018). In the context of this review, prediction models assessed the individualised risk of developing adverse maternal or fetal outcomes by combining prognostic factors of an individual. For further details regarding the characteristics of the prediction models please see Table 2. Study details for the external validation studies are reported in Table 3.

Five studies included women with other hypertensive disorders of pregnancy, in addition to PE: Akkermans 2014, Payne 2014, Payne 2015, Thangaratinam 2017, and Ukah 2018. In these studies, the proportion of women with PE ranged from 43.5% to 98.5%.

Half of the included studies used data from pre-existing datasets of women, which led to some overlap in the sample of patients included. These were the PETRA cohort (Preeclampsia Eclampsia Trial Amsterdam), which was included in Akkermans 2014, Thangaratinam 2017, and Ukah 2018; PIERS cohort (Pre-eclampsia Integrated Estimate of RiSk), which was included in Laskin 2011, Livingston 2014, Payne 2014 and Thangaratinam 2017; PREP cohort (Prediction model for Risks of complications in Early-onset Pre-eclampsia), included in Ukah 2018; and miniPIERS cohort, which was included in Ukah 2017a.

Prognostic test accuracy studies

Six publications were included (Chan 2005, Laskin 2011, Livingston 2014, Thangaratinam 2011, Ukah 2017b, Waugh 2017). These studies aimed to assess the performance of different tests to predict adverse maternal and fetal outcomes. Studies are summarised in Table 4.

See also literature search strategy in appendix B and clinical evidence study selection in appendix C.

Table 2: Description of the prediction models

Prediction model	Description	Factors included in the model
fullPIERS	fullPIERS is a free online tool developed to identify the probability of adverse outcomes in women with pre-eclampsia at 48 hours or 7 days from baseline. fullPIERS has been validated in women up to 37 weeks gestation. For more information please see https://pre-empt.bcchr.ca/monitoring/fullpiers	• Gestational age • Presence/absence of chest pain or dyspnoea • Oxygen saturation • Platelets (x10^9/L) • Creatinine (µmol/L) • AST/ALT (U/L)
miniPIERS[a]	miniPIERS is a free online tool aimed to be used in low and middle income countries. It was developed to identify the probability of adverse outcomes in women with pre-eclampsia up to 7 days before complications arise. For more information please see https://pre-empt.bcchr.ca/monitoring/minipiers	• Gestational age at admission • Previous deliveries before 20 weeks gestation • Presence/absence of chest pain/dyspnoea • Presence/absence of headache and/or visual changes • Presence/absence vaginal bleeding with abdominal pain • Systolic blood pressure (mmHg) • Oxygen saturation (optional)
PREP-L	PREP-L aims to predict the overall risk of maternal complications by discharge only. PREP-L can be used in women up to 34^{+6} weeks gestation. For more information see https://www.evidencio.com/models/show/1043	• Maternal age • Gestational age at diagnosis • Presence/absence of pre-existing conditions (hypertension, renal disease, diabetes mellitus, autoimmune disease, previous occurrence of pre-eclampsia) • Systolic blood pressure (mmHg) • Platelets (x10^9/L) • Urea (mmol/l) • Creatinine (µmol/L) • Protein creatinine ratio (mg/mmol) • Whether woman received any antihypertensive or magnesium sulfate at diagnosis or within 24 hours
PREP-S	PREP-S aims to predict the risk time of adverse outcomes at a number of time periods (from 2 days to 42 days) from baseline. PREP-S can be used	• Maternal age • Gestational age at diagnosis • Presence/absence of tendon reflexes

Prediction model	Description	Factors included in the model
	in women up to 34+6 weeks gestation. For more information see https://www.evidencio.com/models/show/1043	• Presence/absence of pre-existing conditions (hypertension, renal disease, diabetes mellitus, autoimmune disease, previous occurrence of pre-eclampsia) • Systolic blood pressure (mmHg) • Oxygen saturation • Platelets (x10^9/L) • Urea (mmol/l) • Creatinine (µmol/L) • Protein creatinine ratio (mg/mmol) • Whether woman received any antihypertensive or magnesium sulfate at diagnosis or within 24 hours

AST: aspartate transaminase; mmHg: millimetres of mercury; mmol: millimole; mg: milligramme; PIERS: Pre-eclampsia Integrated Estimate of RiSk; PREP-L: Prediction model for Risks of complications in Early-onset Pre-eclampsia (logistic regression model); PREP-S: Prediction model for Risks of complications in Early-onset Pre-eclampsia (survival analysis model); SGOT: serum glutamic-oxaloacetic transaminase; µmol: micromole; U/L: units per litre

[a]This tool was developed to be used in low and middle income countries, however it was included it in the report as it may be useful for triage in a primary care setting, or when results of blood tests are not immediately available.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

A summary of the studies that were included in this review are presented in Table 3 and Table 4.

Table 3: Summary of externally validated clinical prediction model studies

Study name, type and country from which the data was sourced	Population *(definition of pre-eclampsia)*	Predictive prognostic tool	Outcomes	Primary study
Agrawal 2016 Prospective cohort India	N=322 women with PE *sBP/dBP≥ 140/90 mmHg taken twice more than 4 hours apart after 20 weeks of gestational age in combination with proteinuria*	fullPIERS	PIERS composite	von Dadelszen 2011

Study name, type and country from which the data was sourced	Population *(definition of pre-eclampsia)*	Predictive prognostic tool	Outcomes	Primary study
Akkermans 2014 Multicentre prospective cohort The Netherlands	N= 216 women from the PETRA cohort (43.9% with severe PE) *dBP ≥110 mmHg and proteinuria ≥ 0.3 g per 24 hours*	fullPIERS	PIERS composite	von Dadelszen 2011 Note overlap in Thangaratinam 2017 and Ukah 2018 in PETRA dataset
Almeida 2017 Retrospective cohort Brazil	N=325 women with PE *Increased BP (threshold not reported) from the 20th week of pregnancy with proteinuria*	fullPIERS	PIERS composite	von Dadelszen 2011
Payne 2014 Multicentre prospective cohort UK, Canada and New Zealand	N=1300 women from the PIERS cohort (78.5% with PE) *sBP/dBP ≥140/90 mmHg (at least 1 component, measured ≥ 4hours apart, after 20 weeks GA) and either proteinuria (≥0.3g per day by 24 hour collection or ≥ 30mg/ mmol as measured by protein:creatinine ratio) or hyperuricaemia (upper limit greater than normal for non-pregnant women)*	miniPIERS	PIERS composite	Payne 2014 Note overlap with Laskin 2011, Livingston 2014, Thangaratinam 2017 in PIERS cohort
Payne 2015 Prospective cohort Pakistan, South Africa	N=852 (60.56% with PE) *sBP/dBP ≥140/90 mmHg with proteinuria ≥2+ on a dipstick test*	miniPIERS	PIERS composite	Payne 2014
Thangaratinam 2017 Retrospective cohort The Netherlands (PETRA dataset); Australia, Canada, South	N=634 women from the PIERS cohort with PE and N=216 from the PETRA cohort (43.9% with severe PE) *sBP/dBP≥ 140/90 mmHg taken twice more than 4 hours apart after 20 weeks of gestational age in combination with proteinuria (≥ 0.3 g/dl of*	PREP- L and PREP-S	Adapted PIERS composite	Thangaratinam 2017 (the development and external validation study were published in the same article) Note overlap in Ukah 2018, Akkermans 2014 with PETRA

Study name, type and country from which the data was sourced	Population *(definition of pre-eclampsia)*	Predictive prognostic tool	Outcomes	Primary study
Africa, UK (PIERS dataset)	*proteinuria or 2+ on urine dipstick)*			dataset and Laskin 2011, Livingston 2014, Payne 2014 in PIERS cohort.
Ukah 2017a Retrospective cohort Fiji, Uganda, South Africa, Brazil	N=757 women from the miniPIERS cohort with severe PE *sBP/dBP ≥140/90 mmHg (at least 1 component, measured ≥ 4 hours apart, after 20 weeks GA) and either proteinuria or hyperuricaemia, or b) HELLP syndrome, or c) superimposed PE*	fullPIERS	PIERS composite	von Dadelszen 2011
Ukah 2018 Retrospective cohort study Canada (BCW), The Netherlands (PETRA), UK (PREP)	N=218 from the BCW cohort (87.6% with severe PE), n=216 from the PETRA cohort (43.9% with severe PE), n=954 from the PREP cohort (98.5% with severe PE) ***BCW and PREP:*** *sBP/dBP ≥140/90 mmHg (at least 1 component, measured ≥ 4 hours apart, after 20 weeks GA) and either proteinuria or hyperuricaemia, or b) HELLP syndrome, or c) superimposed PE* ***PETRA:*** *dBP≥110 mmHg with fetal growth restriction (estimated fetal weight < 10th centile)*	fullPIERS	PIERS composite	von Dadelszen 2011 Note overlap with Akkermans 2014, Thangaratinam 2017 with PETRA dataset

BCW: British Columbia Women; BP: blood pressure; dBP: diastolic blood pressure; dL: decilitre; GA: gestational age; g: gram; HELLP: Haemolysis, Elevated Liver enzymes and Low Platelet count; mg: milligram; mmHg: millimetres of mercury; mmol: millimole; PE: pre-eclampsia; PETRA: Preeclampsia Eclampsia Trial Amsterdam; PIERS: Pre-eclampsia Integrated Estimate of RiSk; PREP-L: Prediction model for Risks of complications in Early-onset Pre-eclampsia (logistic regression model); PREP-S: Prediction model for Risks of complications in Early-onset Pre-eclampsia (survival analysis model); sBP: systolic blood pressure

Table 4: Summary of prognostic test accuracy studies

Study name, type and country from which the data was sourced	Population *(definition of pre-eclampsia)*	Test	Outcome
Chan 2005 Retrospective cohort Australia	N=321 women with PE *ISSHP research definition*	Spot protein/creatinine (mg/mmol) measured at the initial diagnosis of PE	Adverse maternal and fetal outcomes
Laskin 2011 Prospective cohort Canada, UK, Australia and New Zealand	N=1405 women from the PIERS cohort with PE *sBP/dBP ≥140/90 mmHg (at least 1 component, measured ≥ 4 hours apart, after 20 weeks GA) and either proteinuria or hyperuricemia, or b) HELLP syndrome, or c) superimposed PE*	• Abnormal coagulation (INR>1.06 and serum fibrinogen and serum fibrinogen <3.54 g/L) • Platelet < 100 x 10^9/L	PIERS composite
Livingston 2014 Prospective cohort Canada, UK, Australia and New Zealand	N= 1487 from the PIERS cohort with PE *sBP/dBP ≥ 140/90 mmHg on 2 recordings or more, more than 4 hours apart) without proteinuria (≥ 0.3 g/day by 24 hour urine excretion, or ≥ 30mg/mmol by spot urine:creatinine ratio)*	Uric acid (highest level recorded within 24 hours of enrolment)	PIERS composite Note overlap with Laskin 2011, Payne 2014, Thangaratinam 2017 in PIERS dataset
Thangaratinam 2011 Systematic review of retrospective and prospective cohort; prospective cross-sectional	K= 3[a] studies including women with PE	Liver function tests	Adverse maternal outcome/maternal complications and adverse fetal outcomes
Ukah 2017b Systematic review of prospective cohort studies	K=2[a] studies including women with confirmed PE	Soluble fms-like tyrosine kinase and placental growth factor	Adverse maternal and neonatal outcomes

Study name, type and country from which the data was sourced	Population *(definition of pre-eclampsia)*	Test	Outcome
Waugh 2017 Prospective cohort UK	N= 959 women with PE *sBP/dBP ≥140/90 mmHg and with ≥ 1 trace of proteinuria.*	Test: urinary protein dipstick, sPCR and sACR test, available as a local laboratory or central laboratory measure, in different thresholds	Adverse maternal and fetal outcomes

[a] *Note that only studies reporting composite outcomes have been included, thus the reduced number of studies compared to the original systematic review source*

dBP: diastolic blood pressure; GA: gestational age; g:, gram; HELLP: Haemolysis, Elevated Liver enzymes and Low Platelet count; INR: international normalized ratio; ISHHP: International Society for the Study of Hypertension in Pregnancy; L: litre; mg: milligram; mmHg: millimetres of mercury; mmol: millimoles; PE: Pre-eclampsia; PIERS: Pre-eclampsia Integrated Estimate of Risk; sACR: spot albumin creatinine ratio; sBP: systolic blood pressure; sPCR: spot protein-creatinine ratio; µmol: micromole

See appendix D for full evidence tables.

Quality assessment of clinical outcomes included in the evidence review

The included studies were individually assessed with AMSTAR, CASP CPR, and QUADAS-2 (see Methods chapter for more details).

Overall, studies were rated as of moderate or high quality. The reasons for rating down the studies assessed with AMSTAR (systematic reviews) were as follows: not performing study selection in duplicate; not providing a list of excluded studies; or not reporting the included studies in adequate detail.

The reasons for rating down the quality of the studies assessed with CASP CPR (clinical prediction model studies) were as follows: lack of clarity regarding whether the sample of women included an appropriate spectrum of patients; lack of clarity as to whether the predictor variables and outcomes were evaluated in a blinded fashion; statistical methods not clearly described; and studies including population from low and middle income countries, which affects the generalisability of the results.

The reasons for rating down the studies assessed with the QUADAS-2 (prognostic test accuracy studies) were as follows: not pre-specifying the thresholds; and lack of clarity as to whether the results were interpreted without knowledge of the results of the index test.

Data obtained from the prognostic accuracy studies were assessed according to the outcomes reported using GRADE methodology. The rating for imprecision was assessed based on sensitivity, as this was a critical outcome measure for the review. The pre-specified thresholds were ≥90% (high specificity) and ≥75% (moderate specificity).

The GRADE method has not been adapted for use with clinical prediction models, therefore these articles were quality assessed at the level of the individual studies.

See appendix F for the quality assessment of the included studies.

Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

Excluded studies

Studies not included in this review with reasons for their exclusion are listed in appendix K.

Economic model

An economic analysis was undertaken to estimate the cost-effectiveness of risk prediction models for guiding inpatient and outpatient management in pregnant women with pre-eclampsia (see appendix J for the full report of the economic analysis).

Methods

The analysis was developed in Microsoft Excel® and was conducted from the perspective of the NHS and Personal Social Services (PSS) as outlined in the NICE Reference Case (see Developing NICE guidelines: the manual).

Clinical data and model approach

The economic analysis considered strategies where the decision on whether to manage pre-eclampsia in women as an outpatient or inpatient was based on risk thresholds (e.g. to offer inpatient management with a risk score ≥ 10%). The analysis considered the fullPIERS risk assessment tool, which was selected because it has the best available evidence. Other risk assessment tools such as PREP-S could also be used in clinical practice but it was not possible to include them in the economic model because there is insufficient data on diagnostic accuracy (sensitivity and specificity) at various risk levels.

Management strategies based on risk level were compared against each other and also against strategies where it is assumed that all women are managed as either an inpatient or outpatient.

It is unclear which strategy would best represent current clinical practice as there is known to be variation. However, it is thought that inpatient management is generally more common than outpatient management. Note that this does not affect the current analysis as the intention is to compare all strategies against each other to determine the most cost-effective strategy. This is a separate endeavour to estimating cost impact which aims to estimate the change in cost associated with the adoption of a new strategy compared to current practice.

The economic analysis considered women 34-37 weeks of gestation reflecting the population in which the fullPIERS risk prediction model is applicable. The following management strategies were considered in the analysis:

- All inpatient management
- All outpatient management
- Inpatient management if fullPIERS ≥ 5%
- Inpatient management if fullPIERS ≥ 10%
- Inpatient management if fullPIERS ≥ 20%
- Inpatient management if fullPIERS ≥ 30%

The economic analysis was based on accuracy data (sensitivity and specificity) for the prediction of complications at 2 and 7 days for each of the strategies (see Table 5). In the model, the diagnostic results are linked to subsequent management whereby women with positive results are managed as inpatients and women with negative results are managed as outpatients.

Data on the prevalence of adverse outcomes as well as data on the accuracy of fullPIERS at different thresholds were estimated from an external validation study (Akkermans 2014). Accuracy data for the 'all inpatient management' and 'all outpatient management' were inferred based on the implications of the strategy e.g. all patients managed as an inpatient implies that all patients with complications would be managed as an inpatient and therefore the sensitivity would be 100%.

Table 5: Diagnostic accuracy for women 34-37 weeks of gestation

Strategy	48 hours		7 days	
	Sensitivity	Specificity	Sensitivity	Specificity
All inpatient	100%	0%	100%	0%
Inpatient if fullPIERS ≥ 5%	97%	70%	73%	73%
Inpatient if fullPIERS ≥ 10%	94%	84%	66%	88%
Inpatient if fullPIERS ≥ 20%	91%	93%	56%	95%
Inpatient if fullPIERS ≥ 30%	81%	98%	44%	99%
All outpatient	0%	100%	0%	100%

It has been assumed that women managed in an inpatient setting would have a reduction in the number of adverse maternal outcomes. There is no good evidence available on which to base this reduction. Therefore it was speculatively approximated using data from Broekhuijsen 2015 (HYPITAT II study), which compared immediate delivery with expectant management. It has been assumed that the reduction in adverse outcomes associated with being managed in an inpatient setting rather than an outpatient setting would be similar to the reduction seen with immediate delivery compared with expectant management. In comparison to expectant management, immediate delivery was found to reduce reported adverse maternal outcomes with a relative risk (RR) of 0.36 (95% CI 0.12–1.11). Therefore, this value was applied in the analysis as an estimate of the reduction in adverse maternal outcomes with the inpatient approach.

Mortality was not considered in the analysis as there is no evidence to suggest that the use of risk prediction models may confer a survival benefit.

Costs

The costs considered in the model reflect the perspective of the analysis, thus only costs that are relevant to the UK NHS & PSS were included. Where possible, all costs were estimated in 2016/17 prices. The majority of costs were sourced from NHS reference costs 2016/17 by applying tariffs associated with the appropriate Healthcare Resource Groups (HRG) code.

It was assumed that there is no cost associated with using the fullPIERS risk assessment tool itself as it is freely available online. Furthermore, it was assumed that there was no additional cost associated with performing the tests required to inform the risk factors in the tools as these tests are already carried out as part of routine clinical practice.

Inpatient costs were estimated using the average cost of a day as an elective inpatient from NHS reference costs 2016/17 (£384.50). The average length of stay (LOS) was based on pre-eclampsia audit data, which reported an average time between diagnosis of pre-eclampsia and delivery of 6 days for women 34-37 weeks of gestation. Outpatient costs were based on the cost of consultant led face-to-face follow-up in the obstetrics service from NHS reference costs 2016/17 (£120.20). The average duration of outpatient management was

assumed to be the same as inpatient management and it was assumed that patients would have re-assessments every 2 days.

Birth costs were estimated using data on the proportions of each mode of delivery from Broekhuijsen 2015 (HYPITAT II study). A combined average of the immediate delivery and expectant management arms of the trial was estimated resulting in proportions of 4%, 86% and 10% for spontaneous labour, induction of labour and caesarean section, respectively. Birth costs for the various modes of delivery were sourced from NHS Reference Costs 2016/17 assuming that women with adverse outcomes would have births with complications and co-morbidities (based on CC scores). Birth costs were estimated by taking a weighted average of births recorded in NHS reference costs as an elective inpatient, non-elective long stay and non-elective short stay.

It was assumed that women with an adverse outcome would be admitted to a high dependency unit (HDU). A HDU cost of £860.61 was estimated from NHS reference costs 2016/17, based on the weighted average cost of "adult critical care, 0 organs supported" and "adult critical care, 1 organs supported".

Based on a combined average of the immediate delivery and expectant management arms from Broekhuijsen 2015 (HYPITAT II study), it was assumed that a NICU admission would be required in 5.6% of births. NICU admission costs were estimated from NHS reference costs 2016/17, based on the cost of neonatal critical care, intensive care (£1,295)

Health-related quality of life

As recommended in the NICE reference case, the model estimates effectiveness in terms of quality adjusted life years (QALYs). These are estimated by combining life year estimates with quality of life (QoL) values associated with being in a particular health state.

QoL data were sourced from the economic analysis conducted as part of the previous guideline (NICE CG107). Pregnant women with pre-eclampsia were assumed to have the same QoL value as normotensive pregnant women. The QoL value for normotensive pregnant women was sourced from Sonnenberg 2004, a cost effectiveness analysis of contraception methods in women of average health and fertility, which found that short-term utility loss due to pregnancy was 0.0375.

Experiencing severe compications of pre-eclampsia was assumed to have the same QoL as being admitted to ICU for any reason. As part of a cost effectiveness analysis of meropenem in the treatment of severe infections in hospital intensive care, Edwards 2006 estimated that the QoL weight for someone who stayed in intensive care was 0.712. It was assumed that the QoL decrement for women with severe disease would last for 2 weeks.

In order to estimate QALYs these values were converted to daily weights and applied for the modelled time horizon.

Results

The base case results of the analysis are shown in Table 6. A 'dominance rank' approach was used to compare all strategies against each other, whereby the strategies are rank ordered in terms of cost and then each intervention is compared against the previous intervention that was found to be cost-effective.

A strategy of outpatient management was the least costly strategy overall. All other strategies were found to be more costly and more effective than outpatient management. Inpatient management if fullPIERS ≥ 30% was found to be cost-effective with an ICER value of £10,797 per QALY which is below the NICE threshold of £20,000 per QALY. All other strategies were not found to be cost-effective with ICERs well above the NICE threshold of

£20,000 per QALY. Therefore the strategy of inpatient management if fullPIERS ≥ 30% was found to be the optimal strategy in cost-effectiveness terms.

Table 6: Base case results

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Outpatient management	£3,047	-	0.04969	-	-
Inpatient if fullPIERS ≥ 30%	£3,064	£17	0.05128	-0.00159	£10,797
Inpatient if fullPIERS ≥ 20%	£3,131	£66	0.05148	0.00019	£340,580
Inpatient if fullPIERS ≥ 10%	£3,243	£178	0.05154	0.00026	£685,842
Inpatient if fullPIERS ≥ 5%	£3,424	£359	0.05159	0.00031	£1,147,915
Inpatient management	£4,031	£966	0.05164	0.00036	£2,681,636

QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio

Deterministic sensitivity results

A series of deterministic sensitivity analyses were conducted, whereby an input parameter is changed, the model is re-run and the new cost-effectiveness result is recorded. This is a useful way of estimating uncertainty and determining the key drivers of the model result. The results of the deterministic sensitivity analyses are presented in Table 7. It can be seen that the conclusion of the analysis changes in numerous scenarios with outpatient management found to be cost-effective in certain scenarios. Notably this includes numerous plausible scenarios such as where variations in the RR for adverse outcomes is applied or when the cost of adverse outcomes is changed.

Table 7: Deterministic sensitivity analysis results

Modelled scenario	Optimal strategy
Base case	Inpatient if fullPIERS ≥ 30%
Prevalence of adverse outcomes 25% higher	Inpatient if fullPIERS ≥ 30%
Prevalence of adverse outcomes 25% lower	Inpatient if fullPIERS ≥ 30%
Accuracy based on 7 day test only	*Outpatient management*
Repeat test accuracy based on 7 day data	*Outpatient management*
Adverse outcomes – lower RR (0.12)	Inpatient if fullPIERS ≥ 30%
Adverse outcomes – upper RR (1.11)	*Outpatient management*
Adverse outcomes – RR = 1	*Outpatient management*
Adverse outcomes – RR = 0.75	*Outpatient management*
Adverse outcomes – RR = 0.50	Inpatient if fullPIERS ≥ 30%
Adverse outcomes – RR = 0.25	Inpatient if fullPIERS ≥ 30%
Adverse outcomes – RR = 0.00	Inpatient if fullPIERS ≥ 30%
All births via spontaneous delivery	*Outpatient management*
All births via induction of labour	Inpatient if fullPIERS ≥ 30%
All births via caesarean section	Inpatient if fullPIERS ≥ 30%
No NICU admissions	Inpatient if fullPIERS ≥ 30%
Inpatient and outpatient duration = 7 days	Inpatient if fullPIERS ≥ 30%

Modelled scenario	Optimal strategy
Inpatient and outpatient duration = 14 days	*Outpatient management*
No increased birth costs with adverse outcomes	*Outpatient management*
No admission to critical care with adverse outcomes	*Outpatient management*
No QoL decrement associated with adverse outcomes	Inpatient if fullPIERS ≥ 30%

RR, relative risk; QoL, quality of life

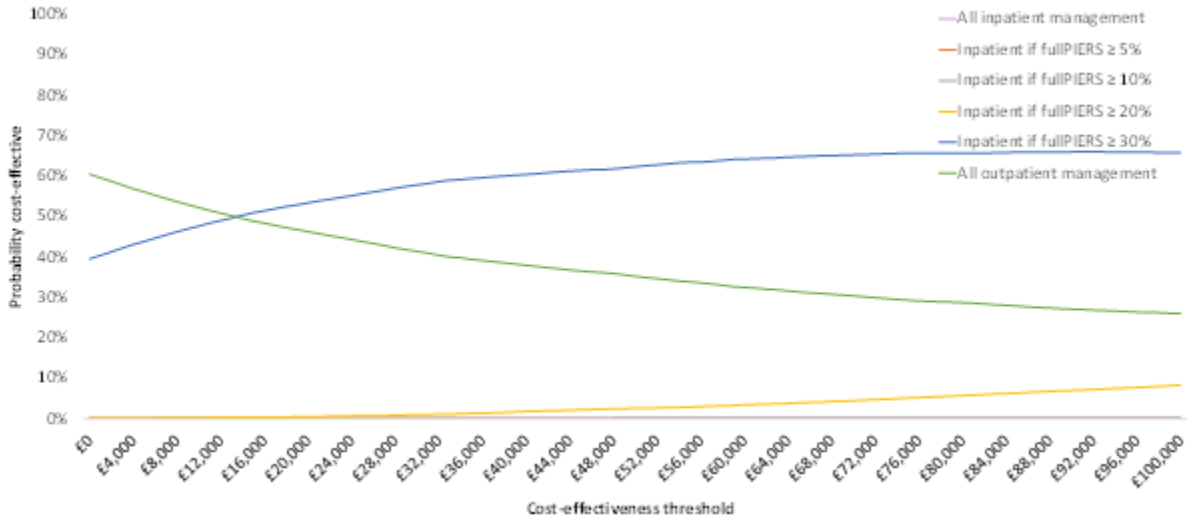
Threshold analysis results

A threshold analysis was conducted to determine the RR for adverse outcomes required for the inpatient management if fullPIERS ≥ 30% strategy to be cost-effective. It was found that a strategy of inpatient management if fullPIERS ≥ 30% was cost-effective with a RR of 0.53.

Probabilistic sensitivity analysis results

Probabilistic sensitivity analysis (PSA) was conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were utilised in the base-case were replaced with values drawn from distributions around the mean values. The results of 10,000 runs of the PSA are shown using cost-effectiveness acceptability curves (CEAC) in Figure 1. The CEAC graph shows the probability of each strategy being considered cost-effective at various cost-effectiveness thresholds on the x axis.

Figure 1: Cost-effectiveness acceptability curves



It can be seen that outpatient management and a strategy of inpatient management if fullPIERS ≥ 30% have the highest probabilities of being cost-effective at all thresholds. At the NICE threshold of £20,000 per QALY used by NICE, inpatient management if fullPIERS ≥ 30% has a 53% probability of being cost-effective while outpatient management has a 46% probability of being cost-effective. All other strategies were found to have a 0% probability of being cost-effective at the NICE threshold of £20,000 per QALY.

Conclusion

The base case results of the analysis suggest that using the fullPIERS risk model with a threshold of 30% for inpatient management is cost-effective in women 34-37 weeks of gestation. However, it should be noted that there are gaps in the clinical evidence base and therefore several assumptions have been made to run the analysis. Most notably, a speculative assumption was made around the reduction in the number of adverse maternal outcomes. Furthermore, deterministic sensitivity analysis suggested that differences in

assumptions have the potential to change the conclusion of the analysis and probabilistic sensitivity analysis demonstrated some uncertainty around the result.

Evidence statements

Externally validated models

fullPIERS model performance

Prediction of adverse maternal outcomes within 48 hours

- Four validation studies of fullPIERS (n=2470 participants) provided moderate to high quality evidence to show the following:
  - LR in the lower predicted risk categories (<1% and 1-2.4%) ranged from uninformative to very informative
  - LR in the middle risk categories (2.5-4.9%, 5.9-9.9% and 10-19%) ranged from uninformative to moderately informative
  - LR in the higher risk category (20-29%) was uninformative
  - LR in the highest risk category (≥30%) ranged from moderately to very informative.
  - Calibration, as assessed by the calibration slope, was found to be poor in the 3 studies that reported this (Akkermans 2016, Ukah 2017a and Ukah 2018)
  - Discrimination, as assessed by the AUC, ranged from moderate to excellent
  - Discrimination, as assessed by sensitivity, ranged from low to high (from 57% to 90.6%)
  - Discrimination, as assessed by specificity, ranged from low to high (from 65.1% to 94%)

Prediction of adverse maternal outcomes within 7 days

- Two validation studies of fullPIERS (n=1388 participants) provided high quality evidence to show the following:
  - LR in the lower predicted risk categories (<1% and 1-2.4%) were uninformative
  - LR in the middle risk categories (2.5-4.9%, 5.9-9.9% and 10-19%) ranged from to uninformative to moderately informative
  - LR in the higher risk category (20-29%) was uninformative
  - LR in the highest risk category (≥30%) was very informative
  - Calibration, as assessed by the calibration slope, was found to be poor in the single study that reported this (Akkermans 2016)
  - Discrimination, as assessed by the AUC, was found to be poor to moderate
  - Discrimination, as assessed by sensitivity, ranged from low to high (from 59 to 90%)
  - Discrimination, as assessed by specificity, was found to be very low to low (<75%)

Prediction of adverse maternal outcomes (timeframe not specified)

- One validation study of fullPIERS (n=322), reporting on adverse maternal outcomes (with predictor variables collected within 24 hours of admission) provided moderate quality evidence to show the following:
  - LR in the lower predicted risk categories (<1% and 1-2.4%) ranged from to uninformative to moderately informative
  - LR in the middle risk categories (2.5-4.9%, 5.9-9.9% and 10-19%) were uninformative
  - LR in the higher risk category (20-29%) was moderately informative
  - LR in the highest risk category (≥30%) was moderately informative

- Discrimination, as assessed by sensitivity, was very low (25%)
- Discrimination, as assessed by specificity, was found to be very high (95.4%)

miniPIERS model performance

Prediction of adverse maternal outcomes within 48 hours

- Two validation studies of miniPIERS (n=2152 participants) provided moderate to high quality evidence to show the following:
  - LR in the lower and middle risk categories (0-24.9%) were uninformative
  - LR in the highest risk category (≥25%) was moderately informative
  - Discrimination, as assessed by the AUC, was found to be moderate
  - Discrimination, as assessed by sensitivity, was found to be low (32.8%)
  - Discrimination, as assessed by specificity, was found to be very high (96.2%)

PREP-L model performance

- One validation study of PREP-L (n=648 participants), reporting on adverse maternal outcomes by discharge, provided moderate to high quality evidence to show the following:
  - Calibration, as assessed by the calibration slope, was found to be good
  - Discrimination, as assessed by the AUC, was found to be moderate to good

PREP-S model performance

Prediction of adverse maternal outcomes within 48 hours

- One validation study of PREP-S (n=339 participants), reporting on adverse maternal outcomes within 48 hrs of admission, provided moderate quality evidence to show the following:
  - Observed: expected ratios in the lower predicted risk category (≤15th centile) showed good calibration
  - Observed: expected ratios in the middle risk categories (>15-50, 50-85th centiles) showed a range from not good to excellent calibration
  - Observed: expected ratios in the highest risk category (>85th centile) showed not good calibration
  - Calibration, as assessed by the calibration slope, was found to be moderate
  - Discrimination, as assessed by the AUC, was found to be moderate

Prediction of adverse maternal outcomes within 7 days

- One validation study of PREP-S (n=339 participants), reporting on adverse maternal outcomes within 7 days of admission, provided moderate quality evidence to show the following:
  - Observed: expected ratios in the lower predicted risk category (≤15th centile) showed excellent calibration
  - Observed: expected ratios in the middle risk categories (>15-50, 50-85th centiles) showed a range from not good to excellent calibration
  - Observed: expected ratios in the highest risk category (>85th centile) showed poor calibration
  - Calibration, as assessed by the calibration slope, was found to be moderate
  - Discrimination, as assessed by the C-statistic, was found to be moderate

Prognostic tests

Prognostic test accuracy of urine spot protein or albumin creatinine ratio

Prediction of adverse maternal outcomes/severe pre-eclampsia

- One cohort study (n=321) provided high quality evidence to show that urine spot protein creatinine ratio (sPCR) > 500 combined with maternal age > 35 years demonstrated:
  - low sensitivity and high specificity
  - very informative LR+ but uninformative LR- to predict adverse maternal outcomes.

- One cohort study (n=959) provided high quality evidence to show that sPCR at a threshold of 30mg/mmol (local lab, recruitment sample) demonstrated:
  - moderate sensitivity and low specificity
  - uninformative LR+ and LR- to predict severe pre-eclampsia.

- One cohort study (n=959) provided high quality evidence to show that sACR at a threshold of 2 mg/mmol (central lab, recruitment sample) demonstrated:
  - high sensitivity and low specificity
  - uninformative LR+ but moderately informative LR- to predict severe pre-eclampsia.

Prediction of adverse perinatal outcomes

- One cohort study (n=959) provided moderate quality evidence to show that sPCR at a threshold of 30mg/mmol (local lab, recruitment sample) demonstrated:
  - low sensitivity and low specificity
  - uninformative LR- and LR+ to predict adverse perinatal outcomes.

- One cohort study (n=959) provided high quality evidence to show that sACR at a threshold of 2 mg/mmol (central lab, recruitment sample) demonstrated:
  - high sensitivity and low specificity
  - uninformative LR- and LR+ to predict adverse perinatal outcomes.

Prognostic test accuracy of abnormal coagulation

Prediction of adverse maternal outcomes

- One cohort study (n=1405) provided moderate quality evidence to show that a platelet count ≤ 100 x 10^9/L demonstrated:
  - low sensitivity and high specificity
  - uninformative LR- and LR+ to predict adverse maternal outcomes within 48 hours.

- One cohort study (n=1405) provided moderate quality evidence to show that abnormal coagulation (international normalised ratio, INR > 1.06 and serum fibrinogen < 3.54 g/L) demonstrated:
  - low sensitivity and high specificity
  - uninformative LR- and LR+ to predict adverse maternal outcomes within 48 hours.

Prognostic test accuracy of liver function

Prediction of adverse maternal outcomes

- One systematic review (n=568) provided low quality evidence to show that aspartate transaminase (AST) (cut-off 150 U/l) demonstrated:
  - low sensitivity and low specificity
  - uninformative LR- and LR+ to predict adverse maternal outcomes.

- One systematic review (n=568) provided moderate quality evidence to show that aspartate transaminase (ALT) (cut-off 100 U/l) demonstrated:
  - low sensitivity and low specificity
  - uninformative LR- and LR+ to predict adverse maternal outcomes.

- One systematic review (n=568) provided low quality evidence to show that lactate dehydrogenase (LDH) (cut-off 1400U/l) demonstrated:
  - low sensitivity and low specificity
  - uninformative LR- and LR+ to predict adverse maternal outcomes.

- One systematic review (n=737) provided moderate quality evidence to show that LDH (cut-off 600U/l) demonstrated:
  - low sensitivity and low specificity
  - uninformative LR- and LR+ to predict adverse maternal outcomes.

- One systematic review (n=737) provided moderate quality evidence to show that ALT (cut-off 40 U/l) and AST (cut-off 55 U/l) demonstrated:
  - low sensitivity and moderate specificity
  - uninformative LR- and LR+ to predict adverse maternal outcomes.

- One systematic review (n=85) provided very low quality evidence to show that AST (cut-off 30 U/l); ALT (cut-off 32 U/l); bilirubin (cut-off 14 µmol/L); gamma glutamyl transferase (GGT) (cut-off 41 U/l) demonstrated:
  - high sensitivity and low specificity
  - uninformative LR+ and moderately informative LR- to predict adverse maternal outcomes.

Prediction of adverse fetal outcomes

- One systematic review (n=85) provided very low quality evidence to show that AST (cut-off 30 U/l); ALT (cut-off 32 U/l); bilirubin (cut-off 14 µmol/L); GGT (cut-off 41 U/l) demonstrated:
  - moderate sensitivity and low specificity
  - uninformative LR- and LR+ to predict adverse fetal outcomes.

Prognostic test accuracy of uric acid

Prediction of adverse maternal outcomes

- One cohort study (n=1487) provided low quality evidence to show that uric acid (cut-off 345µmol/L) demonstrated:
  - moderate sensitivity and low specificity to predict adverse maternal outcomes within 48 hours.

- One cohort study (n=1487) provided moderate quality evidence to show that uric acid (cut-off 345µmol/L) demonstrated:
  - moderate sensitivity and low specificity to predict adverse maternal outcomes within 7 days.

- One cohort study (n=1487) provided moderate quality evidence to show that uric acid (cut-off 345µmol/L) demonstrated:
  - moderate sensitivity and low specificity to predict adverse maternal outcomes at any time.

- One cohort study (n=1487) provided low quality evidence to show that uric acid (cut-off >1 SD above the mean for gestational age) demonstrated:
  - moderate sensitivity and low specificity to predict adverse maternal outcomes within 48 hours.

- One cohort study (n=1487) provided low quality evidence to show that uric acid (cut-off >1 SD above the mean for gestational age) demonstrated:
  - moderate sensitivity and low specificity to predict adverse maternal outcomes within 7 days.

- One cohort study (n=1487) provided low quality evidence to show that uric acid (cut-off >1 SD above the mean for gestational age) demonstrated:
  - moderate sensitivity and low specificity to predict adverse maternal outcomes at any time.

Prediction of adverse perinatal outcomes

- One cohort study (n=1487) provided moderate quality evidence to show that uric acid (cut-off >345µmol/L) demonstrated:
  - moderate sensitivity and low specificity to predict adverse perinatal outcomes.

- One cohort study (n=1487) provided moderate quality evidence to show that uric acid (cut-off >1 SD above the mean for gestational age) demonstrated:
  - high sensitivity and low specificity to predict adverse perinatal outcomes.

Prognostic test accuracy of soluble fms-like tyrosine kinase-1 and placental growth factor

Prediction of adverse maternal outcomes

- One systematic review (n=501) provided moderate quality evidence to show that serum soluble fms-like tyrosine kinase-1 and placental growth factor (sFlt-1/PlGF) ratio ≥ 871 demonstrated:
  - low sensitivity and moderate specificity
  - uninformative LR- and LR+ to predict adverse maternal outcomes.

- One systematic review (n=237) provided low quality evidence to show that sFlt-1/PlGF ratio >85 demonstrated:
  - low sensitivity and low specificity
  - uninformative LR- and LR+ to predict adverse maternal outcomes.

Prognostic test accuracy of maternal characteristics

Prediction of adverse perinatal outcomes

- One cohort study (n-321) provided high quality evidence to show that maternal characteristics (gestational age <34 weeks and booking systolic blood pressure <115mmHg, in women subsequently presenting with suspected pre-eclampsia) for predicting adverse fetal outcomes showed the following:
  - low sensitivity and low specificity
  - uninformative LR- and LR+ to predict adverse perinatal outcomes.

Recommendations

C1. For women with pre-eclampsia, use either the fullPIERS or PREP-S validated risk prediction models to guide decisions about the most appropriate place of care (such as the need for in utero transfer), and thresholds for intervention. When choosing which model to use, take into account:

- fullPIERS is intended for use at any time during pregnancy
- PREP-S is intended for use only up to 34 weeks of pregnancy.

C2. Be aware that the fullPIERS and PREP-S models do not predict outcomes for babies.

C3. Offer admission to hospital for surveillance and any interventions needed if there are concerns for the wellbeing of the woman or baby. For example:

- a predicted high risk of complications using fullPIERS or PREP-S (such as 30% or more)
- sustained systolic blood pressure of 160 mmHg or higher
- any maternal biochemical or haematological investigations that cause concern, for example a new and persistent:
  - rise in creatinine (90 µmol/L or more, 1 mg/dL or more)
  - rise in alanine transaminase (over 70 IU/L, or twice upper limit of normal range)
  - fall in platelet count (under 150,000/µL)
- any clinical signs that cause concern, for example:
  - signs of impending eclampsia
  - pulmonary oedema

- other signs of severe pre-eclampsia
- suspected fetal compromise.

Rationale and impact

Why the committee made the recommendations

There was good evidence that the fullPIERS and PREP-S models are useful tools to identify women at different risks of adverse outcomes because of pre-eclampsia. There was more extensive validation of the fullPIERS model, but some of the validation studies were conducted in populations from lower income settings. In contrast, the PREP-S model had been developed using a UK population, and validated using data from similar settings. It was noted that further validation of PREP-S was unlikely to be conducted, due to the cost of conducting these studies. The committee therefore agreed that both models should be considered as options.

Using the fullPIERS model, a predicted risk of 30% or more correlated strongly with a high actual risk of an adverse outcome. The committee therefore agreed that a risk of 30% or more would be a strong indication to offer admission into hospital for surveillance and appropriate intervention. The high risk threshold was not as well-defined for the PREP-S model - the developers of the model suggest that a risk of 50% at 48 hours might be a suitable threshold to identify women who need transfer to tertiary units. The committee agreed that for the sake of simplicity, and to err on the side of caution, they would prefer to use a suggested high risk of 30% for both models, when considering place of care. However, the committee also agreed that the models should not be used in isolation. Admission to hospital for monitoring might be recommended for women with pre-eclampsia for other reasons, such as severe hypertension or other severe features of pre-eclampsia, even if their risk does not reach the 30% threshold.

The tools predict adverse outcomes in women, but are not designed to predict outcomes for babies. The committee agreed it was important to highlight this.

Impact of the recommendations on practice

The use of models to predict risk will improve consistency in current practice with regard to admission to hospital for women with pre-eclampsia. Some centres offer admission to all women with pre-eclampsia, while others only offer it to a small proportion of women. The guidance might increase the number of women who are admitted to hospital in some centres if admission is not currently routine, but might decrease admission in other centres, thus standardising practice.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Pregnant women with pre-eclampsia may develop serious complications and these prediction models and prognostic tests aim to identify which women were at a greater risk of these complications, in order that more intensive monitoring and treatment (such as steroids for fetal lung maturity, magnesium sulfate and planned early birth) can be instigated. Accuracy to identify adverse maternal and perinatal outcomes, as defined by discrimination and calibration in the clinical prediction model studies, and as sensitivity in the prognostic test accuracy studies, were therefore considered of critical importance in this review.

For the clinical prediction model studies, discrimination indicates how well the model separates women at higher risk and lower risk of developing adverse outcomes, and

calibration defines how well the expected outcomes (as predicted by the model) and the observed outcomes agree. These outcomes were considered critical because they provide information regarding the usefulness of the test in assisting healthcare professionals to make safe decisions regarding management. Maternal outcomes were predicted at different times by the models – most commonly within 48 hours or within 7 days. The committee agreed that the 'within 48 hours' time period was the most useful for assessment of short-term risk, and the prediction model could be repeated if required to obtain an ongoing estimate of risk, but that other prognostic models with a longer time frame were also informative.

For the prognostic test accuracy studies, sensitivity was considered to be critical. It represents the probability that a person at risk of developing adverse outcomes is correctly identified as being at risk. The committee considered that it was important to ensure that women at risk of complications were correctly identified, as the consequences of these complications can be severe.

The quality of the evidence

Eight publications providing external validation of 4 different clinical prediction models were included. For these studies, the quality of the evidence was assessed with the CASP clinical prediction rule. The quality of the evidence ranged from moderate to high. Main sources of bias included not describing the population used to validate the model, which is a limitation because it remains unknown how the demographic characteristics of the population compares to the population that the model will be applied to in clinical practice. Another limitation seen across some of these studies was lack of clarity as to whether the predictor variables were evaluated in a blinded fashion, which is a source of bias because it is not clear whether the prior knowledge of some of the outcomes may have influenced the findings. Finally, not reporting the statistical methods used to construct and validate the tool was a limitation seen in some of the studies.

Two systematic reviews of prognostic test accuracy studies were included. The quality of these systematic reviews ranged from low to moderate. Main limitations were not including enough detail about the included population (such as the definition of pre-eclampsia or total number of women) and not including a list of excluded studies.

Six prognostic test accuracy studies were included. A modified version of GRADE, using the same principles for assessing the quality of the evidence, was used as GRADE is not yet available for prognostic test accuracy studies. The quality of the evidence ranged from very low to high. The domain risk of bias was assessed with the QUADAS-2 checklist and the main limitations seen across studies were lack of clarity about whether the results of the reference standard were interpreted without prior knowledge of the adverse outcomes and vice versa. No serious issues were found regarding inconsistency (heterogeneity) since studies were analysed individually. In evaluating the accuracy of the studies, imprecision was assessed using the 95% confidence interval of sensitivity as the primary measure because of the harmful negative consequence of a false negative (for example, death caused by a woman at high risk of developing serious consequences due to severe pre-eclampsia incorrectly identified as being at low risk). Indirectness was not found in any of the studies, as only women with confirmed or suspected pre-eclampsia were included.

Overall, the committee believed that the quality of the evidence was robust enough to base recommendations on, and the evidence reported was consistent with their clinical experience.

Benefits and harms

Moderate to high quality evidence from 5 prospective and retrospective cohort studies showed that the fullPIERS model has good ability to discriminate women at higher and lower risk of developing adverse outcomes due to pre-eclampsia within 48 hours. The committee noted that the accuracy of the fullPIERS model was best at the extremes of risk – i.e. a

predicted risk of ≥30% correlated strongly with a high actual risk of adverse outcome. The studies included different populations of women, with some samples also including women with HELLP and/or severe onset pre-eclampsia, and varied rates of adverse events were seen, but the discrimination as assessed by the AUC ROC was found to be good across studies and the likelihood ratio in the highest risk category (≥30%) ranged from moderately useful to very useful.

The committee considered that the fullPIERS could be used in all women with pre-eclampsia, despite the majority of external validation studies only including participants at very preterm gestations (with a median gestational age of approximately 30 weeks). This is because the original development and validation study (von Dadelszen 2011) participants included with a wider range of gestations, with a median (IQR) of 33.9 weeks (30.0 to 36.6) for women who developed adverse outcomes and 36.6 weeks (33.4 to 38.3) for women who did not develop adverse outcomes.

The currently available version of the fullPIERS tool uses aspartate transaminase (AST) as a measure of liver function. However, the committee noted that many units in the UK only measure alanine transaminase (ALT) in routine care. The committee were aware that the levels of these two parameters are highly correlated, and subsequent discussion with the authors of fullPIERS have confirmed that AST and ALT can be used interchangeably in the model, and since the committee meeting the model has been updated to allow for use of either AST or ALT in the future (Personal communication, Peter von Dadelszen).

It was noted by the committee that the PREP models were developed within a UK population, and therefore management was likely to be relevant and representative. Whilst there were fewer external validation studies of PREP-S (as compared to fullPIERS), all validation studies were conducted in a high-income setting, similar to the UK. Therefore the relevance of the PREP model and validation to the UK population was felt to be high. The PREP-S model did provide performance data for 48 hours and showed good calibration in the lower risk category, not good to excellent calibration in the middle risk categories, but poor calibration in the highest risk category (although the model over-predicted risk, and therefore was considered to be safe, rather than unsafe). Furthermore, the committee were aware that the high cost of carrying out further validation studies meant that these were unlikely to be conducted. The committee balanced this representation of the population of interest with the other data available on the models and agreed that a choice of fullPIERS or PREP-S should be recommended.

The committee discussed the other models that had been included in the review – miniPIERS and PREP-L. There was a smaller body of externally validated performance evidence for these models compared to the fullPIERS, with only 2 validation studies for miniPIERS, and 1 for PREP-L.The miniPIERS model had a moderately informative likelihood ratio in the highest risk category (compared to moderately to very useful for the fullPIERS). The committee noted that this model was developed and intended for use in low-income settings, where the results of other parameters included in the fullPIERS model (such as blood tests) were not available. Therefore it was not considered to be of such relevance to the UK setting as the fullPIERS and PREP-S models. For the PREP-L model, data was available for adverse maternal outcomes by discharge, and was limited to calibration and discrimination assessed by the C-statistic, although these were found to be good and moderate to good respectively. However, the committee considered that prediction of risk on a shorter timescale (48 hours) was of more value to guide immediate management, such as admission to hospital, as compared to the longer timeframe of PREP-L

The committee discussed the use of the fullPIERS and PREP prediction models in clinical practice. It is suggested by the authors of the fullPIERS model that a ≥30% risk of adverse maternal outcomes within 48 hours is used as a threshold to ‘rule in’ women who require further surveillance and possibly interventions. The committee agreed that at this level the risk is significantly higher than the background risk of adverse outcome for any pregnant

woman, and therefore adopted this threshold and made a recommendation that women with a risk of ≥30% should be offered admission to hospital for surveillance and interventions. The developers of the PREP-S model suggest that a risk of complications of 50% or higher should be an indication for transfer to a tertiary unit, but do not recommend which threshold should be used to guide admission to hospital. The committee agreed that, for simplicity and to err on the side of caution, they would suggest that a high risk threshold of 30% should be adopted when using either fullPIERS or PREP-S. The committee were keen that healthcare professionals should not use the fullPIERS or PREP-S risk of ≥30% in isolation and as the only threshold to offer admission to hospital. The committee agreed that there may be a variety of other circumstances in which admission to hospital should be offered – such as severe hypertension (i.e. systolic BP ≥160mmHg), concerns about the baby, concerns about maternal symptoms of pre-eclampsia or biochemical or haematological results that caused concern. In these circumstances women should be admitted even if their predicted risk using the fullPIERS or PREP-S model was <30%.

The committee were aware that the fullPIERS and PREP models do not predict adverse outcomes for the baby. These are also of serious concern for women with pre-eclampsia and health care professionals, and the committee chose to highlight this in a recommendation, to ensure that those utilising the models for risk prediction consider potential risks to the baby in addition to the woman.

The committee agreed that the fullPIERS and PREP tools were free, easily accessible and easy to use, and would help identify women who were at a high risk of developing complications so they could receive appropriate treatment and monitoring. This would lead to a reduction in complications and adverse events.

The committee discussed the fact that a 'high risk' score might lead to anxiety in women, and as this is only a risk score, not all of these women would subsequently go on to develop an adverse outcome. In balancing the risk of causing unnecessary anxiety to women and the benefits of identifying at-risk women, the committee thought it was more important to identify at-risk women and that this outweighed the potential anxiety the test result might cause.

The committee agreed that none of the other prognostic test performance measures were as useful as the fullPIERS or PREP-S tools. The group specifically discussed the prognostic ability of urine sPCR and urine sACR. Urine sPCR and sACR had a moderate to high sensitivity, but very low specificity for predicting adverse outcomes arising due to pre-eclampsia. Although an elevated sPCR or sACR are common findings in women with pre-eclampsia, they do not help to discriminate between those who will and will not develop an adverse maternal or perinatal outcome. For this reason, the group decided not to recommend the use of these tests to identify women at high risk of adverse outcome, although they were recognised to be useful for the identification of significant proteinuria, as part of the diagnosis of pre-eclampsia (see Evidence report G).

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. An economic analysis was undertaken for this question assessing the cost-effectiveness of risk prediction models for guiding inpatient and outpatient management in pregnant women with pre-eclampsia.

The base case results of the analysis suggest that using the fullPIERS risk model with a threshold of 30% for inpatient management is cost-effective in women 34-37 weeks of gestation. It was found to be more costly than a strategy of outpatient management but also more effective and overall was found to be cost-effective with an ICER below the NICE threshold of £20,000 per QALY. All other strategies were found to be more costly and more effective than using the fullPIERS risk model with a threshold of 30% for inpatient management but none were cost-effective with ICERs well above the NICE threshold of

£20,000 per QALY. However, there was uncertainty around this result in sensitivity analysis, which showed outpatient management to be cost-effective in numerous plausible scenarios.

The fullPIERS and PREP models require input of parameters that are routinely collected in clinical practice (i.e. gestational age, presence/absence of chest pain or dyspnoea, oxygen saturation, platelet count, creatinine, and a liver function test) therefore the recommendations are not likely to lead to more monitoring or blood tests in women, but will improve the consistency of parameters used across centres.

Currently there is variation in practice regarding admission to hospital of women with pre-eclampsia: some units admit all women, some units admit certain women, and some admit very few. The committee believed that the recommendations may lead to increases in workload and use of resources due to a potentially larger number of admissions for pre-eclampsia in some units, but this may be balanced out by more selective admission to other units. However, there may also be a cost saving, as some adverse events should be prevented, by the prompt identification and appropriate management of women at high risk. Furthermore, the occurrence of an adverse event in the community (rather than in hospital) is likely to incur additional resource use, and potentially lead to a worse outcome for the woman and her baby.

Other factors the committee took into account

The committee discussed the threshold of risk for offering admission to hospital in detail. There was consensus that the level of risk that was acceptable to an individual woman was likely to vary greatly – with some women prepared to accept a higher risk, in order to avoid admission to hospital. Therefore, only the highest risk category was identified as being an absolute indication for offering hospital admission. However, the committee agreed that the fullPIERS and PREP tools could help women and clinicians to share decision making regarding place of care, and short term management.

The committee also noted that the fullPIERS tool could be used to predict adverse outcomes in a 48 hour timeframe, and a 7 day timeframe. However, the accuracy of the tool was greater when used to predict risk in the next 48 hours. However, the committee also discussed that the tool could be used repeatedly in the same individual, so a woman who had been assessed as being at low risk could be reviewed again 48 hours later. Also, if there was a change in her condition, the parameters could be re-assessed, and the tool could be used again to predict risk for the next 48 hours.

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Ukah 2017b

Ukah UV, Hutcheon JA, Payne B, Haslam MD, Vatish M, Ansermino JM, Brown H, Magee LA, von Dadelszen P. Placental growth factor as a prognostic tool in women with hypertensive disorders of pregnancy: a systematic review. Hypertension. 2017 Dec;70(6):1228-37.

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Appendices

Appendix A – Review protocol

Table 8: Review protocol

Field (based on PRISMA-P)	Content
Key area in the scope	Assessment of women who present with or develop hypertension and proteinuria during pregnancy (pre-eclampsia), and their management before admission critical care level 2 setting during the peripartum period.
Draft review question from the previous guideline	What investigations and monitoring should take place when pre-eclampsia is diagnosed?
Actual review question	Which tests or clinical prediction models are accurate in identifying or predicting women at risk of severe complications from pre-eclampsia?
Type of review question	Clinical prediction question
Objective of the review	To update the recommendations in CG107 (2010) for the investigation and monitoring of pre-eclampsia to take into consideration models which predict adverse outcomes and thus inform clinical care. Identification of women and infants at risk of complications may guide stratified surveillance and targeted interventions for those at higher risk.
Eligibility criteria – population/disease/condition/issue/domain	Pregnant women with pre-eclampsia
Eligibility criteria - type of study	Externally validated predictive modelling studies Diagnostic test accuracy studies

Field (based on PRISMA-P)	Content
Eligibility criteria – outcome to be modelled	• Maternal adverse outcomes - severe pre-eclampsia - eclampsia - maternal mortality - maternal morbidity, including serious CNS, cardiorespiratory, hepatic, renal or haematological morbidity - placental abruption - need for delivery (any delivery/ delivery for pre-eclampsia) • Perinatal adverse outcomes - preterm delivery (<34 weeks) - perinatal mortality (stillbirths and death during first 7 days of life) - stillbirth - neonatal death (during first 28 days of life) - serious neonatal morbidity, e.g. respiratory, gastrointestinal or CNS complications
Confounding factors	Analysis should adjust for important confounding factors. Multivariate analysis should be used for clinical prediction models
Outcomes and prioritisation	**Model performance** **Critical outcomes:** Discrimination **(**AUC/C-statistic) Calibration **Accuracy of prediction:** **Critical outcome:** Sensitivity **Important outcomes:** Specificity Positive likelihood ratio Negative likelihood ratio

Field (based on PRISMA-P)	Content
Eligibility criteria – study design	Systematic reviews/meta-analyses of predictive models Systematic reviews/meta-analyses of cohort studies Prospective/retrospective cohort studies Cross-sectional studies Studies with fewer than 200 participants will not be included if larger cohort studies are identified
Exclusion criteria	Search date from: N/A Non-English language
Proposed stratified, sensitivity/sub-group analysis, or meta-regression	Stratify by gestational age where applicable Timescale of prediction - up to 48 hours - up to 7 days - over 7 days Stratify outcome data for subgroups/predictors e.g. renal disease, diabetes

Field (based on PRISMA-P)	Content
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, and appraisal of methodological quality will be performed by the reviewing team. Quality control will be performed by the senior systematic reviewer. Dual sifting will be performed on at least 10% of records and where possible all records as this is a prognostic review; 90% agreement is required and any discussions will be resolved through discussion and consultation with senior staff where necessary. Dual quality assessment and data extraction will be performed when capacity allows.
Data management (software)	The CASP checklist for clinical prediction or QUADAS-2 (for diagnostic accuracy studies) will be used to assess the quality of the studies STAR will be used for bibliographies/citations, text mining, and study sifting, data extraction and quality assessment/critical appraisal. Microsoft Word will be used for data extraction and quality assessment/critical appraisal
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA and Embase. Limits (e.g. date, study design): Study design limited to Systematic reviews, Meta-analyses and Cohort studies. Apply standard animal/non-English language filters. No date limit. Supplementary search techniques: No supplementary search techniques were used. See appendix B for full strategies. Key papers: 1. Lancet. 2011 Jan 15;377(9761):219-27. doi: 10.1016/S0140-6736(10)61351-7. Epub 2010 Dec 23.

Field (based on PRISMA-P)	Content
	Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the full PIERS model. von Dadelszen P1, Payne B, Li J, Ansermino JM, Broughton Pipkin F, Côté AM, Douglas MJ, Gruslin A, Hutcheon JA, Joseph KS, Kyle PM, Lee T, Loughna P, Menzies JM, Merialdi M, Millman AL, Moore MP, Moutquin JM, Ouellet AB, Smith GN, Walker JJ, Walley KR, Walters BN, Widmer M, Lee SK, Russell JA, Magee LA; PIERS Study Group. 2. BMC Med. 2017 Mar 30;15(1):68. doi: 10.1186/s12916-017-0827-3. Prediction of complications in early-onset pre-eclampsia (PREP): development and external multinational validation of prognostic models. Thangaratinam S1,2, Allotey J3,4, Marlin N5, Dodds J1,2, Cheong-See F1,2, von Dadelszen P6, Ganzevoort W7, Akkermans J8, Kerry S5, Mol BW9,10, Moons KG11, Riley RD12, Khan KS1,2; PREP Collaborative Network. 3.Diagnostic accuracy in pre-eclampsia using proteinuria assessment ISRCTN82607486 DOI 10.1186/ISRCTN82607486 4. Akkermans J, Payne B, von Dadelszen P, Groen H, Vries Jd, Magee LA, Mol BW, Ganzevoort W. Predicting complications in pre-eclampsia: external validation of the fullPIERS model using the PETRA trial dataset. Eur J Obstet Gynecol Reprod Biol. 2014 Aug;179:58-62. doi: 10.1016/j.ejogrb.2014.05.021. 5. Int J Gynaecol Obstet. 2017 Aug;138(2):142-147. doi: 10.1002/ijgo.12197. Epub 2017 May 23. Validation of fullPIERS model for prediction of adverse outcomes among women with severe pre-eclampsia. Almeida ST[1]

Field (based on PRISMA-P)	Content
Identify if an update	Yes, this question was addressed in the previous version of the guideline. Studies meeting the current protocol criteria and previously included in the 2010 guideline (CG107) will be included in this update. The methods for quantitative analysis –combining studies and exploring (in)consistency- will be the same as for the new evidence (see above).
Author contacts	Developer: National Guideline Alliance NGA-enquiries@RCOG.org.uk
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix B
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables)
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables).
Methods for assessing bias at outcome/study level	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • The CASP clinical prediction rule checklist will be used for prediction studies • QUADAS-2 will be used if relevant diagnostic accuracy studies are identified For details please see section 6.2 of Developing NICE guidelines: the manual
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual

Field (based on PRISMA-P)	Content
Methods for quantitative analysis – combining studies and exploring (in)consistency	Synthesis of data: Meta-analysis will not be conducted Minimum important differences Default values will be used of: Sensitivity and specificity high when ≥ 90% Sensitivity and specificity moderate when between 75 and 89% Good model performance will be defined as AUC > 0.75 and O:E ratio between 0.8 and 1.2 (as suggested by Debray 2017), unless more appropriate values are identified by the guideline committee or in the literature. Double sifting, data extraction and methodological quality assessment: Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual quality assessment and data extraction will be performed where resources permit.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale/context – what is known	For details please see the introduction to the evidence review.

Field (based on PRISMA-P)	Content
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the National Guideline Alliance and chaired by Sarah Fishburn in line with section 3 of Developing NICE guidelines: the manual. Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds the National Guideline Alliance to develop guidelines for the NHS in England.
PROSPERO registration number	Not registered with PROSPERO

Appendix B – Literature search strategies

Databases: Medline; Medline EPub Ahead of Print; and Medline In-Process & Other Non-Indexed Citations

Date of last search: 09/03/18

#	Searches
1	META-ANALYSIS/
2	META-ANALYSIS AS TOPIC/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	cochrane.jw.
10	or/1-9
11	COHORT STUDIES/
12	(cohort adj3 (study or studies)).ti,ab.
13	(Cohort adj3 analy$).ti,ab.
14	FOLLOW-UP STUDIES/
15	(Follow$ up adj3 (study or studies)).ti,ab.
16	LONGITUDINAL STUDIES/
17	longitudinal$.ti,ab.
18	PROSPECTIVE STUDIES/
19	prospective$.ti,ab.
20	RETROSPECTIVE STUDIES/
21	retrospective$.ti,ab.
22	OBSERVATIONAL STUDY/
23	observational$.ti,ab.
24	or/11-23
25	CROSS-SECTIONAL STUDIES/
26	cross sectional$.ti,ab.
27	or/25-26
28	PRE-ECLAMPSIA/
29	HELLP SYNDROME/
30	preeclamp$.ti,ab.
31	pre eclamp$.ti,ab.
32	HELLP.ti,ab.
33	tox?emi$.ti,ab.
34	or/28-33
35	MODELS, STATISTICAL/
36	MODELS, BIOLOGICAL/
37	LOGISTIC MODELS/
38	model$.ti,ab.
39	test$.ti,ab.
40	or/35-39
41	validat$.ti,ab.
42	PREDICTIVE VALUE OF TESTS/
43	PROGNOSIS/ and (test$ or model$ or scor$).ti,ab.
44	((test$ or model$ or scor$) adj5 (diagnos$ or prognos$ or predict$ or identif$ or decision$ or screen$ or investigat$ or monitor$)).ti,ab.
45	RISK ASSESSMENT/ and (test$ or model$ or scor$).ti,ab.
46	((test$ or model$ or scor$) adj5 risk?).ti,ab.
47	or/42-46
48	(adverse adj3 outcome?).ti,ab.
49	MATERNAL MORTALITY/
50	MATERNAL DEATH/
51	(maternal adj3 (mortalit$ or death?)).ti,ab.
52	((maternal or central nervous system? or cardiorespirat$ or cardio respirat$ or hepatic$ or renal$ or h?ematolog$) adj5 morbidit$).ti,ab.
53	ABRUPTIO PLACENTAE/
54	abruptio placentae.ti,ab.
55	placental abruption?.ti,ab.
56	PREGNANCY OUTCOME/
57	(pregnan$ adj3 outcome?).ti,ab.
58	OBSTETRIC LABOR, PREMATURE/
59	((preterm$ or pre-term$ or premature$) adj3 (labo?r or deliver$)).ti,ab.

#	Searches
60	PERINATAL MORTALITY/
61	PERINATAL DEATH/
62	((perinatal$ or neonat$) adj3 (mortalit$ or death?)).ti,ab.
63	STILLBIRTH/
64	FETAL DEATH/
65	stillbirth?.ti,ab.
66	((fetal or fetus$) adj3 (mortalit$ or death?)).ti,ab.
67	((neonat$ or respirat$ or gastrointestin$ or gastro-intestin$ or central nervous system?) adj5 morbidit$).ti,ab.
68	PREGNANCY COMPLICATIONS/
69	complication?.ti,ab.
70	(high adj3 risk?).ti,ab.
71	or/48-70
72	(predict$ adj5 (outcome? or complication? or mortalit$ or death? or morbidit$ or abruptio placentae or placental abruption? or ((preterm$ or pre-term$ or premature$) adj3 (labo?r or deliver$)) or stillbirth?)).ti,ab.
73	(test$ or model$ or scor$).ti,ab.
74	PRENATAL DIAGNOSIS/st [Standards]
75	PRENATAL DIAGNOSIS/mt [Methods]
76	or/74-75
77	34 and 40 and 41
78	34 and 47 and 71
79	34 and 72 and 73
80	34 and 71 and 76
81	or/77-80
82	limit 81 to english language
83	LETTER/
84	EDITORIAL/
85	NEWS/
86	exp HISTORICAL ARTICLE/
87	ANECDOTES AS TOPIC/
88	COMMENT/
89	CASE REPORT/
90	(letter or comment*).ti.
91	or/83-90
92	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
93	91 not 92
94	ANIMALS/ not HUMANS/
95	exp ANIMALS, LABORATORY/
96	exp ANIMAL EXPERIMENTATION/
97	exp MODELS, ANIMAL/
98	exp RODENTIA/
99	(rat or rats or mouse or mice).ti.
100	or/93-99
101	82 not 100
102	10 and 101
103	24 and 101
104	27 and 101
105	or/102-104

Databases: Embase; and Embase Classic

Date of last search: 09/03/18

#	Searches
1	SYSTEMATIC REVIEW/
2	META-ANALYSIS/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	((pool* or combined) adj2 (data or trials or studies or results)).ab.
10	cochrane.jw.
11	or/1-10
12	COHORT ANALYSIS/
13	(cohort adj3 (study or studies)).ti,ab.
14	(Cohort adj3 analy$).ti,ab.
15	FOLLOW UP/

#	Searches
16	(Follow$ up adj3 (study or studies)).ti,ab.
17	LONGITUDINAL STUDY/
18	longitudinal$.ti,ab.
19	PROSPECTIVE STUDY/
20	prospective$.ti,ab.
21	RETROSPECTIVE STUDY/
22	retrospective$.ti,ab.
23	OBSERVATIONAL STUDY/
24	observational$.ti,ab.
25	or/12-24
26	CROSS-SECTIONAL STUDY/
27	cross sectional$.ti,ab.
28	or/26-27
29	PREECLAMPSIA/
30	HELLP SYNDROME/
31	preeclamp$.ti,ab.
32	pre eclamp$.ti,ab.
33	HELLP.ti,ab.
34	tox?emi$.ti,ab.
35	or/29-34
36	STATISTICAL MODEL/
37	BIOLOGICAL MODEL/
38	model$.ti,ab.
39	test$.ti,ab.
40	or/36-39
41	VALIDATION PROCESS/
42	validat$.ti,ab.
43	or/41-42
44	PREDICTIVE VALUE/
45	PROGNOSIS/ and (test$ or model$ or scor$).ti,ab.
46	((test$ or model$ or scor$) adj5 (diagnos$ or prognos$ or predict$ or identif$ or decision$ or screen$ or investigat$ or monitor$)).ti,ab.
47	RISK ASSESSMENT/ and (test$ or model$ or scor$).ti,ab.
48	((test$ or model$ or scor$) adj5 risk?).ti,ab.
49	or/44-48
50	(adverse adj3 outcome?).ti,ab.
51	*MATERNAL MORTALITY/
52	*MATERNAL DEATH/
53	(maternal adj3 (mortalit$ or death?)).ti,ab.
54	*MATERNAL MORBIDITY/
55	((maternal or central nervous system? or cardiorespirat$ or cardio respirat$ or hepatic$ or renal$ or h?ematolog$) adj5 morbidit$).ti,ab.
56	*SOLUTIO PLACENTAE/
57	abruptio placentae.ti,ab.
58	placental abruption?.ti,ab.
59	*PREGNANCY OUTCOME/
60	(pregnan$ adj3 outcome?).ti,ab.
61	*PREMATURE LABOR/
62	((preterm$ or pre-term$ or premature$) adj3 (labo?r or deliver$)).ti,ab.
63	*PERINATAL MORTALITY/
64	*NEWBORN MORTALITY/
65	*PERINATAL DEATH/
66	*NEWBORN DEATH/
67	((perinatal$ or neonat$) adj3 (mortalit$ or death?)).ti,ab.
68	*STILLBIRTH/
69	*FETUS DEATH/
70	stillbirth?.ti,ab.
71	((fetal or fetus$) adj3 (mortalit$ or death?)).ti,ab.
72	*PERINATAL MORBIDITY/
73	*NEWBORN MORBIDITY/
74	((neonat$ or respirat$ or gastrointestin$ or gastro-intestin$ or central nervous system?) adj5 morbidit$).ti,ab.
75	*PREGNANCY COMPLICATION/
76	complication?.ti.
77	complication?.ab. /freq=2
78	(high adj3 risk?).ti.
79	(high adj3 risk?).ab. /freq=2
80	or/50-79
81	(predict$ adj5 (outcome? or complication? or mortalit$ or death? or morbidit$ or abruptio placentae or placental abruption? or ((preterm$ or pre-term$ or premature$) adj3 (labo?r or deliver$)) or stillbirth?)).ti,ab.
82	(test$ or model$ or scor$).ti,ab.

#	Searches
83	35 and 40 and 43
84	35 and 49 and 80
85	35 and 81 and 82
86	or/83-85
87	limit 86 to english language
88	letter.pt. or LETTER/
89	note.pt.
90	editorial.pt.
91	CASE REPORT/ or CASE STUDY/
92	(letter or comment*).ti.
93	or/88-92
94	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
95	93 not 94
96	ANIMAL/ not HUMAN/
97	NONHUMAN/
98	exp ANIMAL EXPERIMENT/
99	exp EXPERIMENTAL ANIMAL/
100	ANIMAL MODEL/
101	exp RODENT/
102	(rat or rats or mouse or mice).ti.
103	or/95-102
104	87 not 103
105	11 and 104
106	25 and 104
107	28 and 104
108	or/105-107

Databases: Cochrane Central Register of Controlled Trials; Cochrane Database of Systematic Reviews; Database of Abstracts of Reviews of Effects; and Health Technology Assessment

Date of last search: 09/03/18

#	Searches
1	MeSH descriptor: [PRE-ECLAMPSIA] this term only
2	MeSH descriptor: [HELLP SYNDROME] this term only
3	preeclamp*:ti,ab
4	pre eclamp*:ti,ab
5	HELLP:ti,ab
6	tox?emi*:ti,ab
7	#1 or #2 or #3 or #4 or #5 or #6
8	MeSH descriptor: [MODELS, STATISTICAL] this term only
9	MeSH descriptor: [MODELS, BIOLOGICAL] this term only
10	MeSH descriptor: [LOGISTIC MODELS] this term only
11	model*:ti,ab
12	test*:ti,ab
13	#8 or #9 or #10 or #11 or #12
14	validat*:ti,ab
15	MeSH descriptor: [PREDICTIVE VALUE OF TESTS] this term only
16	MeSH descriptor: [PROGNOSIS] this term only
17	(test* or model* or scor*):ti,ab
18	#16 and #17
19	((test* or model* or scor*) near/5 (diagnos* or prognos* or predict* or identif* or decision* or screen* or investigat* or monitor*)):ti,ab
20	MeSH descriptor: [RISK ASSESSMENT] this term only
21	(test* or model* or scor*):ti,ab
22	#20 and #21
23	((test* or model* or scor*) near/5 risk?):ti,ab
24	#15 or #18 or #19 or #22 or #23
25	(adverse near/3 outcome?):ti,ab
26	MeSH descriptor: [MATERNAL MORTALITY] this term only
27	MeSH descriptor: [MATERNAL DEATH] this term only
28	(maternal near/3 (mortalit* or death?)):ti,ab
29	((maternal or central nervous system? or cardiorespirat* or cardio respirat* or hepatic* or renal* or h?ematolog*) near/5 morbidit*):ti,ab
30	MeSH descriptor: [ABRUPTIO PLACENTAE] this term only
31	abruptio placentae:ti,ab
32	placental abruption?:ti,ab

#	Searches
33	MeSH descriptor: [PREGNANCY OUTCOME] this term only
34	(pregnan* near/3 outcome?):ti,ab
35	MeSH descriptor: [OBSTETRIC LABOR, PREMATURE] this term only
36	((preterm* or pre-term* or premature*) near/3 (labo?r or deliver*)):ti,ab
37	MeSH descriptor: [PERINATAL MORTALITY] this term only
38	MeSH descriptor: [PERINATAL DEATH] this term only
39	((perinatal* or neonat*) near/3 (mortalit* or death?)):ti,ab
40	MeSH descriptor: [STILLBIRTH] this term only
41	MeSH descriptor: [FETAL DEATH] this term only
42	stillbirth?:ti,ab
43	((fetal or fetus*) near/3 (mortalit* or death?)):ti,ab
44	((neonat* or respirat* or gastrointestin* or gastro-intestin* or central nervous system?) near/5 morbidit*):ti,ab
45	MeSH descriptor: [PREGNANCY COMPLICATIONS] this term only
46	complication?:ti,ab
47	(high near/3 risk?):ti,ab
48	#25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47
49	(predict* near/5 (outcome? or complication? or mortalit* or death? or morbidit* or abruptio placentae or placental abruption? or ((preterm* or pre-term* or premature*) near/3 (labo?r or deliver*)) or stillbirth?)):ti,ab
50	(test* or model* or scor*):ti,ab
51	MeSH descriptor: [PRENATAL DIAGNOSIS] this term only and with qualifier(s): [Standards - ST]
52	MeSH descriptor: [PRENATAL DIAGNOSIS] this term only and with qualifier(s): [Methods - MT]
53	#51 or #52
54	#7 and #13 and #14
55	#7 and #24 and #48
56	#7 and #49 and #50
57	#7 and #48 and #53
58	#54 or #55 or #56 or #57

Health economics search strategies

Databases: Medline; Medline EPub Ahead of Print; and Medline In-Process & Other Non-Indexed Citations

Date of last search: 09/03/18

#	Searches
1	ECONOMICS/
2	VALUE OF LIFE/
3	exp "COSTS AND COST ANALYSIS"/
4	exp ECONOMICS, HOSPITAL/
5	exp ECONOMICS, MEDICAL/
6	exp RESOURCE ALLOCATION/
7	ECONOMICS, NURSING/
8	ECONOMICS, PHARMACEUTICAL/
9	exp "FEES AND CHARGES"/
10	exp BUDGETS/
11	budget*.ti,ab.
12	cost*.ti,ab.
13	(economic* or pharmaco?economic*).ti,ab.
14	(price* or pricing*).ti,ab.
15	(financ* or fee or fees or expenditure* or saving*).ti,ab.
16	(value adj2 (money or monetary)).ti,ab.
17	resourc* allocat*.ti,ab.
18	(fund or funds or funding* or funded).ti,ab.
19	(ration or rations or rationing* or rationed).ti,ab.
20	ec.fs.
21	or/1-20
22	PRE-ECLAMPSIA/
23	HELLP SYNDROME/
24	preeclamp$.ti,ab.
25	pre eclamp$.ti,ab.
26	HELLP.ti,ab.
27	tox?emi$.ti,ab.
28	or/22-27
29	MODELS, STATISTICAL/
30	MODELS, BIOLOGICAL/
31	LOGISTIC MODELS/

#	Searches
32	model$.ti,ab.
33	test$.ti,ab.
34	or/29-33
35	validat$.ti,ab.
36	PREDICTIVE VALUE OF TESTS/
37	PROGNOSIS/ and (test$ or model$ or scor$).ti,ab.
38	((test$ or model$ or scor$) adj5 (diagnos$ or prognos$ or predict$ or identif$ or decision$ or screen$ or investigat$ or monitor$)).ti,ab.
39	RISK ASSESSMENT/ and (test$ or model$ or scor$).ti,ab.
40	((test$ or model$ or scor$) adj5 risk?).ti,ab.
41	or/36-40
42	(adverse adj3 outcome?).ti,ab.
43	MATERNAL MORTALITY/
44	MATERNAL DEATH/
45	(maternal adj3 (mortalit$ or death?)).ti,ab.
46	((maternal or central nervous system? or cardiorespirat$ or cardio respirat$ or hepatic$ or renal$ or h?ematolog$) adj5 morbidit$).ti,ab.
47	ABRUPTIO PLACENTAE/
48	abruptio placentae.ti,ab.
49	placental abruption?.ti,ab.
50	PREGNANCY OUTCOME/
51	(pregnan$ adj3 outcome?).ti,ab.
52	OBSTETRIC LABOR, PREMATURE/
53	((preterm$ or pre-term$ or premature$) adj3 (labo?r or deliver$)).ti,ab.
54	PERINATAL MORTALITY/
55	PERINATAL DEATH/
56	((perinatal$ or neonat$) adj3 (mortalit$ or death?)).ti,ab.
57	STILLBIRTH/
58	FETAL DEATH/
59	stillbirth?.ti,ab.
60	((fetal or fetus$) adj3 (mortalit$ or death?)).ti,ab.
61	((neonat$ or respirat$ or gastrointestin$ or gastro-intestin$ or central nervous system?) adj5 morbidit$).ti,ab.
62	PREGNANCY COMPLICATIONS/
63	complication?.ti,ab.
64	(high adj3 risk?).ti,ab.
65	or/42-64
66	(predict$ adj5 (outcome? or complication? or mortalit$ or death? or morbidit$ or abruptio placentae or placental abruption? or ((preterm$ or pre-term$ or premature$) adj3 (labo?r or deliver$)) or stillbirth?)).ti,ab.
67	(test$ or model$ or scor$).ti,ab.
68	PRENATAL DIAGNOSIS/st [Standards]
69	PRENATAL DIAGNOSIS/mt [Methods]
70	or/68-69
71	28 and 34 and 35
72	28 and 41 and 65
73	28 and 66 and 67
74	28 and 65 and 70
75	or/71-74
76	limit 75 to english language
77	LETTER/
78	EDITORIAL/
79	NEWS/
80	exp HISTORICAL ARTICLE/
81	ANECDOTES AS TOPIC/
82	COMMENT/
83	CASE REPORT/
84	(letter or comment*).ti.
85	or/77-84
86	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
87	85 not 86
88	ANIMALS/ not HUMANS/
89	exp ANIMALS, LABORATORY/
90	exp ANIMAL EXPERIMENTATION/
91	exp MODELS, ANIMAL/
92	exp RODENTIA/
93	(rat or rats or mouse or mice).ti.
94	or/87-93
95	76 not 94
96	21 and 95

Databases: Embase; and Embase Classic

Date of last search: 09/03/18

#	Searches
1	HEALTH ECONOMICS/
2	exp ECONOMIC EVALUATION/
3	exp HEALTH CARE COST/
4	exp FEE/
5	BUDGET/
6	FUNDING/
7	RESOURCE ALLOCATION/
8	budget*.ti,ab.
9	cost*.ti,ab.
10	(economic* or pharmaco?economic*).ti,ab.
11	(price* or pricing*).ti,ab.
12	(financ* or fee or fees or expenditure* or saving*).ti,ab.
13	(value adj2 (money or monetary)).ti,ab.
14	resourc* allocat*.ti,ab.
15	(fund or funds or funding* or funded).ti,ab.
16	(ration or rations or rationing* or rationed).ti,ab.
17	or/1-16
18	PREECLAMPSIA/
19	HELLP SYNDROME/
20	preeclamp$.ti,ab.
21	pre eclamp$.ti,ab.
22	HELLP.ti,ab.
23	tox?emi$.ti,ab.
24	or/18-23
25	STATISTICAL MODEL/
26	BIOLOGICAL MODEL/
27	model$.ti,ab.
28	test$.ti,ab.
29	or/25-28
30	VALIDATION PROCESS/
31	validat$.ti,ab.
32	or/30-31
33	PREDICTIVE VALUE/
34	PROGNOSIS/ and (test$ or model$ or scor$).ti,ab.
35	((test$ or model$ or scor$) adj5 (diagnos$ or prognos$ or predict$ or identif$ or decision$ or screen$ or investigat$ or monitor$)).ti,ab.
36	RISK ASSESSMENT/ and (test$ or model$ or scor$).ti,ab.
37	((test$ or model$ or scor$) adj5 risk?).ti,ab.
38	or/33-37
39	(adverse adj3 outcome?).ti,ab.
40	*MATERNAL MORTALITY/
41	*MATERNAL DEATH/
42	(maternal adj3 (mortalit$ or death?)).ti,ab.
43	*MATERNAL MORBIDITY/
44	((maternal or central nervous system? or cardiorespirat$ or cardio respirat$ or hepatic$ or renal$ or h?ematolog$) adj5 morbidit$).ti,ab.
45	*SOLUTIO PLACENTAE/
46	abruptio placentae.ti,ab.
47	placental abruption?.ti,ab.
48	*PREGNANCY OUTCOME/
49	(pregnan$ adj3 outcome?).ti,ab.
50	*PREMATURE LABOR/
51	((preterm$ or pre-term$ or premature$) adj3 (labo?r or deliver$)).ti,ab.
52	*PERINATAL MORTALITY/
53	*NEWBORN MORTALITY/
54	*PERINATAL DEATH/
55	*NEWBORN DEATH/
56	((perinatal$ or neonat$) adj3 (mortalit$ or death?)).ti,ab.
57	*STILLBIRTH/
58	*FETUS DEATH/
59	stillbirth?.ti,ab.
60	((fetal or fetus$) adj3 (mortalit$ or death?)).ti,ab.
61	*PERINATAL MORBIDITY/
62	*NEWBORN MORBIDITY/
63	((neonat$ or respirat$ or gastrointestin$ or gastro-intestin$ or central nervous system?) adj5 morbidit$).ti,ab.
64	*PREGNANCY COMPLICATION/
65	complication?.ti.

#	Searches
66	complication?.ab. /freq=2
67	(high adj3 risk?).ti.
68	(high adj3 risk?).ab. /freq=2
69	or/39-68
70	(predict$ adj5 (outcome? or complication? or mortalit$ or death? or morbidit$ or abruptio placentae or placental abruption? or ((preterm$ or pre-term$ or premature$) adj3 (labo?r or deliver$)) or stillbirth?)).ti,ab.
71	(test$ or model$ or scor$).ti,ab.
72	24 and 29 and 32
73	24 and 38 and 69
74	24 and 70 and 71
75	or/72-74
76	limit 75 to english language
77	letter.pt. or LETTER/
78	note.pt.
79	editorial.pt.
80	CASE REPORT/ or CASE STUDY/
81	(letter or comment*).ti.
82	or/77-81
83	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
84	82 not 83
85	ANIMAL/ not HUMAN/
86	NONHUMAN/
87	exp ANIMAL EXPERIMENT/
88	exp EXPERIMENTAL ANIMAL/
89	ANIMAL MODEL/
90	exp RODENT/
91	(rat or rats or mouse or mice).ti.
92	or/84-91
93	76 not 92
94	17 and 93

Database: Cochrane Central Register of Controlled Trials

Date of last search: 09/03/18

#	Searches
1	MeSH descriptor: [ECONOMICS] this term only
2	MeSH descriptor: [VALUE OF LIFE] this term only
3	MeSH descriptor: [COSTS AND COST ANALYSIS] explode all trees
4	MeSH descriptor: [ECONOMICS, HOSPITAL] explode all trees
5	MeSH descriptor: [ECONOMICS, MEDICAL] explode all trees
6	MeSH descriptor: [RESOURCE ALLOCATION] explode all trees
7	MeSH descriptor: [ECONOMICS, NURSING] this term only
8	MeSH descriptor: [ECONOMICS, PHARMACEUTICAL] this term only
9	MeSH descriptor: [FEES AND CHARGES] explode all trees
10	MeSH descriptor: [BUDGETS] explode all trees
11	budget*:ti,ab
12	cost*:ti,ab
13	(economic* or pharmaco?economic*):ti,ab
14	(price* or pricing*):ti,ab
15	(financ* or fee or fees or expenditure* or saving*):ti,ab
16	(value near/2 (money or monetary)):ti,ab
17	resourc* allocat*:ti,ab
18	(fund or funds or funding* or funded):ti,ab
19	(ration or rations or rationing* or rationed):ti,ab
20	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
21	MeSH descriptor: [PRE-ECLAMPSIA] this term only
22	MeSH descriptor: [HELLP SYNDROME] this term only
23	preeclamp*:ti,ab
24	pre eclamp*:ti,ab
25	HELLP:ti,ab
26	tox?emi*:ti,ab
27	#21 or #22 or #23 or #24 or #25 or #26
28	MeSH descriptor: [MODELS, STATISTICAL] this term only
29	MeSH descriptor: [MODELS, BIOLOGICAL] this term only
30	MeSH descriptor: [LOGISTIC MODELS] this term only
31	model*:ti,ab
32	test*:ti,ab

#	Searches
33	#28 or #29 or #30 or #31 or #32
34	validat*:ti,ab
35	MeSH descriptor: [PREDICTIVE VALUE OF TESTS] this term only
36	MeSH descriptor: [PROGNOSIS] this term only
37	(test* or model* or scor*):ti,ab
38	#36 and #37
39	((test* or model* or scor*) near/5 (diagnos* or prognos* or predict* or identif* or decision* or screen* or investigat* or monitor*)):ti,ab
40	MeSH descriptor: [RISK ASSESSMENT] this term only
41	(test* or model* or scor*):ti,ab
42	#40 and #41
43	((test* or model* or scor*) near/5 risk?):ti,ab
44	#35 or #38 or #39 or #42 or #43
45	(adverse near/3 outcome?):ti,ab
46	MeSH descriptor: [MATERNAL MORTALITY] this term only
47	MeSH descriptor: [MATERNAL DEATH] this term only
48	(maternal near/3 (mortalit* or death?)):ti,ab
49	((maternal or central nervous system? or cardiorespirat* or cardio respirat* or hepatic* or renal* or h?ematolog*) near/5 morbidit*):ti,ab
50	MeSH descriptor: [ABRUPTIO PLACENTAE] this term only
51	abruptio placentae:ti,ab
52	placental abruption?:ti,ab
53	MeSH descriptor: [PREGNANCY OUTCOME] this term only
54	(pregnan* near/3 outcome?):ti,ab
55	MeSH descriptor: [OBSTETRIC LABOR, PREMATURE] this term only
56	((preterm* or pre-term* or premature*) near/3 (labo?r or deliver*)):ti,ab
57	MeSH descriptor: [PERINATAL MORTALITY] this term only
58	MeSH descriptor: [PERINATAL DEATH] this term only
59	((perinatal* or neonat*) near/3 (mortalit* or death?)):ti,ab
60	MeSH descriptor: [STILLBIRTH] this term only
61	MeSH descriptor: [FETAL DEATH] this term only
62	stillbirth?:ti,ab
63	((fetal or fetus*) near/3 (mortalit* or death?)):ti,ab
64	((neonat* or respirat* or gastrointestin* or gastro-intestin* or central nervous system?) near/5 morbidit*):ti,ab
65	MeSH descriptor: [PREGNANCY COMPLICATIONS] this term only
66	complication?:ti,ab
67	(high near/3 risk?):ti,ab
68	#45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67
69	(predict* near/5 (outcome? or complication? or mortalit* or death? or morbidit* or abruptio placentae or placental abruption? or ((preterm* or pre-term* or premature*) near/3 (labo?r or deliver*)) or stillbirth?)):ti,ab
70	(test* or model* or scor*):ti,ab
71	MeSH descriptor: [PRENATAL DIAGNOSIS] this term only and with qualifier(s): [Standards - ST]
72	MeSH descriptor: [PRENATAL DIAGNOSIS] this term only and with qualifier(s): [Methods - MT]
73	#71 or #72
74	#27 and #33 and #34
75	#27 and #44 and #68
76	#27 and #69 and #70
77	#27 and #68 and #73
78	#74 or #75 or #76 or #77
79	#20 and #78

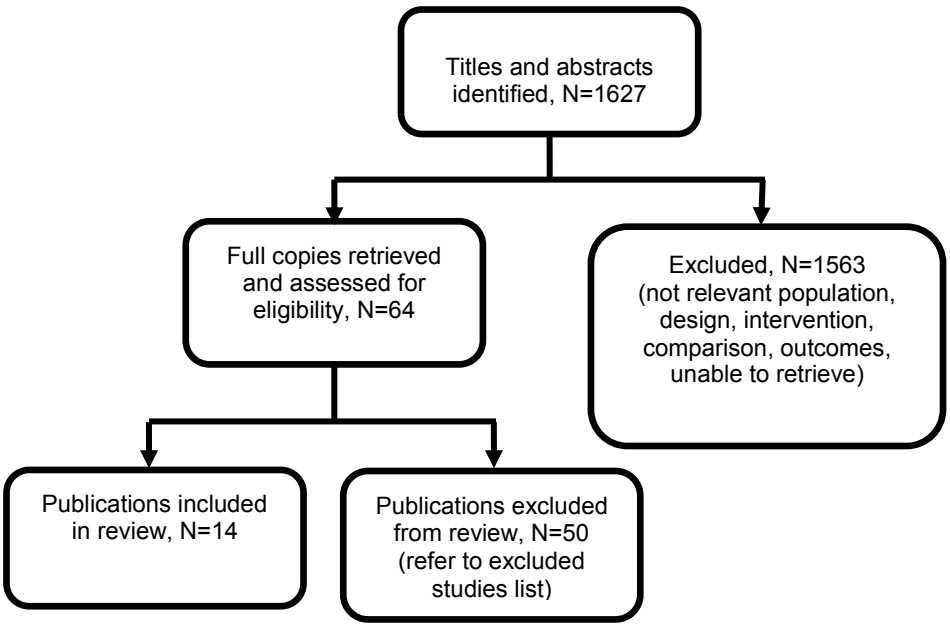
Databases: Health Technology Assessment; and NHS Economic Evaluation Database

Date of last search: 09/03/18

#	Searches
1	MeSH descriptor: [PRE-ECLAMPSIA] this term only
2	MeSH descriptor: [HELLP SYNDROME] this term only
3	preeclamp*:ti,ab
4	pre eclamp*:ti,ab
5	HELLP:ti,ab
6	tox?emi*:ti,ab
7	#1 or #2 or #3 or #4 or #5 or #6
8	MeSH descriptor: [MODELS, STATISTICAL] this term only
9	MeSH descriptor: [MODELS, BIOLOGICAL] this term only
10	MeSH descriptor: [LOGISTIC MODELS] this term only
11	model*:ti,ab
12	test*:ti,ab

#	Searches
13	#8 or #9 or #10 or #11 or #12
14	validat*:ti,ab
15	MeSH descriptor: [PREDICTIVE VALUE OF TESTS] this term only
16	MeSH descriptor: [PROGNOSIS] this term only
17	(test* or model* or scor*):ti,ab
18	#16 and #17
19	((test* or model* or scor*) near/5 (diagnos* or prognos* or predict* or identif* or decision* or screen* or investigat* or monitor*)):ti,ab
20	MeSH descriptor: [RISK ASSESSMENT] this term only
21	(test* or model* or scor*):ti,ab
22	#20 and #21
23	((test* or model* or scor*) near/5 risk?):ti,ab
24	#15 or #18 or #19 or #22 or #23
25	(adverse near/3 outcome?):ti,ab
26	MeSH descriptor: [MATERNAL MORTALITY] this term only
27	MeSH descriptor: [MATERNAL DEATH] this term only
28	(maternal near/3 (mortalit* or death?)):ti,ab
29	((maternal or central nervous system? or cardiorespirat* or cardio respirat* or hepatic* or renal* or h?ematolog*) near/5 morbidit*):ti,ab
30	MeSH descriptor: [ABRUPTIO PLACENTAE] this term only
31	abruptio placentae:ti,ab
32	placental abruption?:ti,ab
33	MeSH descriptor: [PREGNANCY OUTCOME] this term only
34	(pregnan* near/3 outcome?):ti,ab
35	MeSH descriptor: [OBSTETRIC LABOR, PREMATURE] this term only
36	((preterm* or pre-term* or premature*) near/3 (labo?r or deliver*)):ti,ab
37	MeSH descriptor: [PERINATAL MORTALITY] this term only
38	MeSH descriptor: [PERINATAL DEATH] this term only
39	((perinatal* or neonat*) near/3 (mortalit* or death?)):ti,ab
40	MeSH descriptor: [STILLBIRTH] this term only
41	MeSH descriptor: [FETAL DEATH] this term only
42	stillbirth?:ti,ab
43	((fetal or fetus*) near/3 (mortalit* or death?)):ti,ab
44	((neonat* or respirat* or gastrointestin* or gastro-intestin* or central nervous system?) near/5 morbidit*):ti,ab
45	MeSH descriptor: [PREGNANCY COMPLICATIONS] this term only
46	complication?:ti,ab
47	(high near/3 risk?):ti,ab
48	#25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47
49	(predict* near/5 (outcome? or complication? or mortalit* or death? or morbidit* or abruptio placentae or placental abruption? or ((preterm* or pre-term* or premature*) near/3 (labo?r or deliver*)) or stillbirth?)):ti,ab
50	(test* or model* or scor*):ti,ab
51	MeSH descriptor: [PRENATAL DIAGNOSIS] this term only and with qualifier(s): [Standards - ST]
52	MeSH descriptor: [PRENATAL DIAGNOSIS] this term only and with qualifier(s): [Methods - MT]
53	#51 or #52
54	#7 and #13 and #14
55	#7 and #24 and #48
56	#7 and #49 and #50
57	#7 and #48 and #53
58	#54 or #55 or #56 or #57

Appendix C – Clinical evidence study selection



Appendix D – Clinical evidence tables

Table 9: Clinical evidence tables

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Full citation

Agrawal, Shruti, Maitra, Nandita, Prediction of Adverse Maternal Outcomes in Preeclampsia Using a Risk Prediction Model, Journal of obstetrics and gynaecology of India, 66, 104-11, 2016

Ref Id

803137

Country/ies where the study was carried out

India

Aim of the study

To assess the performance o f the fullPIERS model to predict maternal adverse outcomes within 24 hours of</td>
<td>Sample size

N=322

Characteristics
<table>
<tr><th></th><th>With outcome (n = 60)</th><th>Without outcome (n =262)</th></tr>
<tr><td>Age, years (mean, SD)</td><td>24.8 (2.9)</td><td>24.7 (3.9)</td></tr>
<tr><td>Gestational age at entry, weeks (mean, SD)*</td><td>35.47 (3.55)</td><td>34.5 (4.5)</td></tr>
<tr><td>Pre-eclampsia[a] (n ,%)</td><td>60 (100%)</td><td>262 (100%)</td></tr>
<tr><td>Singleton pregnancy (n ,%)</td><td>60 (18.6%)</td><td>262 (81.3%)</td></tr>
<tr><td>Mean (SD) sBP ≥ XY mmHg at entry*</td><td>167.6 (18.8)</td><td>156.6 (15.3)</td></tr>
</table>
</td>
<td>Prognostic tool/test

fullPIERS (Pre-eclampsia Integrated Estimate of Risk). Factors included in the model: gestational age, respiratory pulse oximetry, platelets, creatinine, hepatic aspartate transaminase

Outcome(s)

PIERS composite. Outcomes included: maternal mortality or one or more serious central nervous system, cardiorespiratory, renal, haematological, or hepatic morbidity</td>
<td>Sample selection

This study used a prospective cohort of data. The predictor variables were obtained within 24 hours of admission for pre-eclampsia.

Data collection

Data were collected prospectively, no details regarding sampling were reported. Whether the cohort had missing data and methods for handling missing data was not reported.</td>
<td>Prognostic accuracy (sensitivity, specificity)
<table>
<tr><th>Predicted probability (cut-off)</th><th>Total N</th><th>Total N with outcome</th><th>Sensitivity (95% CI)</th><th>Specificity (95%CI)</th><th>LR+ (95% CI)</th><th>LR- (95% CI)</th></tr>
<tr><td>0.00-0.99%</td><td>223</td><td>18</td><td>0.72 (0.47-0.90)</td><td>0.78 (0.72-0.84)</td><td>1.68 (1.17-2.41)</td><td>0.48 (0.22-1.03)</td></tr>
<tr><td>1.0-2.4%</td><td>23</td><td>6</td><td>0.58(0.37-0.78)</td><td>0.84(0.78-0.88)</td><td>3.59 (2.29-5.64)</td><td>0.49 (0.30-0.79)</td></tr>
<tr><td>2.5-4.9%</td><td>17</td><td>7</td><td>0.42 (0.25-0.61)</td><td>0.88 (0.83-0.92)</td><td>3.47 (2.02-5.96)</td><td>0.66 (0.48-0.89)</td></tr>
<tr><td>5.0-9.9%</td><td>15</td><td>5</td><td>0.39 (0.23-0.57)</td><td>0.92 (0.88-0.95)</td><td>4.95 (2.73 - 8.98)</td><td>0.66 (0.51-0.86)</td></tr>
<tr><td>10.0-19.9%</td><td>12</td><td>6</td><td>0.31 (0.18-0.47)</td><td>0.94 (0.90-0.97)</td><td>5.11 (2.62-9.96)</td><td>0.73 (0.59-0.90)</td></tr>
</table>
</td>
<td>Limitations

The quality of this study was assessed using the CASP tool for clinical prediction rule (CPR).
A. Are the results valid?
1 Is the CPR clearly defined? Yes
2 The population from which the rule was derived included an appropriate spectrum of patients? Can't tell (how patients were selected was not reported)
3 Was the rule validated in a different group of patients? Yes
4 Were the predictor variables and the outcome</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>admission for preeclampsia

Study dates

Not reported

Source of funding

Not reported</td>
<td>
<table>
<tr><td></td><td></td><td></td></tr>
<tr><td>Mean (SD) dBP ≥ XY mmHg at entry*</td><td>102.69 (8.1)</td><td>98.02 (9.1)</td></tr>
</table>
*Between group differences were significant for gestational age at entry, mean SBP and mean sBP (p<0.01)
[a]Pre-eclampsia was defined as hypertension (sBP/dBP≥ 140/90 taken twice more than 4 hours apart after 20 weeks of gestational age) in combination with proteinuria (≥ 0.3 g/dl of proteinuria or 2+)

Inclusion criteria

sBP/dBP≥ 140/90 taken twice more than 4 hours apart after 20 weeks of gestational age; ≥ 0.3 g/dl of proteinuria or 2+ after 20 weeks of gestation; non-hypertensive and non-proteinuric HELLP syndrome; one eclamptic seizure without prior hypertension with or without hypertension and proteinuria

Exclusion criteria

Women admitted in spontaneous labour; occurrence of any element of the composite maternal outcomes prior to their meeting the eligibility criteria or before the collection of predictor variables was possible
</td>
<td></td>
<td>Data analysis

Sensitivity, specificity, and likelihood ratios were calculated using MedCalc software.</td>
<td>
<table>
<tr><td>20.0-29.9%</td><td>5</td><td>3</td><td>0.24 (0.13-0.40)</td><td>0.95 (0.91-0.97)</td><td>4.71 (2.25 -9.86)</td><td>0.79 (0.67-0.94)</td></tr>
<tr><td>≥30%</td><td>27</td><td>15</td><td>0.52 (0.38-0.65)</td><td>0.97 (0.94-0.99)</td><td>16.92 (8.19-34.93)</td><td>0.49 (0.38-0.64)</td></tr>
</table>
Data above are reported by converting the risk estimates into dichotomous data, i.e. the LR for the 0-0.99% category treats 0.99% as the cut-off for a positive test. At this cut-off, a positive test result gives a LR of 1.68, and a negative test result gives a LR of 0.48.
Likelihood ratios were also calculated by the NGA using the method of Deeks and Altman 2004 from raw data reported in the article, with 95% CI calculated using https://www.medcalc.org/calc/relative_risk.php:
<table>
<tr><th>Risk category</th><th>Number with outcome</th><th>Number without outcome</th><th>Likelihood ratio</th><th>95% CI</th></tr>
<tr><td>0-0.99%</td><td>18</td><td>205</td><td>(18/60)/(205/262) = 0.38</td><td>0.26 to 0.57</td></tr>
<tr><td>1-2.4%</td><td>6</td><td>17</td><td>(6/60)/(17/262) = 1.54</td><td>0.63 to 3.74</td></tr>
<tr><td>2.5-4.9%</td><td>7</td><td>10</td><td>(7/60)/(10/262) = 3.06</td><td>1.21 to 7.70</td></tr>
<tr><td>5.0-9.9%</td><td>5</td><td>10</td><td>(5/60)/(10/262) = 2.18</td><td>0.77 to 6.15</td></tr>
<tr><td>10-19.9%</td><td>6</td><td>6</td><td>(6/60)/(6/262) = 4.37</td><td>1.46 to 13.07</td></tr>
</table>
</td>
<td>evaluated in a blinded fashion? Unclear (no details regarding sampling have been provided)
5 Were the predictor variables and the outcome evaluated in the whole sample selected initially? Yes
6 Are the statistical methods used to construct and validate the rule clearly described? No
B. What are the results?
7 Can the performance of the rule be calculated? Yes
8 How precise was the estimate of the treatment effect? The rule is robust, there was not any attempt to refine the rule with other variables to see whether</td>
</tr>
</table>

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
				<table><tr><td>20-29.9%</td><td>3</td><td>2</td><td>(3/60)/(2/262) = 6.55</td><td>1.12 to 38.34</td></tr><tr><td>≥30%</td><td>15</td><td>12</td><td>(15/60)/(12/262) = 5.45</td><td>2.69 to 11.05</td></tr><tr><td>Total</td><td>60</td><td>262</td><td></td><td></td></tr></table> These data refer to the LR obtained when an individual is given each risk category result, i.e. when an individual is given a risk in the 0-0.99% category, her LR for disease is 0.38 **Model calibration** Not reported **Tool discrimination** Not reported	precision could be improved C. Will the results help locally? Are the results applicable to the scenario? 9 Would the prediction rule be reliable and the results interpretable if used for your patient? Yes (UK population) 10 Is the rule acceptable in your case? Yes 11 Would the results of the rule modify your decision about the management of the patient or the information you can give to him/her? Yes **Indirectness** Unclear where sampling was carried out, study was published in India

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Other information</td></tr>
<tr>
<td>Full citation

Akkermans, J., Payne, B., Dadelszen, P. V., Groen, H., Vries, J. D., Magee, L. A., Mol, B. W., Ganzevoort, W., Predicting complications in pre-eclampsia: External validation of the fullPIERS model using the PETRA trial dataset, European Journal of Obstetrics Gynecology and Reproductive Biology, 179, 58-62, 2014

Ref Id

803144

Country/ies where the study was carried out

The Netherlands

Aim of the study</td>
<td>Sample size

N=216 (PETRA cohort)

Characteristics

Participant's characteristics (data extracted from Ganzevoort 2005 as Akkermans 2014 did not report data on the HDP outcomes)
<table>
<tr><th></th><th>Control group* (n = 104)</th><th>Treatment group* (n = 110)</th></tr>
<tr><td>Age, years (median,range)</td><td>30.9 (20-41)</td><td>28.9 (18-41)</td></tr>
<tr><td>No. with severe pre-eclampsia[a] (n, %)</td><td>43 (41%)</td><td>52 (47%)</td></tr>
<tr><td>HELLP at entry[b] (n, %)</td><td>27 (26%)</td><td>27 (25%)</td></tr>
<tr><td>Eclampsia at entry[c] (n,%)</td><td>32 (31%)</td><td>37 (34%)</td></tr>
<tr><td>Fetal growth restriction[d] (n, %)</td><td>56 (54%)</td><td>67 (61%)</td></tr>
</table></td>
<td>Prognostic tool/test

fullPIERS (Pre-eclampsia Integrated Estimate of Risk). Factors included in the model: gestational age, respiratory pulse oximetry, platelets, creatinine, hepatic aspartate transaminase

Outcome(s)

PIERS composite. Out-comes included: maternal mortality or one or more serious central nervous system, cardiorespiratory, renal, haematological, or hepatic morbidity. Outcom es included:</td>
<td>Sample selection

This study used data from the Pre-eclampsia Eclampsia TRial Amsterdam (PETRA), a randomised controlled trial of plasma volume expansion in women with hypertensive disorders of pregnancy between 24 and 34 weeks gestational age. Women were enrolled from 2 different centres in The Netherlands (Department of Obstetrics at the Academic Medical Center [n=118] and the VU</td>
<td>Prognostic accuracy (sensitivity, specificity)

At 48 h of admission, using a cut-off of 20.1%
Sensitivity (95% CI) = 0.91 (95% CI NR)
Specificity (95% CI)= 0.93 (95% CI NR)
At 7 days of admission, using a cut-off of 20.1%

Sensitivity (95% CI) = 0.90 (95% CI NR)

Specificity (95% CI)= 0.23 (95% CI NR)

Model calibration
<u>Risk stratification table - Prediction of complication within 48 hours of admission</u>
<table>
<tr><th>Predicted probability</th><th>Total no of women</th><th>Total no of women with adverse outcomes</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th><th>LR + (95% CI)</th><th>LR - (95% CI)</th></tr>
<tr><td>0.00-0.0099</td><td>37 (17%)</td><td>0 (0%)</td><td>-</td><td>-</td><td>0 (0.00 -1.23)</td><td>-</td></tr>
<tr><td>0.010-0.024</td><td>59 (27%)</td><td>0 (0%)</td><td>-</td><td>-</td><td>0 (0.00-0.76)</td><td>-</td></tr>
<tr><td>0.025-0.049</td><td>34 (16%)</td><td>1 (3%)</td><td>-</td><td>-</td><td>0.17 (0.02-1.23)</td><td>-</td></tr>
</table></td>
<td>Limitations

The quality of this study was assessed using the CASP tool for clinical prediction rule (CPR).
A. Are the results valid?
1 Is the CPR clearly defined? Yes
2 The population from which the rule was derived included an appropriate spectrum of patients? Yes
3 Was the rule validated in a different group of patients? Yes
4 Were the predictor variables and the outcome evaluated in a blinded fashion? Yes (the author who collected the</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>To provide external validation of the fullPIERS model at 48 h within admission

Study dates

1st April 2000 to 31st May 2003

Source of funding

Dutch National Health Insurance Board</td>
<td>
<table>
<tr><td>Ethnicity: non-white (n, %)</td><td>28 (27%)</td><td>21 (28%)</td></tr>
</table>
[a]Severe pre-eclampsia: dBP ≥110 and proteinuria ≥ 0.3 g per 24h
[b]HELLP: haemolysis, elevated liver enzymes, low platelets, with or without hypertension, and proteinuria.
[c]Eclampsia: generalised convulsions not caused by epilepsy
[d]Fetal growth restriction: estimated fetal weight <10th centile
*N=1 participant missing in each group. Were excluded from the Ganzevoort 2005 because of "unanticipated congenital malformations"
<table>
<tr><th></th><th>Women with adverse outcomes (n=73)</th><th>Women without adverse outcomes (n=143)</th></tr>
<tr><td>Gestational age at inclusion (median, IQR)</td><td>29.3 (27.1-31.3)</td><td>30.3 (27.6-31.4)</td></tr>
<tr><td>Parity ≥1 (n,%)</td><td>18 (25%)</td><td>47 (33%)</td></tr>
</table>
Inclusion criteria

Women were entered into the PETRA dataset if they met at least one of the following: HELLP syndrome; severe pre-eclampsia (dBP ≥110 mmHg and proteinuria ≥0.3g per 24 hours); eclampsia; IUGR (< 10th centile); pregnancy induced
</td>
<td>maternal mortality or one or more serious central nervous system, cardiorespiratory, renal, haematological, or hepatic morbidity</td>
<td>University Medical Center [n=98]).

Data collection

Data were collected prospectively, although further retrospective data collection was performed to reduce the amount of outstanding parameters in the fullPIERS dataset. The variable oxygen saturation was often irretrievable, in which cases the value of 97% was imputed (this was also done in the internal validation study by von Dadelszen). For missing data, the method of last observation</td>
<td>
<table>
<tr><td>0.050-0.099</td><td>27 (13%)</td><td>1 (4%)</td><td>-</td><td>-</td><td>0.22 (0.03-1.57)</td><td>-</td></tr>
<tr><td>0.010-0.19</td><td>17 (8%)</td><td>1 (6%)</td><td>-</td><td>-</td><td>0.35 (0.04-2.62)</td><td>-</td></tr>
<tr><td>0.20-0.29</td><td>13 (6%)</td><td>3 (23%)</td><td>-</td><td>-</td><td>1.72 (0.50-5.93)</td><td>-</td></tr>
<tr><td>≥0.30</td><td>29 (13%)</td><td>26 (90%)</td><td>-</td><td>-</td><td>49.89 (16.02-154.98)</td><td>-</td></tr>
<tr><td>Total</td><td>216</td><td>32</td><td></td><td></td><td></td><td></td></tr>
</table>
<u>Risk stratification table - Prediction of complication within 7 days of admission</u>
<table>
<tr><th>Predicted probability</th><th>Total no of women</th><th>Total no of women with adverse outcomes</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th><th>LR + (95% CI)</th><th>LR - (95% CI)</th></tr>
<tr><td>0.00-0.0099</td><td>37 (17%)</td><td>6 (16%)</td><td>-</td><td>-</td><td>0.48 (0.21-1.09)</td><td>-</td></tr>
<tr><td>0.010-0.024</td><td>59 (27%)</td><td>7 (12%)</td><td>-</td><td>-</td><td>0.33 (0.16-0.69)</td><td>-</td></tr>
</table>
</td>
<td>data was not aware of the model parameters)
5 Were the predictor variables and the outcome evaluated in the whole sample selected initially? Yes
6 Are the statistical methods used to construct and validate the rule clearly described? Yes
B. What are the results?
7 Can the performance of the rule be calculated? Yes
8 How precise was the estimate of the treatment effect? In the study it is mentioned that "the model was adjusted to account for underlying prevalence of maternal outcomes in this population" (page 61)</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td></td>
<td>hypertension (dBP ≥ 90 mmHg with the absence of proteinuria).

Exclusion criteria

Signs of fetal distress, maternal condition demanding immediate delivery, or previous diagnosis of a lethal fetal congenital abnormality.</td>
<td></td>
<td>carried forward was used.

Data analysis

Calibration was calculated by assessing the slope of the linear predictor resulting from application of the fullPIERS model to the study data. Further assessment was done by adjusting the intercept of the fullPIERS model to reflect the difference in outcome prevalence of the PETRA dataset. Discrimination was calculated using the area under the curve (AUC) ROC. 95% CIs were calculated for combined</td>
<td>
<table>
<tr><td>0.025-0.049</td><td>39 (16%)</td><td>4 (12%)</td><td>-</td><td>-</td><td>0.33 (0.12-0.90)</td><td>-</td></tr>
<tr><td>0.050-0.099</td><td>27 (13%)</td><td>4 (15%)</td><td>-</td><td>-</td><td>0.43 (0.15-1.19)</td><td>-</td></tr>
<tr><td>0.010-0.19</td><td>17 (8%)</td><td>6 (35%)</td><td>-</td><td>-</td><td>1.35 (0.52-3.50)</td><td>-</td></tr>
<tr><td>0.20-0.29</td><td>13 (6%)</td><td>8 (62%)</td><td>-</td><td>-</td><td>3.97 (1.35-11.67)</td><td>-</td></tr>
<tr><td>≥0.30</td><td>29 (13%)</td><td>27 (93%)</td><td>-</td><td>-</td><td>33.53 (8.22-136.76)</td><td>-</td></tr>
<tr><td>Total</td><td>216</td><td>62</td><td></td><td></td><td></td><td></td></tr>
</table>
Tool discrimination

AUC ROC (95% CI) 48 hours of admission= 0.97 (0.94 to 0.99)
AUC ROC (95% CI) 7 days of admission= 0.80 (0.72 to 0.87)
Calibration slope (95% CI) = 1.69 (1.10-2.28)*
Calibration slope (95% CI) after adjustment for differences between PETRA and fullPIERS population = 1.67 (109-226)

*assumed typographical error in paper, CI reported as 110 to 228
</td>
<td>C. Will the results help locally? Are the results applicable to the scenario? 9 Would the prediction rule be reliable and the results interpretable if used for your patient? Yes (UK population), although 27% of women did not present with pre-eclampsia 10 Is the rule acceptable in your case? Yes 11 Would the results of the rule modify your decision about the management of the patient or the information you can give to him/her? Yes

Indirectness

PETRA dataset - 73% of participants presented with pre-eclampsia</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td>adverse maternal outcomes within 48h and within 7 days after inclusion, with 24h intervals.</td><td></td><td>Other information</td></tr>
<tr><td>Full citation

Almeida, Silvana T., Katz, Leila, Coutinho, Isabela, Amorim, Melania M. R., Validation of fullPIERS model for prediction of adverse outcomes among women with severe pre-eclampsia, International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics, 138, 142-147, 2017

Ref Id

803158</td><td>Sample size

N=325 (non pre-existing cohort)

Characteristics
<table><tr><th></th><th>With outcome

(n =55)</th><th>Without outcome

(n =270)</th></tr><tr><td>Age, years (mean, SD)</td><td>25.4 (6.5)</td><td>25.1 (6.8)</td></tr><tr><td>Ethnicity: white</td><td>14 (25.5)</td><td>68 (25.2)</td></tr><tr><td>Gestational age (mean, SD)</td><td>33.6 (4.8)</td><td>36.1 (3.4)</td></tr><tr><td>Parity (median IQR)</td><td>1 (1-2)</td><td>1 (1-2)</td></tr></table></td><td>Prognostic tool/test

fullPIERS (Pre-eclampsia Integrated Estimate of Risk). Factors included in the model: gestational age, respiratory pulse oximetry, platelets, creatinine, hepatic aspartate transaminase

Outcome(s)

PIERS composite. Outcomes included: maternal mortality or one or more serious central nervous system, cardiorespiratory, renal, haematological, or hepatic morbidity</td><td>Sample selection

This study used data from women admitted to a teaching hospital in Brazil. Sample size calculations were performed using OpenEpi, and it was assessed that for predicting a 7 day complication rate of 10%, the total number of women that would be required would be of 283.</td><td>Prognostic accuracy (sensitivity, specificity)

Sensitivity (95% CI)= 60% (46.8%- 71.80%)
Specificity (95% CI)= 65.1% (59.3% - 70.6%)

Risk stratification table
<table><tr><th>Predicted probability</th><th>With outcome</th><th>Without outcome</th></tr><tr><td>>1.7%</td><td>33 (26%)</td><td>94 (74%)</td></tr><tr><td><1.7%</td><td>22 (11%)</td><td>176 (89%)</td></tr></table>
Model calibration

Not reported

Tool discrimination

AUC ROC (95% CI)= 0.72 (95% CI 0.67 - 0.77)</td><td>Limitations

The quality of this study was assessed using the CASP tool for clinical prediction rule (CPR).
A. Are the results valid?
1 Is the CPR clearly defined? Yes
2 The population from which the rule was derived included an appropriate spectrum of patients? Yes
3 Was the rule validated in a different group of patients? Yes
4 Were the predictor variables and the outcome</td></tr>
</table>

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
Country/ies where the study was carried out Brazil **Aim of the study** To assess the performance of the fullPIERS model to predict maternal adverse outcomes within 48 hours of admission among women with severe pre-eclampsia from Brazil **Study dates** January - December 2014 **Source of funding** Not reported	<table><tr><td>Severe pre-eclampsia[a]</td><td>55 (100%)</td><td>270 (100%)</td></tr><tr><td>Mean (SD) sBP, mmHg</td><td>167.6 (20.5)</td><td>161.4 (18)</td></tr><tr><td>Mean (SD) dBP, mmHg</td><td>110.1 (11.9)</td><td>106.6 (11.6)</td></tr></table> [a]increased BP (threshold not reported) from the 20th weeks of pregnancy with proteinuria, maternal organ dysfunction and/or uteroplacental insufficiency **Inclusion criteria** Women admitted with severe pre-eclampsia (increased BP from the 20th weeks of pregnancy with proteinuria, maternal organ dysfunction and/or uteroplacental insufficiency). **Exclusion criteria** Women with chronic hypertension; diabetes; collagenosis; complications related with cardiology, haematology, or pulmonary; and women with sickle cell anaemia.		**Data collection** Data was applied retrospectively to all patients using the fullPIERS online tool. **Data analysis** Discrimination was calculated using the area under the curve (AUC) ROC. Sensitivity, specificity and likelihood ratios were calculated using the software Medcalc.		evaluated in a blinded fashion? Can't tell (no details regarding sampling have been reported) 5 Were the predictor variables and the outcome evaluated in the whole sample selected initially? Yes 6 Are the statistical methods used to construct and validate the rule clearly described? Yes B. What are the results? 7 Can the performance of the rule be calculated? Yes 8 How precise was the estimate of the treatment effect? The rule is robust (there were not any attempts to refine the rule to see whether precision could be improved)

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
					C. Will the results help locally? Are the results applicable to the scenario? 9 Would the prediction rule be reliable and the results interpretable if used for your patient? Can't tell (data was obtained from a middle income setting)) 10 Is the rule acceptable in your case? Yes 11 Would the results of the rule modify your decision about the management of the patient or the information you can give to him/her? Yes **Indirectness** Data obtained from a low/middle income setting

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Other information</td></tr>
<tr>
<td>Full citation

Chan, Patricia, Brown, Mark, Simpson, Judy M., Davis, Gregory, Proteinuria in pre-eclampsia: how much matters?, BJOG : an international journal of obstetrics and gynaecology, 112, 280-5, 2005

Ref Id

775773

Country/ies where the study was carried out

Australia

Aim of the study

To assess whether in women with proteinuric pre-eclampsia, a specific spot urine/creatinine ratio at the time of antenatal diagnosis exists to</td>
<td>Sample size

N=321 (non pre-existing dataset)

Characteristics

<table><tr><th></th><th>Total cohort (n=321)</th></tr><tr><td>Age (mean, SD)</td><td>30 (5)</td></tr><tr><td>sBP at entry (mean mmHg, SD)</td><td>115 (11)</td></tr><tr><td>Gestational age</td><td>Not reported</td></tr><tr><td>Pre-eclampsia[a] (n, %)</td><td>321 (100)</td></tr><tr><td>dBP at entry (mean mmHg, SD)</td><td>70 (8)</td></tr><tr><td>Nulliparity (n, %)</td><td>233 (73)</td></tr></table>[a]ISHHP research definition

Inclusion criteria</td>
<td>Prognostic tool/test

Spot urine PRCR and maternal age at diagnosis

Outcome(s)

Adverse maternal outcomes: any new episode of severe hypertension (≥170/110); renal insufficiency; liver disease; cerebral irritation and thrombocytopenia. Adverse fetal outcomes: perinatal mortality and/or SGA.</td>
<td>Sample selection

Women with pre-eclampsia (ISSHP definition) who were admitted to the hospital since the year 1987 were entered into the study

Data collection

Data regarding demographic details, laboratory data, time of referral, and delivery were entered into a database between the years 1998 and 2001

Data analysis</td>
<td>Prognostic accuracy (sensitivity, specificity)

Maternal adverse outcomes
<table><tr><th>Total number of women with outcome</th><th>Test</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th><th>LR+ (95%CI)</th><th>LR- (95% CI)</th></tr><tr><td>108</td><td>Spot urine PCR> 500 and maternal age > 35 years</td><td>10.2 (5.4-17.9)</td><td>100 (97.8-100)</td><td>-</td><td>0.9 (0.55-0.71)</td></tr></table>Perinatal adverse outcomes
<table><tr><th>Total number of infants with outcome</th><th>Test</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th><th>LR+ (95%CI)</th><th>LR- (95% CI)</th></tr><tr><td>60</td><td>GA< 34 weeks and sBP < 115 mmHg*</td><td>48.33 (35.39-61.48)</td><td>39.08 (33.17-45.31)</td><td>0.79 (0.60-1.04)</td><td>1.32 (1.02-1.70)</td></tr></table>*PCR reading was a statistically significant predictor but did not add much information to the discriminatory power of the model</td>
<td>Limitations

<u>Limitations assessed with the QUADAS-2 checklist</u>
<u>Domain 1. Patient selection</u>
A. Risk of bias
Was a consecutive or random sample of patients enrolled? yes
Was a case-control design avoided? yes
Did the study avoid inappropriate exclusions? yes
Could the selection of patients have introduced bias? low
B. Concerns regarding applicability
Is there a concern that the included patients do not match the review question? low</td>
</tr>
</table>

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
predict adverse outcomes in women and babies within 24 hours of admission **Study dates** 1998 to 2001 **Source of funding** Not reported	Women with pre-eclampsia (ISSHP research definition) with spot protein creatinine results available **Exclusion criteria** Women with superimposed pre-eclampsia		Area under the curve AUC ROC, sensitivity and specificity were calculated (no details were provided as to how this was done). Likelihood ratios were calculated as sensitivity/ (specificity-1)	**Model calibration** Not reported **Tool discrimination** AUC ROC (95% CI) for adverse maternal outcomes = 0.67(0.55-0.71) AUC ROC (95% CI) for adverse fetal outcomes= 0.72	<u>Domain 2. Index test(s)</u> A. Risk of bias Were the index test results interpreted without knowledge of the results of the reference standard? yes If a threshold was used, was it pre-specified? no (data-driven) **Could the conduct or interpretation of the index test have introduced bias? low** B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? no <u>Domain 3. Reference standard</u> A. Risk of bias Is the reference standard likely to correctly classify the

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
					target condition? yes Were the reference standard results interpreted without knowledge of the results of the index test? yes **Could the reference standard, its conduct, or its interpretation have introduced bias? low** B. Concerns regarding applicability **Is there concern that the target condition as defined by the reference standard does not match the review question? low** Domain 4. Flow and timing Was there an appropriate interval between index test(s) and reference standard? yes

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Did all patients received a reference standard? yes
Did patients receive the same reference standard? yes
Were all patients included in the analysis? yes
Could the patient flow have introduced bias? low

Indirectness

No indirectness

Other information</td></tr>
<tr><td>Full citation

Laskin, Samara, Payne, Beth, Hutcheon, Jennifer A., Qu, Ziguang, Douglas, M. Joanne, Ford, Jason, Lee, Tang, Magee, Laura A., von Dadelszen, Peter, The role of platelet counts in</td><td>Sample size

N=1405 (from the PIERS cohort)

Characteristics
<table><tr><th></th><th>Abnormal coagulation (n=105)</th><th>Normal coagulation (n=1300)</th></tr></table></td><td>Prognostic tool/test

Platelets ≤ 100 x 10^9/L
Platelets ≤ 150 x 10^9/L
Abnormal coagulation (INR> 1.06 and serum fibrinogen < 3.54 g/L)</td><td>Sample selection

Women in the PIERS dataset meeting inclusion criteria were selected to participate in the study.</td><td>Prognostic accuracy (sensitivity, specificity)

Sensitivity and specificity of platelet count and abnormal coagulation for predicting adverse maternal outcomes<table><tr><th>Test</th><th>Total N with adverse outcome</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th><th>LR+ (95% CI)</th><th>LR- (95% CI)</th></tr></table></td><td>Limitations

<u>Limitations assessed with the QUADAS-2 checklist</u>

<u>Domain 1. Patient selection</u>
A. Risk of bias
Was a consecutive or</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>the assessment of inpatient women with preeclampsia, Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC, 33, 900-8, 2011

Ref Id

776230

Country/ies where the study was carried out

Canada, Australia, new Zealand and UK

Aim of the study

To assess the relationship between platelet count and adverse outcomes in pregnant women with pre-eclamspia within 48 hours of admission

Study dates</td>
<td>
<table>
<tr><td>Maternal range (median, IQR)</td><td>30 (26 to 34)</td><td>32 (28 to 36)</td></tr>
<tr><td>GA at eligibility in weeks (median, IQR)</td><td>32.7 (30.3 to 36.7)</td><td>36.4 (33.4 to 38.4)</td></tr>
<tr><td>Multiple pregnancy (n, %)</td><td>10 (9.5)</td><td>142 (10.9)</td></tr>
<tr><td>Parity ≥1</td><td>30 (28.6)</td><td>354 (27.2)</td></tr>
<tr><td>Hypertension and proteinuria[a]</td><td>76 (72.4)</td><td>841 (64.7)</td></tr>
<tr><td>Hypertension and hyperuricaemia[b]</td><td>11 (10.5)</td><td>212 (16.3)</td></tr>
<tr><td>HELLP with hypertension and proteinuria[c]</td><td>7 (6.7)</td><td>39 (3)</td></tr>
<tr><td>Superimposed pre-eclampsia[d]</td><td>11 (10.5)</td><td>208 (16)</td></tr>
</table>
</td>
<td>Outcome(s)

PIERS composite. Outcomes included: maternal mortality or one or more serious central nervous system, cardiorespiratory, renal, haematological, or hepatic morbidity</td>
<td>Data collection

The data used in this study were extracted from the PIERS dataset. it was prospectively collected and it covers women who were admitted to tertiary obstetric centres. Data were collected between September 2003 and January 2010. The list of adverse maternal outcomes was developed by Delphi consensus

Data analysis

The diagnostic value of the different thresholds was assessed by calculating sensitivity and</td>
<td>
<table>
<tr><td>Platelet <100 x 10^9/L</td><td>152</td><td>15.8 (10.6 to 22.8)</td><td>92.2 (90.5 to 93.6)</td><td>2 (1.3-3.1)</td><td>0.9 (0.9-1)</td></tr>
<tr><td>Abnormal coagulation</td><td>105</td><td>15.1 (10 to 22.1)</td><td>93.5 (91.9 to 94.7)</td><td>2.17 (1.32-3.56)</td><td>0.91 (0.84-0.98)</td></tr>
</table>
Model calibration

Not reported

Tool discrimination

Not reported
</td>
<td>random sample of patients enrolled? yes
Was a case-control design avoided? yes
Did the study avoid inappropriate exclusions? yes
Could the selection of patients have introduced bias? low
B. Concerns regarding applicability
Is there a concern that the included patients do not match the review question? low

<u>Domain 2. Index test(s)</u>
A. Risk of bias
Were the index test results interpreted without knowledge of the results of the reference standard? unclear(no details were provided)
If a threshold was used, was</td>
</tr>
</table>

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
Sep 2003 - Jan 2010 **Source of funding** Canadian Institutes for Health Research: CIHR, UNDP, UNFPA, WHO, World Bank Speical Programme of Research, Development and Research Training in Human Reproduction	sBP, mmHg (median, iQR) 161 (150 to 180) 162 (151 to 178) dBP,mmHg (median, IQR) 103 (100 to 110) 102 (98 to 110) [a]sBP/dBP ≥140/90 mmHg (at least 1 component, measured ≥ 4h apart, after 20 w GA) and proteinuria (≥0.3g per day by 24h collection or ≥ 30mg mmol as measured by protein:creatinine ratio) [b]sBP/dBP ≥140/90 mmHg (at least 1 component, measured ≥ 4h apart, after 20 w GA) and hyperuricaemia (upper limit greater than normal for non-pregnant women) [c]Definition not reported [d]rapidly increasing requirements for antihypertensive drugs, sBP> 170 mmHg or dBP> 120 mmHg, new proteinuria or new hyperuricaemia **Inclusion criteria** Women with either a)sBP/dBP ≥140/90 mmHg (at least 1 component, measured ≥ 4h apart, after 20 w GA) and either proteinuria (≥0.3g per day by 24h collection or ≥ 30mg mmol as measured by protein:creatinine ratio) or hyperuricaemia (upper limit greater than normal for non-pregnant women), or b) HELLP syndrome, or c) superimposed PE (rapidly increasing requirements for antihypertensive drugs, sBP> 170 mmHg or dBP> 120 mmHg, new proteinuria or new hyperuricaemia) Women with recorded values for INR and fibrinogen and a platelet count within 12 hours of their relevant platelet count.		specificity (no further details were provided)		it pre-specified? not pre-specified **Could the conduct or interpretation of the index test have introduced bias? unclear** B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? no Domain 3. Reference standard A. Risk of bias Is the reference standard likely to correctly classify the target condition? yes Were the reference standard results interpreted without knowledge of the results of the index test? unclear(no details were provided)

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
	Exclusion criteria Women admitted in labour or those who had any of the maternal outcomes prior to data collection				**Could the reference standard, its conduct, or its interpretation have introduced bias? unclear** B. Concerns regarding applicability **Is there concern that the target condition as defined by the reference standard does not match the review question? low** Domain 4. Flow and timing Was there an appropriate interval between index test(s) and reference standard? yes Did all patients received a reference standard? yes Did patients receive the same reference standard? yes Were all patients included in the analysis? yes

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Could the patient flow have introduced bias? low

Indirectness

No indirectness

Other information</td></tr>
<tr><td>Full citation

Livingston, J. R., Payne, B., Brown, M., Roberts, J. M., Cote, A. M., Magee, L. A., von Dadelszen, P., Uric Acid as a predictor of adverse maternal and perinatal outcomes in women hospitalized with preeclampsia, Journal of Obstetrics & Gynaecology Canada: JOGC, 36, 870-7, 2014

Ref Id</td><td>Sample size

N= 1487

Characteristics
<table><tr><th></th><th>Full cohort (n=1487)</th></tr><tr><td>Age at expected day of delivery (median, IQR)</td><td>31 (26 to 35)</td></tr><tr><td>Gestational age at entry (median weeks, IQR)</td><td>35 (33 to 38)</td></tr><tr><td>Parity ≥1 (N,%)</td><td>390 (26)</td></tr></table></td><td>Prognostic tool/test

Uric acid (highest level recorded within 24 h of enrolment)

Outcome(s)

PIERS composite outcome. Outcomes included: maternal mortality or one or more serious central nervous system, cardiorespiratory, renal, haematological, or hepatic morbidity Perinatal outcome comprised perinat</td><td>Sample selection

PIERS cohort of women (only women with pre-eclampsia were included)

Data collection

Serum uric acid concentration was measured within 24 hours of enrolment. Local laboratories were</td><td>Prognostic accuracy (sensitivity, specificity)

Predictors by outcome for hyperuricemia (uric acid >345 µmol/L)<table><tr><th>Outcome type</th><th>Total outcomes</th><th>Time since admission</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th></tr><tr><td>All adverse maternal</td><td>-</td><td>48h</td><td>0.80 (0.70-0.87)</td><td>0.28 (0.25-0.30)</td></tr><tr><td></td><td>-</td><td>7 d</td><td>0.82 (0.76-0.88)</td><td>0.28 (0.26-0.31)</td></tr><tr><td></td><td>199</td><td>Any time</td><td>0.83 (0.77-0.88)</td><td>0.29 (0.26-0.31)</td></tr></table></td><td>Limitations

<u>Limitations assessed with the QUADAS-2 checklist</u>
<u>Domain 1. Patient selection</u>
A. Risk of bias
Was a consecutive or random sample of patients enrolled? yes
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? Yes</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>658299

Country/ies where the study was carried out

Canada, UK, Australia and New Zealand

Aim of the study

To analyse data from an existing cohort of women with pre-eclampsia and assess whether uric acid is a good predictor of adverse and perinatal outcomes within 48 hours and 7 days of admission

Study dates

September 2003 to December 2011

Source of funding

Canadian Institutes of Health Research; UNDP; UNFPA; WHO; World Bank Special</td>
<td>
<table>
<tr><td>Median sBP (IQR), mmHg</td><td>160 (150-175)</td></tr>
<tr><td>Median dBP (IQR), mmHg</td><td>100 (95-110)</td></tr>
<tr><td>Preeclampsia[a] (N,%)</td><td>1487 (100)</td></tr>
</table>
[a]Preeclampsia was defined as hypertension (sBP/dBP ≥ 140/90 mmHg on 2 recordings or more, more than 4 hours apart) with proteinuria (≥ 0.3 g/day by 24 hour urine excretion, or ≥ 30mg/mmol by spot urine:creatinine ratio)
Demographic data of the subset of women included in the analyses was not available

Inclusion criteria

Not reported

Exclusion criteria

Women who developed any of the outcomes before the clinical predictors were measured; women admitted in spontaneous labour</td>
<td>al or infant mortality, admission to NICU for greater than 48 hours, or both.</td>
<td>responsible for measurement of serum acid.

Data analysis

AUC ROC was calculated using univariate logistic regression using STATA. AUC ROC of 0.7 was determined as the minimum value for a discriminative test.
The sensitivity and specificity of hyperuricemia and hyperuricemia corrected for GA was assessed to assess the relationship with neonatal and maternal outcomes.</td>
<td>
<table>
<tr><td>Adverse maternal (non-renal)</td><td>-</td><td>48 h</td><td>0.79 (0.70-0.87)</td><td>0.28 (0.25-0.30)</td></tr>
<tr><td></td><td>-</td><td>7 d</td><td>0.82 (0.75-0.87)</td><td>0.28 (0.26-0.31)</td></tr>
<tr><td></td><td>196</td><td>Any time</td><td>0.83 (0.77-0.88)</td><td>0.29 (0.26-0.31)</td></tr>
<tr><td>Perinatal</td><td>420</td><td>Any time</td><td>0.78 (0.073-0.82)</td><td>0.29 (0.27-0.32)</td></tr>
</table>
Predictors by outcome for hyperuricemia corrected for gestational age (defined as 1 SD above the mean value for GA)
<table>
<tr><th>Outcome type</th><th>Total outcomes</th><th>Time since admission</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th></tr>
<tr><td>All adverse maternal</td><td>-</td><td>48h</td><td>0.86 (0.77-0.92)</td><td>0.21 (0.19-0.24)</td></tr>
<tr><td></td><td>-</td><td>7 d</td><td>0.86 (0.80-0.91)</td><td>0.22 (0.20-0.24)</td></tr>
<tr><td></td><td>199</td><td>Any time</td><td>0.86 (0.80-0.90)</td><td>0.22 (0.20-0.24)</td></tr>
<tr><td>Adverse maternal (non-renal)</td><td>-</td><td>48 h</td><td>0.86 (0.77-0.92)</td><td>0.21 (0.19-0.24)</td></tr>
</table>
</td>
<td>Could the selection of patients have introduced bias? low
B. Concerns regarding applicability
Is there a concern that the included patients do not match the review question? low

<u>Domain 2. Index test(s)</u>
A. Risk of bias
Were the index test results interpreted without knowledge of the results of the reference standard? uncle ar
If a threshold was used, was it pre-specified? thresholds have not been used
Could the conduct or interpretation of the index test have introduced bias? low</td>
</tr>
</table>

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
Programme of Research, Development & Research Training in Human Reproduction; Preeclampsia Foundation; International Federation of Obstetricians and Gynaecologists; Michael Smith Foundation for Heath Research; Child and Family Research Institute				<table><tr><td></td><td>-</td><td>7 d</td><td>0.86 (0.80-0.91)</td><td>0.22 (0.20-0.24)</td></tr><tr><td></td><td>196</td><td>Any time</td><td>0.86 (0.80-0.90)</td><td>0.22 (0.20-0.24)</td></tr><tr><td>Perinatal</td><td>420</td><td>Any time</td><td>0.92 (0.90-0.95)</td><td>0.26 (0.24-0.29)</td></tr></table> **Model calibration** Not applicable	B. Concerns regarding applicability **Is there concern that the index test, its conduct, or interpretation differ from the review question? low** <u>Domain 3. Reference standard</u> A. Risk of bias Is the reference standard likely to correctly classify the target condition? yes Were the reference standard results interpreted without knowledge of the results of the index test? unclear **Could the reference standard, its conduct, or its interpretation have introduced bias? no** B. Concerns regarding applicability

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
					Is there concern that the target condition as defined by the reference standard does not match the review question? low <u>Domain 4. Flow and timing</u> Was there an appropriate interval between index test(s) and reference standard? yes Did all patients received a reference standard? yes Did patients receive the same reference standard? yes Were all patients included in the analysis? yes **Could the patient flow have introduced bias? low** **Indirectness** No indirectness

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Other information</td></tr>
<tr><td>Full citation

Payne, B. A., Hutcheon, J. A., Ansermino, J. M., Hall, D. R., Bhutta, Z. A., Bhutta, S. Z., Biryabarema, C., Grobman, W. A., Groen, H., Haniff, F., Li, J., Magee, L. A., Merialdi, M., Nakimuli, A., Qu, Z., Sikandar, R., Sass, N., Sawchuck, D., Steyn, D. W., Widmer, M., Zhou, J., von Dadelszen, P., Walley, K., Joseph, K. S., Mirembe, F., Noovao, A., Qureshi, R., Duan, T., van Papendorp, E., Ssegirinya, M., Sewagaba, M., Byenkya, R. M., Namulema, B., Namiiro, J., Nakayiza, R. M., Akao, G., Nankabirwa, I.,</td>
<td>Sample size

N= 1300 (PIERS cohort)

Characteristics
<table><tr><th></th><th>Total cohort (n=1300)</th></tr><tr><td>Maternal range (mean, SD)</td><td>31.7 (6)</td></tr><tr><td>GA at eligibility in weeks (median, IQR)</td><td>37 (34.1-38.9)</td></tr><tr><td>Parity ≥1 (n, %)</td><td>403 (31)</td></tr><tr><td>Pre-eclampsia[a] (n, %)</td><td>1020 (78.5)</td></tr><tr><td>Other HDP[b] (n, %)</td><td>280 (21.5)</td></tr><tr><td>sBP, mmHg (median, IQR)</td><td>166 (155-180)</td></tr><tr><td>dBP,mmHg (median, IQR)</td><td>104 (98-110)</td></tr></table></td>
<td>Prognostic tool/test

miniPIERS model 25% predicted probability. Factors included in the model are: gestational age at admission, previous deliveries before 20 weeks gestation, presence/absence of chest pain/dyspnoea, presence/absence of headache and/or visual changes, presence/absence vaginal bleeding with abdominal pain, sBP (mmHg), SpO2 (optional).

Outcome(s)

PIERS composite. Out-comes included: maternal mortality or one or more</td>
<td>Sample selection

Data collected after the 1 March 2008 in the PIERS dataset meeting inclusion criteria were selected to participate in the study. Prior to this date, the PIERS dataset was not collecting data regarding abdominal pain, vaginal bleeding or any headache.

Data collection

The data used in this study were extracted from the PIERS</td>
<td>Prognostic accuracy (sensitivity, specificity)

Not reported for the external validation model

Model calibration

Not reported

Tool discrimination

Complete cohort
AUC ROC (95% CI) = 0.71 (0.65-0.76)
Complete cohort - including only women who were admitted ≤34+6wk GA
AUC ROC (95% CI) = 0.72 (0.63-0.82)
Complete cohort - include all but transfusion as an adverse outcome
AUC ROC (95% CI) = 0.75 (0.73-0.78)
Women with pre-eclampsia only
AUC ROC (95% CI) = 0.72 (0.64-0.79)</td>
<td>Limitations

The quality of this study was assessed using the CASP tool for clinical prediction rule (CPR).
A. Are the results valid?
1 Is the CPR clearly defined? Yes
2 The population from which the rule was derived included an appropriate spectrum of patients? Yes
3 Was the rule validated in a different group of patients? Yes
4 Were the predictor variables and the outcome evaluated in a blinded</td></tr>
</table>

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
Nakazibwe, R., Noorjahan, A., Azeem, F., Menzies, J., Pipkin, F. B., Cote, A. M., Douglas, M. J., Gruslin, A., Kyle, P., Lee, T., Loughna, P., Mahajan, S., Millman, A., Moore, M. P., Moutquin, J. M., Ouellet, A., Smith, G., Walker, J., Walters, B., Lee, S., Russell, J., Brown, M., Davis, G., Robson, S., de Swiet, M., Lindheimer, M., Roberts, J., Shaw, D., Donnay, F., A Risk Prediction Model for the Assessment and Triage of Women with Hypertensive Disorders of Pregnancy in Low-Resourced Settings: The miniPIERS (Pre-eclampsia Integrated Estimate of RiSk) Multi-country Prospective Cohort Study, PLoS Medicine,	[a]sBP/dBP ≥140/90 mmHg (at least 1 component, measured ≥ 4h apart, after 20 w GA) and either proteinuria (≥0.3g per day by 24h collection or ≥ 30mg mmol as measured by protein:creatinine ratio) or hyperuricaemia (upper limit greater than normal for non-pregnant women) [b]Other HPD duch as estational hypertension, chronic hypertension, partial HELLP. **Inclusion criteria** Women with either a)suspected or confirmed pre-eclampsia after 20 weeks of gestational age defined as BP ≥ 140/90 (at least 1 component; measured 2 times at least between 4 and 24 hours apart) and either proteinuria (≥0.3g per day by 24h collection or ≥ 30mg mmol as measured by protein:creatinine ratio) or hyperuricaemia (upper limit greater than normal for non-pregnant women); b) HELLP syndrome, even in the absence of hypertension or proteinuria; c) superimposed pre-eclampsia. Women with other hypertensive disorders of pregnancy, such as gestational hypertension, chronic hypertension, partial HELLP. **Exclusion criteria** Women who were admitted in labour or who had developed any of the adverse outcomes prior eligibility or collection of predictor variables. Women with positive HIV/AIDS status with CD4 count < 250 cells/ml or AIDS-defining illness.	serious central nervous system, cardiorespiratory, renal, haematological, or hepatic morbidity	dataset. it was prospectively collected and it covers women who were admitted to tertiary obstetric centres in the UK, Australia and New Zealand. **Data analysis** Discrimination was calculated using the area under the curve (AUC) ROC. Owing to the underlying difference in adverse outcomes between the miniPIERS and fullPIERS dataset (6.5% in the fullPIERS versus 12.5% in the miniPIERS), the model intercept was adjusted prior the estimation of the		fashion? Unclear 5 Were the predictor variables and the outcome evaluated in the whole sample selected initially? Yes 6 Are the statistical methods used to construct and validate the rule clearly described? Yes B. What are the results? 7 Can the performance of the rule be calculated? No 8 How precise was the estimate of the treatment effect? In the study it is mentioned that "the model intercept was adjusted before estimating predictive performance" (page 4) C. Will the results help locally? Are the results

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
11, e1001589, 2014 **Ref Id** 776498 **Country/ies where the study was carried out** Canada **Aim of the study** To provide external validation of the miniPIERS clinical prediction tool within 48 hours of admission **Study dates** July 2008- March 2012 **Source of funding** "Bill & Mellinda Gates Foundation; UNDP/UNFPA/WHO/World Bank Special Programme of Research; Development and Research Training			predictive performance. Sensitivity analyses were carried out in various subsets of the study data to assess the generalis-ability of the miniPIERS prognostic tool.		applicable to the scenario? 9 Would the prediction rule be reliable and the results interpretable if used for your patient? Yes (high income settting population), although 21.5% of women did not present with pre-eclampsia 10 Is the rule acceptable in your case? Yes 11 Would the results of the rule modify your decision about the management of the patient or the information you can give to him/her? Yes **Indirectness** 21.5% of the population did not present with pre-eclampsia **Other information**

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td>in Human Reproduction; Canadian Institutes of Health Research; Preeclampsia Foundation; the Rockefeller Foundation; United States Agency for International Development; the International Federation of Gynecology and Obstetric; and the Child and Family Research Institute" (page 1)</td><td></td><td></td><td></td><td></td><td>Conflicts of interest: PVD id a paid consultant of Alere International; JMA is the founder of Lions Gate Technologies and is focused on commercializing a device for measuring pulse oximeter; JMA holds <5% equity in the company. ZAM is a member of the Educational Board of PLOS medicine.</td></tr>
<tr><td>Full citation

Payne, B. A., Hutcheon, J. A., Dunsmuir, D., Cloete, G., Dumont, G., Hall, D., Lim, J., Magee, L. A., Sikandar, R., Qureshi, R., van Papendorp, E., Mark Ansermino, J., von Dadelszen, P., Assessing the Incremental Value of Blood Oxygen</td><td>Sample size

N= 852

Characteristics
<table><tr><th></th><th>Pakistan cohort (n=617)</th><th>SA cohort (n=235)</th></tr><tr><td>Maternal age (median, IQR)</td><td>29 (26-33)</td><td>27 (23-33)</td></tr></table></td><td>Prognostic tool/test

miniPIERS model and oxygen saturation, 25% predicted probability

Outcome(s)

PIERS composite (within 48 hours of admission=. Outcomes included: maternal mortality</td><td>Sample selection

Women meeting inclusion criteria were recruited from participating centres in Pakistan and South Africa.

Data collection</td><td>Prognostic accuracy (sensitivity, specificity)
<table><tr><th>Predicted probability (cut off)</th><th>Sensitivity (95% CI)</th><th>Specificity (95%CI)</th><th>LR+ (95% CI)</th><th>LR- (95% CI)</th></tr><tr><td>15%</td><td>68.1 (58.8-76.1)</td><td>77.9 (74.7-80.8)</td><td>3.1 (2.6-3.7)</td><td>0.4 (0.4-0.69</td></tr><tr><td>25%</td><td>49.6 (40.3-58.8)</td><td>91.5 (89.2-93.4)</td><td>5.9 (4.3-7.9)</td><td>0.6 (0.5-0.7)</td></tr></table></td><td>Limitations

The quality of this study was assessed using the CASP tool for clinical prediction rule (CPR).
A. Are the results valid?
1 Is the CPR clearly defined? Yes
2 The population from</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Saturation (SpO2) in the miniPIERS (Pre-eclampsia Integrated Estimate of RiSk) Risk Prediction Model, Journal of Obstetrics and Gynaecology Canada, 37, 16-24, 2015

Ref Id

803790

Country/ies where the study was carried out

Canada

Aim of the study

To examine the incremental value of blood oxygen saturation as a predictor in the miniPIERS clinical prediction model within 48 hours of admission

Study dates

January 2011-March 2012 (recruitment in Pakistan); November 2012 -</td>
<td>
<table>
<tr><td>GA at delivery (median, IQR)</td><td>37.2 (35.4-38.2)</td><td>34.6 (30-37.9)</td></tr>
<tr><td>Multiple pregnancy (n,%)</td><td>13 (2.1)</td><td>1 (0.4)</td></tr>
<tr><td>Parity ≥1</td><td>350 (51.9)</td><td>126 (53.6)</td></tr>
<tr><td>Pre-eclampsia[a] (n,%)</td><td>343 (55.6)</td><td>173 (73.6)</td></tr>
<tr><td>Other HDP (n,%)</td><td>274 (44.4)</td><td>62 (26.4)</td></tr>
<tr><td>sBP (median, IQR), mmHg</td><td>150 (140-160)</td><td>146 (140-160)</td></tr>
<tr><td>dBP (median, IQR), mmHg</td><td>100 (90-110)</td><td>69 (90-101)</td></tr>
</table>
[a]sBP/dBP ≥140/90 with proteinuria ≥2+ on a dipstick test

Inclusion criteria

Women with new (onset after 20 weeks gestation) or chronic hypertension (sBP/dBP ≥140/90) on at least 2 occasions between 4 and 24 h apart after 20 weeks gestation with or without proteinuria (≥2+ on a dipstick test) or other conditions.
</td>
<td>or one or more serious central nervous system, cardiorespiratory, renal, haematological, or hepatic morbidity</td>
<td>Data were collected prospectively during inpatient stays, except for Pakistan, where it was collected from medical records. POM application was used for data collection.

Data analysis

The miniPIERS equation was used as the linear predictor variable. A 25% predicted probability was used to define thise at high risk, based on the optimal threshold identified. AUC ROC was used to discriminate the predicted ability of oxygen saturation to</td>
<td>
<table>
<tr><td>35%</td><td>39.5 (30.8-48.9)</td><td>96.3 (94.6-97.5)</td><td>10.7 (7.0-16.5)</td><td>0.6 (0.5-0.7)</td></tr>
</table>
Data above are reported by converting the risk estimates into dichotomous data, i.e. the LR for the 15% category treats 15% as the cut-off for a positive test. At this cut-off, a positive test result gives a LR of 3.1, and a negative test result gives a LR of 0.4.
Likelihood ratios were also calculated by the NGA using the method of Deeks and Altman 2004 from raw data reported in the article, with 95% CI calculated using https://www.medcalc.org/calc/relative_risk.php:
<table>
<tr><th>Risk category</th><th>Number with outcome</th><th>Number without outcome</th><th>Likelihood ratio</th><th>95% CI</th></tr>
<tr><td><25%</td><td>80</td><td>705</td><td>(80/119)/(705/733) = 0.70</td><td>0.61 to 0.79</td></tr>
<tr><td>≥25%</td><td>39</td><td>28</td><td>(39/119)/(28/733) = 8.58</td><td>5.50 to 13.39</td></tr>
<tr><td>Total</td><td>119</td><td>733</td><td></td><td></td></tr>
</table>
These data refer to the LR obtained when an individual is given each risk category result, i.e. when an individual is given a risk in the ≥25% category, her LR for disease is 8.58

Model calibration

Not reported

Tool discrimination

AUC ROC (95% CI)
Oxygen saturation alone 0.72 (0.68-0.77)
Oxygen saturation adjusted 0.81 (0.76-0.85)
AUC ROC (95% CI) - Sensitivity analyses -using non cardiorespiratory outcomes
</td>
<td>which the rule was derived included an appropriate spectrum of patients? Yes
3 Was the rule validated in a different group of patients? Yes
4 Were the predictor variables and the outcome evaluated in a blinded fashion? Uncle ar (no details regarding sampling have been provided)
5 Were the predictor variables and the outcome evaluated in the whole sample selected initially? Yes
6 Are the statistical methods used to construct and validate the rule clearly described? Yes
B. What are the results?
7 Can the performance of the rule be</td>
</tr>
</table>

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
December 2013 (recruitment in South Africa) **Source of funding** Grand Challenge Canada; University of British Columbia PRE-EMPT initiative; Bill & Melinda Gates Foundation.	**Exclusion criteria** Not reported		differentiate women at risk of developing adverse outcomes. The association between oxygen saturation and the composite maternal outcome was done using logistic regression.	0.69 (0.63-0.74) - unadjusted 0.75 (0.69-0.81) - adjusted using miniPIERS outcomes	calculated? No (TP,FP,TN,FN or total % of women with AE at each predicted probability have not been reported) 8 How precise was the estimate of the treatment effect? The rule was recalibrated by fitting to 2 variables C. Will the results help locally? Are the results applicable to the scenario? 9 Would the prediction rule be reliable and the results interpretable if used for your patient? No, the study was conducted in a low/middle income setting 10 Is the rule acceptable in your case? Yes 11 Would the results of the rule modify your decision about

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
					the management of the patient or the information you can give to him/her? Yes **Indirectness** 39.4% of the population did not present with PE **Other information** PVD is a consultant of Alere International (for work not related to the manuscript); JMA and GD are co-founders of LGT medical and hold <5% of equity for the company.
Full citation Thangaratinam, S., Allotey, J., Marlin, N., Dodds, J., Cheong-See, F., von Dadelszen, P.,	**Sample size** For the validation component: N=634 in the PIERS dataset and N=216 in the PETRA dataset.	**Prognostic tool/test** Prediction of complications in early-onset pre-eclampsia (PREP)	**Sample selection** For the validation component, this study used data	**Prognostic accuracy (sensitivity, specificity)** **Risk stratification table, PIERS cohort*** **48 hours** | **7 days**	**Limitations** **The quality of this study was assessed using the CASP tool for clinical**

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Ganzevoort, W., Akkermans, J., Kerry, S., Mol, B. W., Moons, K. G. M., Riley, R. D., Khan, K. S., Prediction of complications in early-onset pre-eclampsia (PREP): Development and external multinational validation of prognostic models, BMC Medicine, 15, 68, 2017

Ref Id

776782

Country/ies where the study was carried out

UK

Aim of the study

To provide external validation of the PREP model within 48 hours and 7 days of admission

Study dates</td>
<td>Characteristics
<table>
<tr><th></th><th>PIERS (n=634)</th><th>PETRA (n=216)</th></tr>
<tr><td>Age, years (median, range)</td><td>31.2 (6.3)</td><td>30 (5)</td></tr>
<tr><td>Gestational age at diagnosis (mean, SD)</td><td>30.2 (3)</td><td>29.4 (2.6)*</td></tr>
<tr><td>New-onset PE (n,%)</td><td>51.9 (82)</td><td>96 (44)*,d</td></tr>
<tr><td>Superimposed PE (n,%)</td><td>95 (15)</td><td>-</td></tr>
<tr><td>HELLP (n,%)</td><td>22 (3)</td><td>54 (25)*,e</td></tr>
<tr><td>Eclampsia (n,%)</td><td>-</td><td>5 (2.3)*,f</td></tr>
<tr><td>Fetal growth restriction/pregnancy induced hypertension (n,%)</td><td>-</td><td>125 (58)*,g</td></tr>
</table>
*Some women matched with more than 1 diagnostic criteria
[a]sBP/dBP ≥140/90 mmHg (at least 1 component, measured ≥ 4h apart, after 20 w GA) with either proteinuria (≥0.3g per day by 24h collection or ≥ 30mg mmol as measured by protein:creatinine ratio) or</td>
<td>Outcome(s)

PIERS composite. Outcomes included: maternal mortality or one or more serious central nervous system, cardiorespiratory, renal, haematological, or hepatic morbidity</td>
<td>from 2 datasets: PIERS (Pre-eclampsia integrated estimate of risk) and PETRA (pre-eclampsia trial Amsterdam)

Data collection

Data were collected retrospectively. Missing predictor values were dealt with by using the ICE package in Stata with five imputations.

Data analysis

Calibration was assessed using calibration plots and estimating the calibration slope. Discrimination was assessed with the c-statistic from</td>
<td>
<table>
<tr><td>5/59</td><td>11/59</td></tr>
<tr><td>8/70</td><td>27/70</td></tr>
<tr><td>12/123</td><td>74/123</td></tr>
<tr><td>47/87</td><td>75/87</td></tr>
</table>
*Calculated by the NGA using the observed survival probability and predicted survival probability reported in the study

Model calibration

Observed and expected probability of survival using the PREP-S model at different time points in the PIERS cohort
<table>
<tr><th>Risk stratification</th><th>No of women</th><th>Time point</th><th>Observed (O)</th><th>Expected (E)</th><th>O:E ratio</th></tr>
<tr><td>≤15th</td><td>59</td><td>48 hours</td><td>0.91</td><td>0.95</td><td>0.96</td></tr>
<tr><td></td><td></td><td>1 week</td><td>0.81</td><td>0.79</td><td>1.0</td></tr>
<tr><td>>15th-50th</td><td>70</td><td>48 hours</td><td>0.88</td><td>0.89</td><td>1.0</td></tr>
<tr><td></td><td></td><td>1 week</td><td>0.62</td><td>0.60</td><td>1.0</td></tr>
<tr><td>>50th-85th</td><td>123</td><td>48 hours</td><td>0.90</td><td>0.70</td><td>1.3</td></tr>
<tr><td></td><td></td><td>1 week</td><td>0.40</td><td>0.23</td><td>1.7</td></tr>
</table>
</td>
<td>prediction rule (CPR).
A. Are the results valid?
1 Is the CPR clearly defined? Yes
2 The population from which the rule was derived included an appropriate spectrum of patients? Yes
3 Was the rule validated in a different group of patients? Yes
4 Were the predictor variables and the outcome evaluated in a blinded fashion? Can't tell
5 Were the predictor variables and the outcome evaluated in the whole sample selected initially? Yes, although a reduced version was developed since not all the predictor variables were</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Not reported

Source of funding

National Institute for Health Research - Health Technology Assessment programme</td>
<td>hyperuricaemia (upper limit greater than normal for non-pregnant women)
[b]rapidly increasing requirements for antihypertensive drugs, sBP> 170 mmHg or dBP> 120 mmHg, new proteinuria or new hyperuricaemia
[c]Definition not reported
[d]dBP ≥110 mmHg in combination with proteinuria (≥0.3 g/24h)
[e]platelet count <100x10^9/L and AST ≥ 70U/L and/or LDH ≥ 600U/L
[f]convulsions in pregnancy in the absence of epilepsy
[g]abdominal circumference<5th percentile for GA or estimated fetal weight<10th percentile for GA and dBP≥90 mmHg

Inclusion criteria

PIERS cohort: Women with either a)suspected or confirmed pre-eclampsia after 20 weeks of gestational age defined as BP ≥ 140/90 (at least 1 component; measured 2 at least 4 hours apart) and either proteinuria or hyperuricaemia; b) HELLP syndrome, even in the absence of hypertension or proteinuria; c) superimposed pre-eclampsia.
PETRA cohort: HELLP syndrome; fetal growth restriction and pregnancy induced hypertension; severe pre-eclampsia or eclampsia, singleton pregnancies.

Exclusion criteria

Women in whom the outcome took place before the assessment of predictors; women in whom there was insufficient time to obtain the informed consent</td>
<td></td>
<td>the PREP-L model.
The ratio of observed and predicted probability of outcomes was assessed at 48 hours, 1 week and overall.
For missing data, the ICE package in STATA was used.
The study reported the external validation of 2 prediction models: PREP-S and PREP-L. The PREP-S is a survival model that predicts the time to adverse outcomes before 34 weeks of gestational age, whereas the PREP-L is a model to predict the overall risk of maternal complications by discharge only. For</td>
<td>
<table>
<tr><td>>85th</td><td>87</td><td>48 hours</td><td>0.46</td><td>0.28</td><td>1.6</td></tr>
<tr><td></td><td></td><td>1 week</td><td>0.14</td><td>0.02</td><td>7.0</td></tr>
</table>
Comparison of predicted versus observed risk of outcome for reduced PREP-L model (data obtained from Thangaratinam S, Allotey J, Marlin N, Mol BW, Von Dadelszen P, Ganzevoort W, et al. Development and validation of Prediction models for Risks of complications in Early-onset Pre-eclampsia (PREP): a prospective cohort study. Health Technol Assess 2017;21 (18).)
<table>
<tr><th>Risk stratification</th><th>PIERS cohort
observed/predicted (%)</th><th>PETRA cohort
observed/predicted (%)</th></tr>
<tr><td>≤10th</td><td>0/0</td><td>0/0</td></tr>
<tr><td>10-20th</td><td>0/3 (0%)</td><td>0/0</td></tr>
<tr><td>20-30th</td><td>6/20 (30%)</td><td>2/4 (50%)</td></tr>
<tr><td>30-40th</td><td>8/24 (33%)</td><td>1/1 (100%)</td></tr>
<tr><td>40-50th</td><td>16/33 (48%)</td><td>4/11 (36%)</td></tr>
<tr><td>50-60th</td><td>21/34 (62%)</td><td>8/13 (62%)</td></tr>
<tr><td>60-70th</td><td>19/38 (50%)</td><td>18/22 (82%)</td></tr>
<tr><td>70-80th</td><td>42/58 (72%)</td><td>25/30 (83%)</td></tr>
<tr><td>80-90th</td><td>59/72 (82%)</td><td>70/74 (95%)</td></tr>
</table>
</td>
<td>available in the PREP and PETRA datasets
6 Are the statistical methods used to construct and validate the rule clearly described? Yes
B. What are the results?
7 Can the performance of the rule be calculated? No
8 How precise was the estimate of the treatment effect? The rule was simplified because not all the predictor variables were available from the PREP and PETRA datasets
C. Will the results help locally? Are the results applicable to the scenario?
9 Would the prediction rule be reliable and the results interpretable if used for your</td>
</tr>
</table>

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
			validating the PREP-S, only data from the PIERS was used as the PETRA dataset did not have time to event outcomes. Since not all the predictors from the PREP model were available in the PETRA and PIERS dataset, a slightly reduced model was used to externally validate the tool (rPREP). To develop this, coefficients were re-estimated and then adjusted for optimism. The reduced version of the PREP-S did not have serum urea and deep tendon reflex and the reduced version of	**90-100th** 147/155 (95%) 52/56 (93%) **Tool discrimination** **<u>PREP-S model performance</u>** **PIERS cohort** *C-statistic (95% CI)* At 48 hours: 0.75 (0.69 to 0.81) At 1 week: 0.72 (0.68 to 0.76) Overall: 0.71 (0.67 to 0.75) *Calibration slope (95% CI)* At 48 hours: 0.80 (0.62 to 0.99) At 1 week: 0.75 (0.61 to 0.89) Overall: 0.67 (0.56 to 0.79) **<u>PREP- L model performance</u>** **PIERS cohort** *C-statistic (95% CI)* = 0.81 (0.77-0.85) *Calibration slope (95% CI)*= 0.93 (0.72 - 1.13) **PETRA cohort** *AUC (95% CI)*= 0.75 (0.64-0.86) *Calibration slope (95% CI)* = 0.90 (0.48 - 1.32)	patient? Yes (the populations from which the data was obtained were high income settings) 10 Is the rule acceptable in your case? Yes 11 Would the results of the rule modify your decision about the management of the patient or the information you can give to him/her? Yes **Indirectness** The model was modified for the validation, as not all predictor variables were included in the validation datasets. 27% of women in the PETRA dataset did not present with pre-eclampsia No indirectness in the PIERS cohort

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td>PREP-L did not have serum urea.</td><td></td><td>Other information</td></tr>
<tr><td>Full citation

Thangaratinam, S., Koopmans, C. M., Iyengar, S., Zamora, J., Ismail, K. M. K., Mol, B. W. J., Khan, K. S., Accuracy of liver function tests for predicting adverse maternal and fetal outcomes in women with preeclampsia: A systematic review, Acta Obstetricia et Gynecologica Scandinavica, 90, 574-585, 2011

Ref Id

804009

Country/ies where the study was carried out

UK

Aim of the study

To assess the accuracy of liver</td><td>Sample size

Median sample size was 230 (range 64 - 737)

Characteristics

There were 13 included studies, assessing maternal and fetal outcomes

Inclusion criteria

Test accuracy studies; including women with pre-eclampsia in which liver function tests (AST, ALT, LDH, GGT, ALP) were carried out, reporting composite maternal or fetal outcomes.

Exclusion criteria

Case reports</td><td>Prognostic tool/test

Liver function tests (AST,ALT,LDH,GGT,ALP)

Outcome(s)

Adverse maternal outcomes
Maternal complications
Adverse fetal outcomes</td><td>Sample selection

A prospective protocol was carried out, MEDLINE, EMBASE, and the Cochrane Library were searched for relevant citations. Corresponding authors were contacted to retrieve relevant data. Language restrictions were not applied

Data collection

The electronic searches were screened and the studies likely to meet the predefined criteria were</td><td>Prognostic accuracy (sensitivity, specificity)

Adverse maternal outcome
<table>
<tr><th>Study</th><th>Liver test</th><th>Cut-off</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th><th>LR+ (95% CI)</th><th>LR- (95% CI)</th></tr>
<tr><td>Martin 1999</td><td>AST</td><td>150</td><td>0.70 (0.63-0.77)</td><td>0.48 (0.43-0.53)</td><td>1.4 (1.2 - 1.5)</td><td>0.62 (0.48-0.8)</td></tr>
<tr><td>Martin 1999</td><td>LDH</td><td>1400</td><td>0.72 (0.65-0.79)</td><td>0.49 (0.44-0.54)</td><td>1.4 (1.2-1.6)</td><td>0.57 (0.44-0.74)</td></tr>
<tr><td>Martin 1999</td><td>ALT</td><td>100</td><td>0.66 (0.59-0.73)</td><td>0.47 (0.42-0.52)</td><td>1.2 (1.1-1.4)</td><td>0.72 (0.57-0.91)</td></tr>
<tr><td>Girling 1997</td><td>AST/ALT/Bil/GGT</td><td>30/32/14/41</td><td>0.93 (0.52-1)</td><td>0.57 (0.37-0.76)</td><td>2.2 (1.4-3.5)</td><td>0.12 (0.01-1.7)</td></tr>
<tr><td>Menzies 2007</td><td>ALT/AST</td><td>40/55</td><td>0.33 (0.22-0.45)</td><td>0.80 (0.77-0.84)</td><td>1.7 (1.2-2.4)</td><td>0.83 (0.71-0.99)</td></tr>
</table></td><td>Limitations

Systematic review assessed using AMSTAR checklist. Total score: 11/16

Indirectness

No indirectness

Other information

Only studies reporting on composite adverse maternal outcomes have been extracted</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>function tests in women with pre-eclampsia for the prediction of maternal or fetal complications

Study dates

Not reported

Source of funding

"No specific funding"</td>
<td></td>
<td></td>
<td>selected by 2 independent reviewers; final exclusion and inclusion was done by the reviewers; the studies meeting the inclusion criteria were selected and information regarding study characteristics, quality, and accuracy data were extracted.

Data analysis

A 2x2 table was constructed for each of the studies identified</td>
<td>
<table>
<tr><td>Menzies 2007</td><td>LDH</td><td>600</td><td>0.62 (0.49-0.74)</td><td>0.60 (0.56-0.64)</td><td>1.6(1.3-1.9)</td><td>0.63 (0.46-0.86)</td></tr>
</table>
Adverse fetal outcome
<table>
<tr><th>Study</th><th>Liver test</th><th>Cut-off</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th><th>LR+ (95% CI)</th><th>LR- (95% CI)</th></tr>
<tr><td>Girling 1997</td><td>AST/ALT/Bi/GGT</td><td>30/32/14/41</td><td>0.86 (0.23-1)</td><td>0.5 (0.32-0.68)</td><td>1 (0.99-3)</td><td>0.27 (0.02-3.8)</td></tr>
</table>
Model calibration

Not reported

Tool discrimination

Not reported
</td>
<td></td>
</tr>
<tr>
<td>Full citation

Ukah, U. Vivian, Hutcheon, Jennifer A., Payne, Beth, Haslam, Matthew D., Vatish, Manu, Ansermino, J. Mark, Brown,</td>
<td>Sample size

17 studies were included in total, although for the purpose of this review, 2 studies have been included (those including women with suspected or confirmed pre-eclampsia and reporting on maternal adverse outcomes)</td>
<td>Prognostic tool/test

Placental growth factor

Outcome(s)</td>
<td>Sample selection

A electronic search was performed in MEDLINE, Embase, CINAHL until January 2017.</td>
<td>Prognostic accuracy (sensitivity, specificity)

Composite maternal outcomes
<table>
<tr><th>Author, year</th><th>Test/cut-off for sFlt-1/PLGF ratio</th><th>Total N and outcome (%)</th><th>Sensitivity (95%CI)</th><th>Specificity (95% CI)</th><th>LR+ (95% CI)</th><th>LR- (95% CI)</th></tr>
</table>
</td>
<td>Limitations

AMSTAR overall quality score: 13/16

Indirectness

No indirectness</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Helen, Magee, Laura A., von Dadelszen, Peter, Placental Growth Factor as a Prognostic Tool in Women With Hypertensive Disorders of Pregnancy: A Systematic Review, Hypertension (Dallas, Tex. : 1979), 70, 1228-1237, 2017

Ref Id

804045

Country/ies where the study was carried out

Canada

Aim of the study

To systematically review the evidence examining the ability of the placental growth factor (both independently and combined with other factors) to predict maternal and fetal complications</td>
<td>Characteristics
<table>
<tr><th>Type of PE</th><th>Maternal characteristics</th><th>Outcomes</th></tr>
<tr><td colspan="3">Leaños-Miranda 2013
Prospective cohort, Mexico</td></tr>
<tr><td>PE</td><td>GA at presentation: 32
Mean age: 28.3
Primigravida: 43.5%</td><td>Composite maternal outcome
Composite fetal/ neonatal outcomes</td></tr>
<tr><td colspan="3">Palomaki 2015
Prospective cohort, USA</td></tr>
<tr><td>Suspected preterm PE (GA ≤34 W)</td><td>Mean GA:30</td><td>Composite maternal outcomes</td></tr>
</table>
Inclusion criteria

Studies in which PlGF was used either as an independent or combined marker with women with hypertensive disorders of pregnancy*. Studies should perform at least one predictive performance measure or sufficient data for this to be calculated

Exclusion criteria

Not reported</td>
<td>PIERS composite. Outcomes included: maternal mortality or one or more serious central nervous system, cardiorespiratory, renal, haematological, or hepatic morbidity</td>
<td>Google scholar and grey literature sources were also searched. Titles and abstracts were screened by 2 reviewers.

Data collection

Study details were extracted and, as part of the predictive performance measures, study quality was assessed with QUIPS (Quality in Prognostic Studies Checklist).

Data analysis

2x2 tables were constructed for each of the outcomes reported, and LRs were used for interpreting</td>
<td>
<table>
<tr><td>Leaños-Miranda 2013</td><td>Serum sFlt-PlGF ratio ≥ 871</td><td>501 (9.5)</td><td>52.1 (37.4-66.5)</td><td>77.9 (73.8-81.6)</td><td>2.36 (1.71-3.26)</td><td>0.61 (0.46 - 0.83)</td></tr>
<tr><td>Palomaki 2015</td><td>sFlt-1/PlGF ratio>85</td><td>237 (8.9)</td><td>61.9 (38.7-81.0)</td><td>69.4 (62.8-75.4)</td><td>2.0 (1.4-3.0)</td><td>0.5 (0.3-1.0)</td></tr>
</table>
Model calibration

Not reported

Tool discrimination

Not reported</td>
<td>Other information

*Please note that for the purpose of this review, only studies including women with PE (with confirmed and suspected) have been included</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td>resulting from hypertensive disorder of pregnancy

Study dates

Studies published before 30th of January 2017

Source of funding

Canadian Institutes of Health Research (CIHR)</td><td></td><td></td><td>the usefulness of a given test.</td><td></td><td></td></tr>
<tr><td>Full citation

Ukah, U. V., Payne, B., Lee, T., Magee, L. A., Von Dadelszen, P., External Validation of the fullPIERS Model for Predicting Adverse Maternal Outcomes in Pregnancy Hypertension in Low- and Middle-Income Countries, Hypertension, 69, 705-711, 2017</td><td>Sample size

N=757 (miniPIERS cohort)

Characteristics
<table><tr><td></td><td>miniPIERS cohort (n=757)</td></tr><tr><td>Age, years (median, IQR)</td><td>28 (24-33)</td></tr><tr><td>No. with pre-eclampsia[a] n (%)</td><td>568 (75.03%)</td></tr></table></td><td>Prognostic tool/test

fullPIERS (Preeclampsia Integrated Estimate of Risk). Factors included in the model: gestational age, respiratory pulse oximetry, platelets, creatinine, hepatic aspartate transaminase

Outcome(s)</td><td>Sample selection

This study used data from the miniPIERS cohort, a multi-country prospective study for developing a tool to predict adverse outcomes during pregnancy in low and middle income countries.</td><td>Prognostic accuracy (sensitivity, specificity)

With a cut-off of 30%
Sensitivity 78 (95% CI NR)
Specificity 0.66 (95% CI NR)

Model calibration

Risk stratification of women with and without adverse outcomes and risk stratification at varying predicted probability within 48 hours<table><tr><th>Predicted probability</th><th>Total no of women</th><th>Total no of observed adverse outcomes</th><th>LR +(95% CI)</th></tr></table></td><td>Limitations

The quality of this study was assessed using the CASP tool for clinical prediction rule (CPR).
A. Are the results valid?
1 Is the CPR clearly defined? Yes
2 The population from which the rule was derived included an</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Ref Id

804075

Country/ies where the study was carried out

Canada

Aim of the study

To provide external validation of the fullPIERS model within 48 hours of admission with data from low and middle income countries

Study dates

July 2008 to March 2012

Source of funding

Canadian Institutes of Health Research (CIHR)</td>
<td>
<table>
<tr><td>Other HDP (type not specified) n (%)</td><td>189 (24.97%)</td></tr>
<tr><td>Gestational age at eligibility, weeks (median, IQR)</td><td>36.6 (33.1-38.1)</td></tr>
<tr><td>Multiple pregnancy n (%)</td><td>18 (2.4%)</td></tr>
<tr><td>Parity N (%)</td><td>406 (53.6%)</td></tr>
<tr><td>sBP ≥ XY mmHg at entry (median, IQR)</td><td>160 (150 - 170)</td></tr>
<tr><td>dBP ≥ XY mmHg at entry (median, IQR)</td><td>100 (100-110)</td></tr>
</table>
[a] severe pre-eclampsia: BP≥ 140/90 (at least one component, twice, measured more than 4 hours apart at or after 20 weeks GA) without significant proteinuria

Inclusion criteria

Women with any hypertensive disorder of pregnancy.

Exclusion criteria

Having experienced any adverse outcome (i.e. hepatic dysfunction, hepatic hematoma or rupture, stroke, cortical blindness.) before</td>
<td>PIERS composite. Outcomes included: maternal mortality or one or more serious central nervous system, cardiorespiratory, renal, haematological, or hepatic morbidity</td>
<td>Women from Fiji, Uganda, South Africa, Brazil and Pakistan were enrolled.

Data collection

Data was collected prospectively and entered into a standardised form. The variable oxygen saturation was often irretrievable, in which cases the value of 97% was imputed (this was also done in the internal validation study by von Dadelszen). Only women with complete predictor data were included. Sensitivity analyses were conducted to ensure that there were not</td>
<td>
<table>
<tr><td>0-0.99%</td><td>30 (4%)</td><td>2 (6.7%)</td><td>-</td></tr>
<tr><td>1.0-2.4%</td><td>107 (14.1%)</td><td>3 (2.8%)</td><td>0.17 (0.06-0.53)</td></tr>
<tr><td>2.5-4.9%</td><td>140(18.5%)</td><td>12 (8.6%)</td><td>0.56 (0.32-0.97)</td></tr>
<tr><td>5.0-9.9%</td><td>178 (23.5%)</td><td>8 (4.5%)</td><td>0.28 (0.14-0.55)</td></tr>
<tr><td>10.0-29.9%</td><td>204(26.9%)</td><td>35 (32.1%)</td><td>1.23 (0.91-1.67)</td></tr>
<tr><td>≥0.30</td><td>98 (12.1%)</td><td>49 (50%)</td><td>5.9 (4.23-8.35)</td></tr>
</table>
Tool discrimination

Calibration slope = 0.67 (95% CI nor reported)
AUC ROC (95% CI)= 0.77 (0.72 - 0.82)</td>
<td>appropriate spectrum of patients? Yes
3 Was the rule validated in a different group of patients? Yes
4 Were the predictor variables and the outcome evaluated in a blinded fashion? Yes (the author who collected the data was not aware of the model parameters)
5 Were the predictor variables and the outcome evaluated in the whole sample selected initially? Yes
6 Are the statistical methods used to construct and validate the rule clearly described? Yes
B. What are the results?
7 Can the performance of</td>
</tr>
</table>

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
	hospital admission or having been admitted in spontaneous labour.		any bias because of missing data. **Data analysis** Discrimination was calculated using the area under the AUC ROC. Calibration was assessed by estimating the slope in a calibration plot of predicted versus observed outcomes.		the rule be calculated? Yes 8 How precise was the estimate of the treatment effect? The authors of the study did not try to refine/simplify the tool C. Will the results help locally? Are the results applicable to the scenario? 9 Would the prediction rule be reliable and the results interpretable if used for your patient? No (study was developed in low and middle income countries, a different setting than the UK) 10 Is the rule acceptable in your case? Can´t tell 11 Would the results of the rule modify your decision about the management of

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>the patient or the information you can give to him/her? Can´t tell

Indirectness

Sample obtained from low and middle income settings (Fiji, Uganda, South Africa, Brazil)
No conflicts of interest have been declared

Other information</td></tr>
<tr><td>Full citation

Ukah, U. V., Payne, B., Hutcheon, J. A., Ansermino, J. M., Ganzevoort, W., Thangaratinam, S., Magee, L. A., von Dadelszen, P., Assessment of the fullPIERS Risk Prediction Model in Women With Early-Onset Preeclampsia,</td><td>Sample size

N=1388 (n=218 in the BCW cohort; N=216 in the PETRA cohort; and N= 954 in the PREP cohort)

Characteristics
<table><tr><th></th><th>BCW cohort (n=218)</th><th>PETRA cohort (N=216)</th><th>PREP cohort (n=954)</th></tr></table></td><td>Prognostic tool/test

fullPIERS (Pre-eclampsia Integrated Estimate of Risk). Factors included in the model: gestational age, respiratory pulse oximetry, platelets, creatinine, hepatic aspartate transaminase</td><td>Sample selection

The data from this study was obtained from 3 pre-existing cohorts: BCW cohort; PETRA cohort; PREP cohort.
Sample size calculations were performed by</td><td>Prognostic accuracy (sensitivity, specificity)

<u>PETRA, PREP and BCW cohorts combined</u>
<table><tr><th>Time since admission</th><th>Total N with outcomes</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th></tr><tr><td>48 hours</td><td>101</td><td>0.57 (95% CI NR)</td><td>0.94 (95% CI NR)</td></tr><tr><td>7 days</td><td>179</td><td>0.68 (95% CI NR)</td><td>0.70 (95% CI NR)</td></tr></table></td><td>Limitations

The quality of this study was assessed using the CASP tool for clinical prediction rule (CPR).
A. Are the results valid?
1 Is the CPR clearly defined?
yes</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Hypertension, 71, 659-665, 2018

Ref Id

867315

Country/ies where the study was carried out

Canada

Aim of the study

To externally validate the fullPIERS model within 48 hours and 7 days of admission using data from 3 pre-existing cohorts of women

Study dates

Data was collected at different time points depending on the cohort. All data was collected between the years 2000 and 2014

Source of funding</td>
<td>
<table>
<tr><td>Maternal age at estimated day of delivery (median, IQR)</td><td>35 (30-39)</td><td>30 (27-34)</td><td>30 (26-35)</td></tr>
<tr><td>No. with severe pre-eclampsia [a] n (%)</td><td>191 (87.6%)</td><td>123 (56.9%)</td><td>940 (98.5%)</td></tr>
<tr><td>HELLP syndrome [b] n (%)</td><td>27 (12.4%)</td><td>93 (43%)</td><td>10 (1%)</td></tr>
<tr><td>Multiple pregnancy</td><td>40 (18.4%)</td><td>-</td><td>84 (8.8%)</td></tr>
<tr><td>Gestational age at eligibility (median weeks, IQR)</td><td>31 (28.4-32.7)</td><td>30 (27.4-31.4)</td><td>31.4 (28.7-32.7)</td></tr>
<tr><td>Median sBP (IQR), mmHg</td><td>161 (150-173)</td><td>160 (145-170)</td><td>155 (145-169)</td></tr>
<tr><td>Median dBP</td><td>100 (94-106)</td><td>105 (95-110)</td><td>99 (32-105)</td></tr>
</table>
</td>
<td>Outcome(s)

PIERS composite. Outcomes included: maternal mortality or one or more serious central nervous system, cardiorespiratory, renal, haematological, or hepatic morbidity</td>
<td>simulations studies. It was concluded that validation studies should at minimum have 100 events to have 80% power at the 5% significance level.

Data collection

Data from the PETRA and PREP were collected prospectively whereas data from the BCW were collected retrospectively. Data collection took between 3 and 4 years in the 3 cohorts and was obtained between the years 2000 and 2014. The variable oxygen saturation was often irretrievable, in which cases</td>
<td><u>Sensitivity analyses (prognostic accuracy after exclusion of the PETRA cohort)</u>
<table>
<tr><th>Time since admission</th><th>Total N with outcomes</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th></tr>
<tr><td>48 hours</td><td>69</td><td>0.68 (95% CI NR)</td><td>0.72 (95% CI NR)</td></tr>
<tr><td>7 days</td><td>117</td><td>0.59 (95% CI NR)</td><td>0.74 (95% CI NR)</td></tr>
</table>
Model calibration

<u>Risk stratification table within 48 hours</u>
<table>
<tr><th>Predicted probability</th><th>Total no of women</th><th>Total no of women with adverse outcomes</th><th>LR (95% CI)</th></tr>
<tr><td>0.00-0.0099</td><td>594 (30.5%)</td><td>14 (1.7%)</td><td>-</td></tr>
<tr><td>0.010-0.024</td><td>409 (33.1%)</td><td>17 (2.8%)</td><td>0.55 (0.36-0.86)</td></tr>
<tr><td>0.025-0.049</td><td>158 (19.1%)</td><td>8 (4.5%)</td><td>0.68 (0.34-1.34)</td></tr>
<tr><td>0.050-0.099</td><td>91 (7.8%)</td><td>6 (13.7%)</td><td>0.90 (0.40-2.01)</td></tr>
<tr><td>0.010-0.29</td><td>68 (5.1%)</td><td>12 (15.6%)</td><td>2.73 (1.51-4.92)</td></tr>
</table>
</td>
<td>2 The population from which the rule was derived included an appropriate spectrum of patients? yes
3 Was the rule validated in a different group of patients? yes
4 Were the predictor variables and the outcome evaluated in a blinded fashion? unclear BCW and PREP cohort; yes for PETRA dataset
5 Were the predictor variables and the outcome evaluated in the whole sample selected initially? yes
6 Are the statistical methods used to construct and validate the rule clearly described? yes
B. What are the results?</td>
</tr>
</table>

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
Canadian Institutes of Health Research	(IQR), mmHg [a,b]See inclusion criteria **Inclusion criteria** BCW and the PREP study included only women with pre-eclampsia (a) sBP/dBP ≥140/90 mmHg (at least 1 component, measured ≥ 4h apart, after 20 with a) proteinuria (≥0.3g per day by 24h collection or ≥ 30mg mmol as measured by protein:creatinine ratio) or hyperuricaemia, or b) HELLP syndrome, or c) superimposed PE (rapidly increasing requirements for antihypertensive drugs, sBP> 170 mmHg or dBP> 120 mmHg, new proteinuria or new hyperuricaemia). The PETRA study included women with severe pre-eclampsia (defined as dBP ≥110 mmHg), HELLP syndrome, gestational hypertension, and fetal growth restriction. All cohorts included women before 34 weeks of gestation. **Exclusion criteria** Not reported		the value of 97% was imputed (this procedure is in line with the validation study developed by von Dadelszen). **Data analysis** Data from the 3 cohorts was merged into a single dataset. Discrimination was calculated using the area under the curve (AUC) ROC. Calibration was calculate d by assessing the slope of the linear predictor. Sensitivity analyses excluding the PETRA cohort were undertaken to account for differences in the study design and	≥0.30 | 68 (4.4%) | 44 (54.5%) | 23.4 (14.83-36.79) **Tool discrimination** **<u>AUC within 48 hours of admission (individual datasets)</u>** **BCW (N= 218)** AUC ROC (95% CI) =0.72 (0.59-0.86) Calibration slope (95% CI) = 0.31 (0.21-0.41) **PETRA (N=216)** AUC ROC (95% CI)= 0.97 (0.94-0.99) Calibration slope (95% CI) = 1.69 (1.39-1.99) **PREP (N=695)** AUC ROC (95% CI) = 0.73 (0.64-0.81) Calibration slope (95% CI) = 0.74 (0.63-0.86) **Combined dataset** Calibration slope (95% CI) = 0.68 (0.86-0.79) **<u>AUC ROC combined dataset</u>** **AUC ROC within 48 h of admission** AUC ROC (95% CI) 0.80 (0.75 - 0.86) **AUC ROC within 7 days of admission** AUC ROC (95% CI) 0.74 (0.70-0.79) **<u>Sensitivity analyses (prognostic accuracy after exclusion of the PETRA cohort)</u>** **Within 48 h of admission** AUC ROC (95% CI) 0.74 (0.67-0.81) **Within 7 days of admission** AUC ROC (95% CI) 0.70 (0.65-0.75)	7 Can the performance of the rule be calculated? yes 8 How precise was the estimate of the treatment effect? In the study it is mentioned that "recalibration of the model was also performed to account for differences between the development and validation cohort" (page 3) C. Will the results help locally? Are the results applicable to the scenario? 9 Would the prediction rule be reliable and the results interpretable if used for your patient? Yes (UK, Canada and Dutch population) 10 Is the rule acceptable in your case? Yes 11 Would the results of the rule modify your

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
			definitions for PE in the PETRA cohort as compared to the BCW and PREP.		decision about the management of the patient or the information you can give to him/her? Yes **Indirectness** BCW cohort: 12.4% of women did not present with PE PETRA cohort: 43% of women did not present with PE PREP cohort: 1% of women did not present with PE **Other information** Note overlap with PETRA dataset (Thangaratinam 2017)
Full citation Waugh, Jason, Hooper, Richard, Lamb, Edmund, Robson, Stephen, Shennan, Andrew,	**Sample size** N=959 **Characteristics**	**Prognostic tool/test** Tests done in the urine sample:	**Sample selection** Women were identified through different	**Prognostic accuracy (sensitivity, specificity)** **Prognostic accuracy of the four index tests and the two 24-hour urine samples assessments to predict severe pre-eclampsia at pre-defined thresholds**	**Limitations** **Limitations assessed with the QUADAS-2 checklist**

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Milne, Fiona, Price, Christopher, Thangaratinam, Shakila, Berdunov, Vladislav, Bingham, Jenn, Spot protein-creatinine ratio and spot albumin-creatinine ratio in the assessment of pre-eclampsia: a diagnostic accuracy study with decision-analytic model-based economic evaluation and acceptability analysis, Health technology assessment (Winchester, England), 21, 1-90, 2017

Ref Id

776890

Country/ies where the study was carried out

UK

Aim of the study

To assess the ability of spot</td>
<td>
<table>
<tr><th></th><th>Women included in main analysis (n =959)</th></tr>
<tr><td>Age, years (median, IQR)</td><td>30 (26-34)</td></tr>
<tr><td>Gestational age (median)</td><td>37</td></tr>
<tr><td>Origin: UK (n, %)</td><td>706 (74)</td></tr>
<tr><td>Origin: Africa (n, %)</td><td>59 (6)</td></tr>
<tr><td>Origin: Europe (n, %)</td><td>88 (9)</td></tr>
<tr><td>Origin: other (n, %)</td><td>106 (11)</td></tr>
<tr><td>With severe PE[a]</td><td>417 (43)</td></tr>
<tr><td>Without severe PE</td><td>542(57)</td></tr>
<tr><td>sBP mmHg (median, IQR)</td><td>145 (140-152)</td></tr>
<tr><td>dBP mmHg (median, IQR)</td><td>94 (90-100)</td></tr>
</table>
[a]sBP/dBP ≥160/110 after 20 weeks' gestation and significant proteinuria (≥ 300 from 24 hour urine collection using the central lab BZC assay)
</td>
<td>

"(1) sPCR test (conducted at the local laboratory),
(2) sPCR test (conducted at the local laboratory using the benzethonium chloride (BZC) assay),
(3) sPCR test (conducted at the central laboratory using the pyrogallol red (PGR) assay),
(4) sACR test (conducted at the central laboratory using an automated chemistry analyser)" (page 24, para 6)

Outcome(s)

Adverse maternal and fetal
</td>
<td>hospital settings, across 37 UK trusts, including maternity units, delivery suites or the outpatient setting.Those with confirmed hypertension and trace of proteinuria were detected through antenatal care and invited to participate in the study by the midwife. The revised sample calculations estimated that the recruitment target should be of 1790 women. This figure was based on the prevalence of severe pre-eclampsia of the first 500 participants recruited, and under the assumption that 14%</td>
<td>
<table>
<tr><th></th><th>Threshold (mg/mmol)</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th><th>LR+ (95% CI)</th><th>LR- (95% CI)</th></tr>
<tr><td>Recruitment sample</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>sPCR (local lab)</td><td>30</td><td>85 (80-90)</td><td>40 (37-44)</td><td>1.43 (1.31-1.55)</td><td>0.36 (0.23-0.45)</td></tr>
<tr><td>sPCR (using the BZC assay)</td><td>30</td><td>84 (78-89)</td><td>43 (40-47)</td><td>1.48 (1.35-1.61)</td><td>0.37 (0.25-0.50)</td></tr>
<tr><td>sPCR (using the PGR assay)</td><td>30</td><td>85 (80-90)</td><td>39 (35-42)</td><td>1.39 (1.28-1.51)</td><td>0.38 (0.24-0.51)</td></tr>
<tr><td>sACR (central lab)</td><td>2</td><td>97 (93-99)</td><td>16 (14-19)</td><td>1.15 (1.11-1.20)</td><td>0.19 (0.04-0.35)</td></tr>
<tr><td>24-h sample</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>sPCR (using the BZC assay)</td><td>30</td><td>83 (77-88)</td><td>44 (41-48)</td><td>1.49 (1.36-1.63)</td><td>0.38 (0.25-0.50)</td></tr>
</table>
</td>
<td>Domain 1. Patient selection
A. Risk of bias
Was a consecutive or random sample of patients enrolled? yes
Was a case-control design avoided? yes
Did the study avoid inappropriate exclusions? yes
Could the selection of patients have introduced bias? no
B. Concerns regarding applicability
Is there a concern that the included patients do not match the review question? no

Domain 2. Index test(s)
A. Risk of bias
Were the index test results interpreted without knowledge of the results of</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>protein:creatinine ratio (sPCR) and spot albumin-creatinine ratio (sACR) in predicting severe pre-eclampsia as compared to 24 hour urine collection

Study dates

Feb 2013 - Nov 2015

Source of funding</td>
<td>Inclusion criteria

Pregnant women, of 16 years old and older, who were ≥20 weeks pregnant, with confirmed gestational hypertension (sBP/dBP ≥140/90) and with 1 trace or more of proteinuria.

Exclusion criteria

Women with pre-gestational diabetes or chronic hypertension and women with pre-existing renal disease (proteinuria before 20 weeks gestation)</td>
<td>outcomes (composite identified by Delphi survey of clinicians)</td>
<td>would have some missing data.

Data collection

Three different urine samples were taken from the study participants:

1. Urine sample for POC test.
2. Urine sample for 24 hours: women were given instructions as to when start and finish the collection
3. Urine sample immediately before birth

The laboratory was blinded to</td>
<td>
<table>
<tr><td>sPCR (using the PGR assay)</td><td>30</td><td>84 (78-89)</td><td>39 (3643)</td><td>1.38 (1.26-1.50)</td><td>0.41 (0.27-0.55)</td></tr>
<tr><td>POC-proteinuria dipstick test</td><td>1+</td><td>92 (88-96)</td><td>13 (11-16)</td><td>1.06 (1.01-1.12)</td><td>0.58 (0.28-0.89)</td></tr>
</table>
Prognostic accuracy of the four index tests and the two 24-hour urine samples assessments to predict adverse perinatal outcomes at pre-defined thresholds
<table>
<tr><th></th><th>Threshold (mg/mmol)</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th><th>LR+ (95% CI)</th><th>LR- (95% CI)</th></tr>
<tr><td>Recruitment sample</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>sPCR (local lab)</td><td>30</td><td>69 (56-80)</td><td>35 (32-39)</td><td>1.07 (0.89-1.26)</td><td>0.87 (0.53-1.20)</td></tr>
<tr><td>sPCR (using the BZC assay)</td><td>30</td><td>77 (65-87)</td><td>39 (36-42)</td><td>1.26 (1.08-1.45)</td><td>0.58 (0.31-0.85)</td></tr>
<tr><td>sPCR (using the PGR assay)</td><td>30</td><td>79 (67-88)</td><td>35 (32-38)</td><td>1.21 (1.04-1.38)</td><td>0.60 (0.31-0.90)</td></tr>
</table>
</td>
<td>the reference standard? yes
If a threshold was used, was it pre-specified? yes
Could the conduct or interpretation of the index test have introduced bias? no
B. Concerns regarding applicability
Is there concern that the index test, its conduct, or interpretation differ from the review question? no

<u>Domain 3. Reference standard</u>
A. Risk of bias
Is the reference standard likely to correctly classify the target condition? yes
Were the reference standard results interpreted without knowledge of the results of</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>clinical info and POC

Data analysis

ROC curves were plotted with different cut-offs using sPCR and sACR as index tests and the NICE definition of severe pre-eclampsia as the reference standard.
AUC ROC curve, sensitivity and specificity LR+, LR- were summarised using pre-established cut-off points (30 mg/mmol for sPCR and 2ng/mml for sACR).</td>
<td>
<table>
<tr><td>sACR (central lab)</td><td>2</td><td>94 (84-98)</td><td>14 (12-16)</td><td>1.09 (1.01-1.16)</td><td>0.46 (0.02-0.91)</td></tr>
<tr><td>24-h sample</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>sPCR (using the BZC assay)</td><td>30</td><td>68 (55-79)</td><td>39 (36-42)</td><td>1.11 (0.91-1.31)</td><td>0.83 (0.52-1.13)</td></tr>
<tr><td>sPCR (using the PGR assay)</td><td>30</td><td>71 (58-82)</td><td>35 (32-38)</td><td>1.09 (0.91-1.27)</td><td>0.83 (0.50-1.16</td></tr>
</table>
Model calibration

Not applicable

Tool discrimination

AUC ROC of the four index tests and the two 24-hour urine samples assessments to predict severe PE
<table>
<tr><td></td><td>AUC ROC

(95% CI)</td></tr>
<tr><td>Recruitment sample</td><td></td></tr>
<tr><td>sPCR (local lab)</td><td>0.70 (0.66 - 0.74)</td></tr>
</table>
</td>
<td>the index test? yes
Could the reference standard, its conduct, or its interpretation have introduced bias? no
B. Concerns regarding applicability
Is there concern that the target condition as defined by the reference standard does not match the review question? no

<u>Domain 4. Flow and timing</u>
Was there an appropriate interval between index test(s) and reference standard? yes
Did all patients received a reference standard? yes
Did patients receive the same reference standard? yes</td>
</tr>
</table>

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
				sPCR (using the BZC assay) 0.72 (0.68 - 0.76) sPCR (using the PGR assay) 0.71 (0.67-0.75) sACR (central lab) 0.72 (0.68-0.76) **24-h sample** sPCR (using the BZC assay) 0.74 (0.70-0.78) sPCR (using the PGR assay) 0.73 (0.69 - 0.77) **AUC ROC of the four index tests and the two 24-hour urine samples assessments to predict adverse perinatal outcome** **AUC ROC (95% CI)** **Recruitment sample** sPCR (local lab) 0.59 (0.51-0.67) sPCR (using the BZC assay) 0.64 (0.56-0.71) sPCR (using the PGR assay) 0.63 (0.56-0.70) sACR (central lab) 0.63 (0.56-0.71) **24-h sample** sPCR (using the BZC assay) 0.60 (0.52-0.68)	Were all patients included in the analysis? yes **Could the patient flow have introduced bias? no** **Indirectness** No indirectness **Other information**

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results		Comments
				sPCR (using the PGR assay)	0.60 (0.52-0.68)	

Appendix E – Forest plots

No forest plots were generated for this review question as it is not applicable to this review question.

Appendix F – GRADE tables

Table 10: fullPIERS model performance for prediction of adverse maternal outcomes within 48 hours

	Akkermans 2014	Almeida 2017	Ukah 2017a	Ukah 2018	Ukah 2018[c]
Cohorts included	PETRA n = 216	Brazilian cohort n = 325	Subset of the miniPIERS dataset n = 757	British Columbia Women PETRA PREP n = 1388	British Columbia Women PREP n = 1172
Timescale of prediction	48 hrs	48 hrs	48 hrs	48 hrs	48 hrs
Gestational age at recruitment	24 to 34 weeks (median 30.0)	>20 weeks (mean 35.6)	>20 weeks (median 36.6)	BCW: <34 weeks (median 31) PETRA: 24 to 34 weeks (median 30.0) PREP: <34 weeks (median 31.4)	BCW: <34 weeks (median 31) PREP: <34 weeks (median 31.4)
Quality of the evidence (CASP CPR)	High	High	Moderate	High	High
Calibration					
Calibration slope	1.69 (1.10-2.28)[b]	NR	0.67 (95% CI NR)	0.68 (0.86-0.79)	BCW 0.31 (0.21-0.41)

	Akkermans 2014	Almeida 2017	Ukah 2017a	Ukah 2018	Ukah 2018[c]
					PREP 0.74 (0.63-0.86)
Calibration: Risk stratification - number of women in each risk category who developed adverse outcome/total number in category (%)					
Predicted risk <1%	0/37 (0%)	Predicted risk <1.7%: 22/198 (11%)	2/30 (6.66%)	14/594 (1.7%)	NR
1-2.4%	0/59 (0%)		3/107 (2.8%)	17/409 (2.8%)	NR
2.5-4.9%	1/34 (3%)	Predicted risk > 1.7%: 33/127 (26%)	12/140 (8.57%)	8/158 (4.5%)	NR
5-9.9%	1/27 (4%)		8/178 (4.49%)	6/91 (13.7%)	NR
10-19%	1/17 (6%)		35/204 (17.15%)	12/68 (15.6%)	NR
20-29%	3/13 (23%)				NR
≥30%	26/29 (90%)		49/98 (50%)	44/68 (54.5%)	NR
Calibration: Risk stratification - Likelihood ratio for each predicted risk category (95% CI)					
Predicted risk <1%	0 (0.00-1.23)	NR	-	-	NR
1-2.4%	0 (0.00-0.77)	NR	0.17 (0.06-0.53)	0.55 (0.36-0.86)	NR
2.5-4.9%	0.17 (0.02-1.23)	NR	0.56 (0.32-0.97)	0.68 (0.34-1.34)	NR
5-9.9%	0.22 (0.03-1.57)	NR	0.28 (0.14-0.55)	0.90 (0.40-2.01)	NR
10-19%	0.35 (0.05-2.62)	NR	1.23 (0.91-1.67)	2.73 (1.51-4.92)	NR

	Akkermans 2014	Almeida 2017	Ukah 2017a	Ukah 2018	Ukah 2018[c]
20-29%	1.72 (0.50-5.93)	NR			NR
≥30%	49.88 (16.02-154.98)	NR	5.9 (4.23-8.35)	23.4 (14.83-36.79)	NR
Discrimination					
AUC ROC	0.97 (0.94-0.99)	0.72 (0.67-0.77)	0.77 (0.72-0.82)	0.80 (0.75-0.86)	0.74 (0.67-0.81)
Criterion/cut-off used	20.1%	1.7%	30%	NR	NR
Sensitivity (overall)	0.91 (95% CI NR)[c]	0.60 (0.47-0.72)	0.78 (95% CI NR)	0.57 (95% CI NR)	0.68 (95% CI NR)
Specificity (overall)	0.94 (95% CI NR)[c]	0.65 (0.59-0.71)	0.66 (95% CI NR)	0.94 (95% CI NR)	0.72 (95% CI NR)

AUC ROC: area under receiver operating characteristic curve; BCW: British Columbia Women; CASP CPR: Critical Appraisal Skills Program Clinical Prediction Rule checklist; CI: confidence interval; miniPIERS: Pre-eclampsia Integrated Estimate of RiSk; NR: not reported; PETRA: Preeclampsia Eclampsia Trial Amsterdam; PREP: Prediction model for Risks of complications in Early-onset Pre-eclampsia;
a LR calculated using the method of Deeks and Altman (Deeks 2004), and 95% CI calculated using https://www.medcalc.org/calc/relative_risk.php
b assumed typographical error in paper, CI reported as 110 to 228
c Ukah 2018 conducted sensitivity analyses excluding the PETRA cohort to account for differences in the study design and definitions in the PETRA cohort as compared to the BCW and PREP cohorts

Table 11: fullPIERS model performance for prediction of adverse maternal outcomes within 7 days

	Akkermans 2016	Ukah 2018	Ukah 2018[b]
Cohorts included	PETRA n = 216	British Columbia Women PETRA PREP n = 1388	British Columbia Women PREP n = 1172

	Akkermans 2016	Ukah 2018	Ukah 2018[b]
Timescale of prediction	7 days	7 days	7 days
Gestational age at recruitment	24 to 34 weeks (median 30.0)	BCW: <34 weeks (median 31) PETRA: 24 to 34 weeks (median 30.0) PREP: <34 weeks (median 31.4)	BCW: <34 weeks (median 31) PREP: <34 weeks (median 31.4)
Quality of the evidence (CASP CPR)	High	High	High
Calibration			
Calibration slope	1.69 (1.10-2.28)[a]	NR	NR
Calibration: Risk stratification - number of women in each risk category who developed adverse outcome/total number in category (%)			
Predicted risk <1%	6/37 (16%)	NR	NR
1-2.4%	7/59 (12%)	NR	NR
2.5-4.9%	4/34 (12%)	NR	NR
5-9.9%	4/27 (15%)	NR	NR
10-19%	6/17 (35%)	NR	NR
20-29%	8/13 (62%)	NR	NR
≥30%	27/29 (93%)	NR	NR
Calibration: Risk stratification - Likelihood ratio for each predicted risk category (95% CI)			

	Akkermans 2016	Ukah 2018	Ukah 2018[b]
Predicted risk <1%	0.48 (0.21-1.09)	NR	NR
1-2.4%	0.33 (0.16-0.69)	NR	NR
2.5-4.9%	0.33 (0.12-0.90)	NR	NR
5-9.9%	0.43 (0.15-1.19)	NR	NR
10-19%	1.35 (0.52-3.50)	NR	NR
20-29%	3.97 (1.35-11.67)	NR	NR
≥30%	33.53 (8.22-136.76)	NR	NR
Discrimination			
AUC ROC	0.80 (0.72-0.87)	0.74 (0.70-0.79)	0.70 (0.65-0.75)
Criterion/cut-off used	20.1%	NR	NR
Sensitivity (overall)	0.90 (0.80-0.96)	0.68 (95% CI NR)	0.59 (95% CI NR)
Specificity (overall)	0.23 (0.17-0.31)	0.70 (95% CI NR)	0.74 (95% CI NR)

AUC ROC: area under the receiver operating characteristic curve; BCW: British Columbia Women; CASP CPR: Critical Appraisal Skills Program Clinical Prediction Rule checklist; CI confidence interval; NR: not reported; PETRA: Preeclampsia Eclampsia Trial Amsterdam; PREP: Prediction model for Risks of complications in Early-onset Pre-eclampsia
a assumed typographical error in article, CI reported as 110 to 228
b Ukah 2018 conducted sensitivity analyses excluding the PETRA cohort to account for differences in the study design and definitions in the PETRA cohort as compared to the BCW and PREP cohorts

Table 12: fullPIERS model performance for prediction of adverse maternal outcomes (timeframe not specified)

	Agrawal 2016
Timescale for collection of predictor variables	24 h
Gestational age	>20 weeks (mean 34.68 weeks)[a]

	Agrawal 2016
Quality of the evidence (CASP CPR)	Moderate
Calibration	
Calibration slope	NR
Calibration: Risk stratification - number of women in each risk category who developed adverse outcome/total number in category (%)	
Predicted risk <1%	18/223 (8.07%)
1-2.4%	6/23 (26.08%)
2.5-4.9%	7/17 (41.1%)
5-9.9%	5/15 (33.3%)
10-19%	6/12 (50%)
20-29%	3/5 (60%)
≥30%	15/27 (55.5%)
Calibration: Risk stratification - Likelihood ratio for each predicted risk category (95% CI)	
Predicted risk <1%	0.38 (0.26-0.57)[b]
1-2.4%	1.54 (0.63-3.74)[b]
2.5-4.9%	3.06 (1.21-7.70)[b]
5-9.9%	2.18 (0.77-6.15)[b]
10-19%	4.37 (1.46-13.07)[b]
20-29%	6.55 (1.12-38.34)[b]
≥30%	5.45 (2.69-11.05)[b]
Discrimination	
AUC ROC	NR
Criterion	≥30% risk
Sensitivity (overall)	0.25 (0.15 to 0.38)
Specificity (overall)	0.95 (0.92 to 0.98)

AUC ROC: area under the receiver operating characteristic curve; CASP CPR: Critical Appraisal Skills Program Clinical Prediction Rule checklist; CI: confidence interval; NR: not reported
a A possible typographical error was identified. Article reports mean gestation at delivery as less than mean gestation at recruitment for women with adverse outcome

b LR reported in the paper are reported for each risk group as if it was a dichotomous test. LR calculated by the NGA using the method of Deeks and Altman (Deeks 2004) from raw data reported in the article, and 95% calculated using https://www.medcalc.org/calc/relative_risk.php

Table 13: miniPIERS model performance for prediction of adverse maternal outcomes within 48 hours

	Payne 2014	Payne 2015
Cohorts included	PIERS n = 1300	Pakistan and South African cohorts n = 852
Tool details	miniPIERS	miniPIERS
Timescale of prediction	48 h	48 h
Gestational age	>20 weeks (median 37 weeks)	>20 weeks (median 37.2 weeks for Pakistan cohort; median 34.6 weeks for South Africa cohort)
Quality of the evidence (CASP CPR)	High	Moderate
Calibration		
Calibration slope	NR	NR
Calibration: Risk stratification - number of women in each risk category who developed adverse outcome/total number in category (%)		
0-24.9%	NR	80/785 (10.2%)
≥25%	NR	39/67 (58.2%)
Calibration: Risk stratification - Likelihood ratio for each predicted risk category (95% CI)		
0-24.9%	NR	0.70 (0.61-0.79)[a]
≥25%	NR	8.58 (5.50-13.39)[a]
Discrimination		

	Payne 2014	Payne 2015
AUC ROC (95% CI)	**Complete cohort** 0.71 (0.65-0.76)[b] **Women >34+6 weeks** 0.72 (0.63-0.82) **All women except those with transfusion as an adverse event** 0.75 (0.73-0.78) **Women with PE only** 0.72 (0.64-0.79)	0.78 (0.73-0.82)
Criterion	NR	25%
Sensitivity (overall)	NR	0.33 (0.25-0.42)
Specificity (overall)	NR	0.96 (0.65-0.97)

AUC ROC area under receiver operating characteristic curve; CASP CPR: Critical Appraisal Skills Program Clinical Prediction Rule checklist; CI: confidence interval; miniPIERS Pre-eclampsia Integrated Estimate of RiSk; NR not reported; PE; pre-eclampsia; PIERS Pre-eclampsia Integrated Estimate of RiSk
[a]LR reported in the paper are reported for each risk group as if it was a dichotomous test. LR calculated by the NGA using the method of Deeks and Altman (Deeks 2004) from raw data reported in the article, and 95% calculated using https://www.medcalc.org/calc/relative_risk.php
[b]Intercept of model was adjusted to account for differences in the outcome rate between the miniPIERS and fullPIERS cohorts.

Table 14: PREP-L and PREP-S model performance for prediction of adverse maternal outcomes by discharge/ within 48 hours/ 7 days

	Thangaratinam 2017		
Cohorts included	subset of PIERS n=437 PETRA n=211	subset of PIERS n=339	subset of PIERS n=339
Tool details	PREP-L	PREP-S[a]	PREP-S[a]

	Thangaratinam 2017			
Timescale of prediction	By discharge		48 hrs	7 days
Gestational age	PIERS subset <34 weeks (mean 30.2) PETRA 24-34 weeks (mean 29.4)		PIERS subset <34 weeks (mean 30.2)	PIERS subset <34 weeks (mean 30.2)
Quality of the evidence (CASP CPR)	Moderate		Moderate	Moderate
Calibration				
Calibration slope	PIERS cohort 0.93 (0.72-1.13) PETRA cohort 0.90 (0.48-1.32)		0.80 (0.62-.99)	0.75 (0.61-0.89)
Calibration: Risk stratification - number of women in each risk category who developed adverse outcome/total number in category (%)				
	PIERS cohort	PETRA cohort	PIERS cohort[b]	
Risk stratification ≤ 15th centile	NR	NR	5/59 (8.47%)	11/59 (18.64%)
>15-50th centile	NR	NR	8/70 (11.42%)	27/70 (38.57%)
>50-85th centile	NR	NR	12/123 (9.75%)	74/123 (60.16%)
>85th centile	NR	NR	47/87 (54.02%)	75/87 (86.20%)
Risk stratification < 10th centile	0/0	0/0	NR	NR
10-20th centile	0/3 (0%)	0/0	NR	NR
20-30th centile	6/20 (30%)	2/4 (50%)	NR	NR
30-40th centile	8/24 (33%)	1/1 (100%)	NR	NR
40-50th centile	16/33 (48%)	4/11 (36%)	NR	NR
50-60th centile	21/34 (62%)	8/13 (62%)	NR	NR
60-70th centile	19/38 (50%)	18/22 (82%)	NR	NR
70-80th centile	42/58 (72%)	25/30 (83%)	NR	NR

	Thangaratinam 2017			
80-90th centile	59/72 (82%)	70/74 (95%)	NR	NR
>90th centile	147/155 (95%)	52/56 (93%)	NR	NR
Calibration: Risk stratification – O:E ratio				
Risk stratification ≤ 15th centile	NR	NR	0.96	1.0
>15-50th centile	NR	NR	1.0	1.0
>50-85th centile	NR	NR	1.3	1.7
>85th centile	NR	NR	1.6	7.0
Discrimination				
AUC ROC (95% CI)	PIERS cohort 0.81 (0.77-0.85) PETRA cohort 0.75 (0.64-0.86)		PIERS cohort 0.75 (0.69-0.81)	PIERS cohort 0.72 (0.68-0.76)
Sensitivity (overall)	NR		NR	NR
Specificity (overall)	NR		NR	NR

PIERS Pre-eclampsia Integrated Estimate of RiSk; PETRA Preeclampsia Eclampsia Trial Amsterdam; PREP-L Prediction model for Risks of complications in Early-onset Pre-eclampsia (logistic regression model); PREP-S Prediction model for Risks of complications in Early-onset Pre-eclampsia (survival analysis model)
a Only data from the PIERS was used as the PETRA dataset did not have time to event outcomes
b Calculated by the NGA using the observed survival probability and predicted survival probability reported in the study

Table 15: Quality assessment of prognostic test accuracy studies for spot urine creatinine ratio: adverse maternal outcomes

Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
Urine spot PCR >500; maternal age >35 years ***Prediction of maternal adverse outcomes within 24 hours.***											
1 (Chan 2005)	321	no serious	no serious inconsistency	no serious indirectness	no serious	none	0.10 (0.05-0.18)	1.00 (0.98-1.00)	Not calculable[a]	0.9 (0.8-1.0)	HIGH

Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
		risk of bias									
sPCR (local lab; recruitment sample); 30 mg/mmol threshold ***Prediction of severe pre-eclampsia (clinician diagnosis[b]) until hospital discharge.***											
1 (Waugh 2017)	959	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious	none	0.85 (0.80-0.90)	0.40 (0.37-0.44)	1.43 (1.31-1.55)	0.36 (0.23-0.49)	HIGH
sACR (central lab; recruitment sample); 2 mg/mmol threshold ***Prediction of severe pre-eclampsia (clinician diagnosis[b]) until hospital discharge.***											
1 (Waugh 2017)	959	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious	none	0.97 (0.93-0.99)	0.16 (0.14-0.19)	1.15 (1.11-1.20)	0.19 (0.04-0.35)	HIGH

PCR: protein creatinine ratio; GA: gestational age; sBP: systolic blood pressure; sPCR: spot protein-creatinine ratio; mg: milligram; mmol: millimoles; BZC: benzethonium chloride; PGR: pyrogallol red; sACR: spot albumin-creatinine ratio; POC: point of care; CI: confidence interval; LR: likelihood ratio
[a] Specificity of 100%, therefore positive likelihood ratio and CI not estimable
[b] Defined as those instances where women were treated with magnesium sulfate or put on a severe pre-eclampsia pathway

Table 16: Quality assessment of prognostic test accuracy studies for spot urine creatinine ratio: adverse perinatal outcomes

Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
sPCR (local lab; recruitment sample); 30 mg/mmol threshold ***Prediction of adverse perinatal outcomes until hospital discharge.***											

1 (Waugh 2017)	959	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	0.69 (0.56-0.80)	0.35 (0.32-0.39)	1.07 (0.89-1.26)	0.87 (0.53-1.20)	MODERATE
sACR (central lab; recruitment sample); 2 mg/mmol threshold ***Prediction of adverse perinatal outcomes until hospital discharge.***											
1 (Waugh 2017)	959	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	0.94 (0.84-0.98)	0.14 (0.12-0.16)	1.09 (1.01-1.16)	0.46 (0.02-0.91)	MODERATE

PCR: protein- creatinine ratio; GA: gestational age; sBP: systolic blood pressure; CI: confidence interval; LR: likelihood ratio; sPCR: spot protein-creatinine ratio; mg: milligram; mmol: millimoles; BZC: benzethonium chloride; PGR: pyrogallol red; sACR: spot albumin-creatinine ratio; NR: not reported; CI: confidence interval; LR: likelihood ratio
1 The quality of the evidence was downgraded by 1 level as the 95% CI for sensitivity crossed 1 MID threshold (75%)
2 The quality of the evidence was downgraded by 1 level as the 95% CI for sensitivity crossed 1 MID threshold (90%)

Table 17: Quality assessment of prognostic test accuracy studies for abnormal coagulation

Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
Platelets ≤ 100 x 10^9/L ***Prediction of adverse maternal outcomes within 48 hours***											
1 (Laskin 2011)	1405	serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0.16 (0.11-0.23)	0.92 (0.91-0.94)	2 (1.3-3.1)	0.9 (0.9-1)	MODERATE
Abnormal coagulation (INR> 1.06 and serum fibrinogen < 3.54 g/L) ***Prediction of adverse maternal outcomes within 48 hours***											
1 (Laskin 2011)	1405	serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0.15 (0.10-0.22)	0.94 (0.92-0.95)	2.17 (1.32-3.56)	0.91 (0.84-0.98)	MODERATE

INR International Normalised ratio; PIERS Pre-eclampsia Integrated Estimate of RiSk; CI confidence interval; LR likelihood ratio
1 The quality of the evidence was downgraded by 1 level as it was unclear whether the index test results were interpreted without knowledge of the reference standard and unclear whether the reference standard results were interpreted without knowledge of the results of the index test

Table 18: Quality assessment of prognostic test accuracy studies for liver function

Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
AST (cut-off 150 U/l) ***Prediction of adverse maternal outcomes***											
1 (Thangaratinam 2011)	568	serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0.70 (0.63-0.77)	0.48 (0.43-0.53)	1.4 (1.2-1.5)	0.62 (0.48-0.8)	LOW
ALT (cut-off 100 U/l) ***Prediction of adverse maternal outcomes***											
1 (Thangaratinam 2011)	568	serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0.66 (0.59-0.73)	0.47 (0.42-0.52)	1.2 (1.1-1.4)	0.72 (0.57-0.91)	MODERATE
LDH (cut-off 1400 U/l) ***Prediction of adverse maternal outcomes***											
1 (Thangaratinam 2011)	568	serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0.72 (0.65-0.79)	0.49 (0.44-0.54)	1.4 (1.2-1.6)	0.57 (0.44-0.74)	LOW
LDH (cut-off 600 U/l) ***Prediction of adverse maternal outcomes***											
1 (Thangaratinam 2011)	737	serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0.62 (0.49-0.74)	0.60 (0.56-0.64)	1.6 (1.3-1.9)	0.63 (0.46-0.86)	MODERATE
ALT (cut-off 40 U/l); AST (cut-off 55 U/l) ***Prediction of adverse maternal outcomes***											

Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
1 (Thangaratinam 2011)	737	serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0.33 (0.22-0.45)	0.80 (0.77-0.84)	1.7 (1.2-2.4)	0.83 (0.71-0.99)	MODERATE
AST (cut-off 30 U/l); ALT (cut-off 32 U/l); Bili (cut-off 14 U/l); GGT (cut-off 41 U/l) ***Prediction of adverse maternal outcomes***											
1 (Thangaratinam 2011)	85	serious risk of bias[1]	no serious inconsistency	no serious indirectness	very serious imprecision[3]	none	0.93 (0.52-1.00)	0.57 (0.37-0.76)	2.2 (1.4-3.5)	0.12 (0.01-1.7)	VERY LOW
AST (cut-off 30 U/l); ALT (cut-off 32 U/l); Bili (cut-off 14 U/l); GGT (cut-off 41 U/l) ***Prediction of adverse perinatal outcomes***											
1 (Thangaratinam 2011)	85	serious risk of bias[1]	no serious inconsistency	no serious indirectness	very serious imprecision[3]	none	0.86 (0.23-1.00)	0.50 (0.32-0.68)	1.7 (0.99-3)	0.27 (0.02-3.8)	VERY LOW

AST: aspartate aminotransferase; LDH: lactate dehydrogenase; ALT: alanine aminotransferase; Bili: bilirubin; GGT: gamma-glutamyl transferase; CI: confidence interval; LR: likelihood ratio
1 The quality of the evidence was downgraded by 1 level as the table of included studies did not have enough detail (the total number of participants was missing for some of the studies; authors did not provide a list of excluded studies)
2 The quality of the evidence was downgraded by 1 level as the 95% CI for sensitivity crossed 1 MID threshold (75%)
3 The quality of the evidence was downgraded by 2 levels as the 95% CI for sensitivity crossed 2 default MID thresholds (75 and 90%)

Table 19: Quality assessment of prognostic test accuracy studies for uric acid

Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
Uric acid >345µmol/L ***Prediction of adverse maternal outcomes (PIERS composite) within 48 hours***											
1 (Livingston 2014)	1487	serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	0.80 (0.70-0.87)	0.28 (0.25-0.30)	1.11 (95% CI NC)[a]	0.71 (95% CI NC)[a]	LOW

Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
Uric acid >345µmol/L ***Prediction of adverse maternal outcomes (PIERS composite) within 7 days***											
1 (Livingston 2014)	1487	serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0.82 (0.76-0.88)	0.28 (0.26-0.31)	1.14 (95% CI NC)[a]	0.64 (95% CI NC)[a]	MODERATE
Uric acid >345µmol/L ***Prediction of adverse maternal outcomes (PIERS composite) at any time***											
1 (Livingston 2014)	1487	serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0.83 (0.77-0.88)	0.29 (0.26-0.31)	1.17 (95% CI NC)[a]	0.59 (95% CI NC)[a]	MODERATE
Uric acid >1 SD above the mean for gestational age ***Prediction of adverse maternal outcomes (PIERS composite) within 48 hours***											
1 (Livingston 2014)	1487	serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	0.86 (0.77-0.92)	0.21 (0.19-0.24)	1.09 (95% CI NC)[a]	0.67 (95% CI NC)[a]	LOW
Uric acid >1 SD above the mean for gestational age ***Prediction of adverse maternal outcomes (PIERS composite) within 7 days***											
1 (Livingston 2014)	1487	serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	0.86 (0.80-0.91)	0.22 (0.20-0.24)	1.10 (95% CI NC)[a]	0.64 (95% CI NC)[a]	LOW
Uric acid >1 SD above the mean for gestational age ***Prediction of adverse maternal outcomes (PIERS composite) at any time***											
1 (Livingston 2014)	1487	serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	0.86 (0.80-0.90)	0.22 (0.20-0.24)	1.10 (95% CI NC)[a]	0.64 (95% CI NC)[a]	LOW
Uric acid >345µmol/L ***Prediction of adverse perinatal outcomes at any time***											

Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
1 (Livingston 2014)	1487	serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	0.78 (0.73-0.82)	0.29 (0.27-0.32)	1.10 (95% CI NC)[a]	0.76 (95% CI NC)[a]	MODERATE
Uric acid >1 SD above the mean for gestation ***Prediction of adverse perinatal outcomes at any time***											
1 (Livingston 2014)	1487	serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0.92 (0.90-0.95)	0.26 (0.24-0.29)	1.24 (95% CI NC)[a]	0.31 (95% CI NC)[a]	MODERATE

CI: confidence interval; LR: likelihood ratio; NC not calculable
a Number of true positive/true negatives were not reported, therefore 95% confidence interval for LR could not be calculated.
1 The quality of the evidence was downgraded by 1 level as it was unclear whether the index text results were interpreted without knowledge of the reference standard and vice versa
2 The quality of the evidence was downgraded by 1 level as the 95% CI for sensitivity crossed 1 MID threshold (75%)
3 The quality of the evidence was downgraded by 1 level as the 95% CI for sensitivity crossed 1 MID threshold (90%)

Table 20: Quality assessment of prognostic test accuracy studies for soluble fms-like tyrosine kinase-1 and placental growth factor

Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
Serum sFlt-1/PlGF ratio ≥ 871[a] ***Prediction of adverse maternal outcomes***											
1 (Ukah 2017[b])	501	serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0.52 (0.37-0.67)	0.78 (0.74-0.82)	2.36 (1.71-3.26)	0.61 (0.46-0.83)	MODERATE
Serum sFlt-1/PlGF ratio > 85[b] ***Prediction of adverse maternal outcomes***											

Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
1 (Ukah 2017[b])	237	serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	0.62 (0.39-0.81)	0.69(0.63-0.75)	2.0 (1.4-3.0)	0.5 (0.3-1.0)	LOW

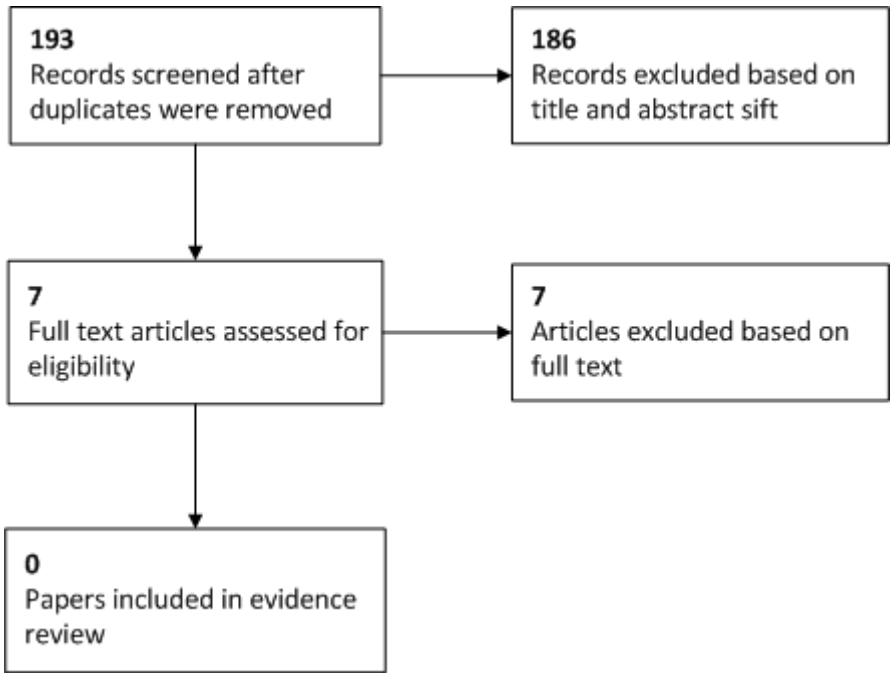
sFlt: Soluble fms-like tyrosine kinase; PlGF: placental growth factor; CI: confidence interval; LR: likelihood ratio
[a] Participants were women with confirmed pre-eclampsia, ACOG definition.
[b] Participants were women presenting for evaluation of possible pre-eclampsia at <34 weeks' gestation
1 The quality of the evidence was downgraded by 1 level as it was unclear whether study selection was performed in duplicate; authors did not provide a list of excluded studies
2 The quality of the evidence was downgraded by 1 level as the 95% CI for sensitivity crossed 1 MID threshold (75%)

Table 21: Quality assessment of prognostic test accuracy studies for maternal characteristics: adverse fetal outcomes

Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sensitivity % (95% CI)	Specificity % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Quality
GA <34 weeks and sBP <115mmHg ***Prediction of fetal adverse outcomes within 24 hours.***											
1	353	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious	none	0.48 (0.35-0.61)	0.39 (0.33-0.45)	0.79 (0.60-1.04)	1.32 (1.02-1.70)	HIGH

GA: gestational age; LR: likelihood ratio; CI: confidence interval

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

No economic evidence was identified for this review question.

Appendix I – Health economic evidence profiles

No economic evidence was identified for this review question.

Appendix J – Health economic analysis

Aim

The aim of this economic analysis is to estimate the cost-effectiveness of risk prediction models for guiding inpatient and outpatient management in pregnant women with pre-eclampsia.

Methods

Existing economic evidence

A systematic literature review was conducted to identify economic evaluations that may be applicable to the current decision problem. No relevant economic studies were identified that were directly applicable.

De novo economic evaluation

Since the current economic literature did not adequately address the decision problem, a de novo economic evaluation was undertaken to assess cost-effectiveness. The analysis was developed in Microsoft Excel® and was conducted from the perspective of the NHS and Personal Social Services (PSS) as outlined in the NICE reference case (see Developing NICE guidelines: the manual).

The modelled time horizon was 20 days, which reflects the estimated amount of time between women being assessed and giving birth (6 days) plus two additional weeks to capture the duration of QoL effects. This short time horizon was selected because the model is focusing on short term outcomes and currently there is no evidence to inform longer term differences between the strategies. Discounting of costs and benefits was not undertaken because of the short time horizon.

Clinical data and model approach

The economic analysis considered strategies where the decision on whether to manage pre-eclampsia in women as an outpatient or inpatient was based on risk thresholds (e.g. to offer inpatient management with a risk score ≥ 10%). The analysis considered the fullPIERS risk assessment tool, which was selected because it has the best available evidence. Other risk assessment tools such as PREP-S could also be used in clinical practice but it was not possible to include them in the economic model because there is insufficient data on diagnostic accuracy (sensitivity and specificity) at various risk levels.

Management strategies based on risk leve were compared against each other and also against strategies where it is assumed that all women are managed as either an inpatient or outpatient.

It is unclear which strategy would best represent current clinical practice as there is known to be variation. However, it is thought that inpatient management is generally more common than outpatient management. Note that this does not affect the current analysis as the intention is to compare all strategies against each other to determine the most cost-effective

strategy. This is a separate endeavour to estimating cost impact which aims to estimate the change in cost associated with the adoption of a new strategy compared to current practice.

The economic analysis considered women 34-37 weeks of gestation reflecting the population in which the fullPIERS risk prediction model is applicable. The following management strategies were considered in the analysis:

- All inpatient management
- All outpatient management
- Inpatient management if fullPIERS ≥ 5%
- Inpatient management if fullPIERS ≥ 10%
- Inpatient management if fullPIERS ≥ 20%
- Inpatient management if fullPIERS ≥ 30%

Prevalence and accuracy data

The economic analysis was based on accuracy data (sensitivity and specificity) for the prediction of complications at 2 and 7 days for each of the strategies (see Table 22). In the model, the diagnostic results are linked to subsequent management whereby women with positive results are managed as inpatients and women with negative results are managed as outpatients.

Data on the prevalence of adverse outcomes as well as data on the accuracy of fullPIERS at different thresholds were estimated from an external validation study (Akkermans 2014). Akkermans showed that 32 of 216 women (14.8%) had an adverse outcome after 48 hours and 62 of 216 women (28.7%) had an adverse outcome after 7 days. Accuracy data for the 'all inpatient management' and 'all outpatient management' were inferred based on the implications of the strategy e.g. all patients managed as an inpatient implies that all patients with complications would be managed as an inpatient and therefore the sensitivity would be 100%.

In clinical practice risk models are likely to only be used to predict short term outcomes. This reflects the available data which suggests a much better performance when predicting short term outcomes (as can be seen from the accuracy data at 48 hours and 7 days). To reflect the manner in which risk models are employed in clinical practice, it was therefore assumed that women that are managed on an outpatient basis would be re-assessed evey two days. In the model this is estimated by applying the 48 hour diagnostic accuracy data again for women that were being managed as an outpatient following the initial test (i.e. initially found to have a risk score under the threshold).

Table 22: Diagnostic accuracy

Strategy	48 hours		7 days	
	Sensitivity	Specificity	Sensitivity	Specificity
All inpatient	100%	0%	100%	0%
Inpatient if fullPIERS ≥ 5%	97%	70%	73%	73%
Inpatient if fullPIERS ≥ 10%	94%	84%	66%	88%

Strategy	48 hours		7 days	
	Sensitivity	Specificity	Sensitivity	Specificity
Inpatient if fullPIERS ≥ 20%	91%	93%	56%	95%
Inpatient if fullPIERS ≥ 30%	81%	98%	44%	99%
All outpatient	0%	100%	0%	100%
All inpatient	100%	0%	100%	0%

Effectiveness data

It has been assumed that women managed in an inpatient setting would have a reduction in the number of adverse maternal outcomes. There is no good evidence available on which to base this reduction. Therefore it was speculatively approximated using data from Broekhuijsen 2015 (HYPITAT II study), which compared immediate delivery with expectant management. It has been assumed that the reduction in adverse outcomes associated with being managed in an inpatient setting rather than an outpatient setting would be similar to the reduction seen with immediate delivery compared with expectant management. In comparison to expectant management, immediate delivery was found to reduce reported adverse maternal outcomes with a relative risk (RR) of 0.36 (95% CI 0.12–1.11). Therefore, this value was applied in the analysis as an estimate of the reduction in adverse maternal outcomes with the inpatient approach.

Mortality was not considered in the analysis as there is no evidence to suggest that the use of risk prediction models may confer a survival benefit. Also it is unlikely that there would be mortality differences between outpatient and inpatient management strategies.

Costs

The costs considered in the model reflect the perspective of the analysis, thus only costs that are relevant to the UK NHS and PSS were included. Where possible, all costs were estimated in 2016/17 prices. The majority of costs were sourced from NHS reference costs 2016/17 by applying tariffs associated with the appropriate Healthcare Resource Groups (HRG) code.

Risk assessment tool costs

It was assumed that there is no cost associated with using the fullPIERS risk assessment tool itself as it is freely available online. Furthermore, it was assumed that there was no additional cost associated with performing the tests required to inform the risk factors in the tool as these tests are already carried out as part of routine clinical practice.

Inpatient and outpatient management costs

Inpatient costs were estimated using the average cost of a day as an elective inpatient from NHS reference costs 2016/17 (£384.50). The average length of stay (LOS) was based on pre-eclampsia audit data, which reported an average time between diagnosis of pre-eclampsia and delivery of 6 days for women 34-37 weeks of gestation. To avoid the potential duplication of LOS costs associated with the birth itself, the average LOS associated with births was estimated from NHS reference costs (2.09 days) and deducted from the total days from the survey (resulting in 3.91 days). Outpatient costs were based on the cost of

consultant led face-to-face follow-up in the obstetrics service from NHS reference costs 2016/17 (£120.20). The average duration of outpatient management was assumed to be the same as inpatient management and it was assumed that patients would have re-assessments every 2 days.

Birth and complication costs

Birth costs were estimated using data on the proportions of each mode of delivery from Broekhuijsen 2015 (HYPITAT II study) and are shown in Table 23. A combined average of the immediate delivery and expectant management arms of the trial was estimated resulting in proportions of 4%, 86% and 10% for spontaneous labour, induction of labour and caesarean section, respectively. Birth costs for the various modes of delivery were sourced from NHS Reference Costs 2016/17 assuming that women with adverse outcomes would have births with complications and co-morbidities (based on CC scores). Birth costs were estimated by taking a weighted average of births recorded in NHS reference costs as an elective inpatient, non-elective long stay and non-elective short stay.

Table 23: Birth costs

Strategy	Proportion	Unit cost		Reference
		Without complications	With complications	
Spontaneous delivery	4%	£1,772.19	£2,141.38	NHS reference costs 2016/17
Delivery with epidural or induction	86%	£2,229.52	£2,867.83	NHS reference costs 2016/17
Planned caesarean section	10%	£3,112.88	£4,371.20	NHS reference costs 2016/17
Weighted average	-	£2,296.05	£2,983.35	Estimated

It was assumed that women with an adverse outcome would be admitted to a high dependency unit (HDU). A HDU cost of £860.61 was estimated from NHS reference costs 2016/17, based on the weighted average cost of “adult critical care, 0 organs supported” and “adult critical care, 1 organs supported” (see Table 24).

Table 24: Critical care costs

Outcome	Proportion	Cost	Source
Adult Critical Care, 0 Organs Supported	51%	£660.05	NHS Reference costs 2016/17
Adult Critical Care, 1 Organs Supported	49%	£1,067.34	NHS Reference costs 2016/17
Weighted average		£860.61	NHS Reference costs 2016/17

Based on a combined average of the immediate delivery and expectant management arms from Broekhuijsen 2015 (HYPITAT II study), it was assumed that a NICU admission would be required in 5.6% of births. NICU admission costs were estimated from NHS reference costs 2016/17, based on the cost of neonatal critical care, intensive care (£1,295)

Health-related quality of life

As recommended in the NICE reference case, the model estimates effectiveness in terms of quality adjusted life years (QALYs). These are estimated by combining life year estimates with quality of life (QoL) values associated with being in a particular health state.

QoL data were sourced from the economic analysis conducted as part of the previous guideline (NICE CG107). Pregnant women with pre-eclampsia were assumed to have the same QoL value as normotensive pregnant women. The QoL value for normotensive pregnant women was sourced from Sonnenberg 2004, a cost effectiveness analysis of contraception methods in women of average health and fertility, which found that short-term utility loss due to pregnancy was 0.0375. Therefore the baseline utility value applied in the model for pregnant women with pre-eclampsia was estimated to be 0.9625 (1-0.0375).

Experiencing severe complications of pre-ecalmpsia was assumed to have the same QoL as being admitted to ICU for any reason. As part of a cost effectiveness analysis of meropenem in the treatment of severe infections in hospital intensive care, Edwards 2006 estimated that the QoL weight for someone who has stayed in intensive care was 0.712. The QoL weight for women with complications was assumed to be the product of the QoL value for being admitted to ICU for any reason (0.712) and the QoL value for pregnant women with pre-eclampsia (0.9625). The QoL value for experiencing adverse outcomes was parameterised in the model as a QoL decrement (estimated by deducting the QoL weight for women with complications from the baseline value for pregnant women with pre-eclampsia) and applied accordingly.

Following the methodology adopted in the economic analysis conducted as part of the previous guideline (NICE CG107), it was assumed that the QoL decrement for women with severe disease would last for 2 weeks, reflecting the estimated period of time that women may stay in ICU.

In order to estimate QALYs these values were converted to daily weights and applied for the modelled time horizon.

Sensitivity analysis

Uncertainty was assessed in the economic model through deterministic and probabilistic sensitivity analysis. A series of deterministic sensitivity analyses were conducted, whereby an input parameter was changed, the model was re-run and the new cost-effectiveness result was recorded. This form of analysis is a useful way of estimating uncertainty and determining the key drivers of the model results.

Probabilistic sensitivity analysis (PSA) was conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were utilised in the base-case were replaced with values drawn from distributions around the mean values. Table 25 gives a full list of the input parameters included in the model along with details of the distributions applied in the PSA.

Table 25: Full list of model inputs with details of PSA distributions

Input	Mean value	PSA distribution
Probability of adverse outcomes		
Proportion of women with outcomes at 48 hours	15%	Beta (α = 32, β= 184)
Proportion of women with outcomes at 7 days	29%	Beta (α = 62, β = 154)

Input	Mean value	PSA distribution
Diagnostic accuracy at 48 hours - sensitivity		
All inpatient	100%	Not varied
Inpatient based on FullPIERS ≥ 5%	97%	Beta (α =31, β = 1)
Inpatient based on FullPIERS ≥ 10%	94%	Beta (α =30, β = 2)
Inpatient based on FullPIERS ≥ 20%	91%	Beta (α =29, β = 3)
Inpatient based on FullPIERS ≥ 30%	81%	Beta (α =26, β = 6)
All outpatient	0%	Not varied
Diagnostic accuracy at 48 hours - specificity		
All inpatient	0%	Not varied
Inpatient based on FullPIERS ≥ 5%	70%	Beta (α =129, β = 55)
Inpatient based on FullPIERS ≥ 10%	84%	Beta (α =155, β = 29)
Inpatient based on FullPIERS ≥ 20%	93%	Beta (α =171, β = 13)
Inpatient based on FullPIERS ≥ 30%	98%	Beta (α =181, β = 3)
All outpatient	100%	Not varied
Diagnostic accuracy at 7 days - sensitivity		
All inpatient	100%	Not varied
Inpatient based on FullPIERS ≥ 5%	73%	Beta (α = 45, β = 17)
Inpatient based on FullPIERS ≥ 10%	66%	Beta (α =41, β = 21)
Inpatient based on FullPIERS ≥ 20%	56%	Beta (α =35, β = 27)
Inpatient based on FullPIERS ≥ 30%	44%	Beta (α =27, β = 35)
All outpatient	0%	Not varied
Diagnostic accuracy at 7 days - specificity		
All inpatient	0%	Not varied
Inpatient based on FullPIERS ≥ 5%	73%	Beta (α =113, β = 41)
Inpatient based on FullPIERS ≥ 10%	88%	Beta (α =136, β = 18)
Inpatient based on FullPIERS ≥ 20%	95%	Beta (α =147, β = 7)
Inpatient based on FullPIERS ≥ 30%	99%	Beta (α =152, β = 2)
All outpatient	100%	Not varied
Effectiveness (benefits of inpatient management)		
RR for immediate vs expectant monitoring	0.36	Lognormal (SD = 0.57)
Mode of birth		
Spontaneous	4.4%	Dirichlect (α = 31)
Induction of labour	85.8%	Dirichlect (α = 603)
Caesarean section	9.8%	Dirichlect (α = 69)
NICU admission		
NICU admission	5.6%	Beta (α =39, β = 663)
Inpatient cost per day		
Elective Inpatients Excess Bed Days	£384.50	Gamma (SE=0.2, α = 2945257, β = 0.0001)
Outpatient visit cost		
Consultant Led - non-admitted face to face attendance, follow up - obstetrics	£120.20	Gamma (SE=0.05, α = 6020837, β = 0.00002)

Input	Mean value	PSA distribution
Spontaneous delivery without complications		
Elective Inpatient - proportion	1%	Dirichlect (α = 1119)
Non-Elective Long Stay - proportion	22%	Dirichlect (alpha = 30292)
Non-elective Short Stay - proportion	78%	Dirichlect (α = 109269)
Elective Inpatient - cost	£1,472.52	Gamma (SE=37, α = 1578, β = 1)
Non-Elective Long Stay - cost	£2,622.47	Gamma (SE=4, α = 446806, β = 0.01)
Non-elective Short Stay - cost	£1,539.55	Gamma (SE=2, α = 623744, β = 0.002)
Spontaneous delivery with complications		
Elective Inpatient - proportion	1%	Dirichlect (α = 191)
Non-Elective Long Stay - proportion	38%	Dirichlect (α = 7011)
Non-elective Short Stay - proportion	61%	Dirichlect (α = 11306)
Elective Inpatient - cost	£5,979.76	Gamma (SE=436, α = 188, β = 32)
Non-Elective Long Stay - cost	£2,889.29	Gamma (SE=8, α = 117275, β = 0.02)
Non-elective Short Stay - cost	£1,612.74	Gamma (SE=6, α = 64414, β = 0.03)
Delivery, with epidural or induction, without complications		
Elective Inpatient - proportion	1%	Dirichlect (α = 931)
Non-Elective Long Stay - proportion	48%	Dirichlect (α = 35802)
Non-elective Short Stay - proportion	51%	Dirichlect (α = 37744)
Elective Inpatient - cost	£1,908.98	Gamma (SE=48, α = 1599, β = 1)
Non-Elective Long Stay - cost	£2,811.90	Gamma (SE=4, α = 489163, β = 0.01)
Non-elective Short Stay - cost	£1,685.01	Gamma (SE=4, α = 183918, β = 0.01)
Delivery, with epidural or induction, with complications		
Elective Inpatient - proportion	1%	Dirichlect (α = 410)
Non-Elective Long Stay - proportion	71%	Dirichlect (α = 19773)
Non-elective Short Stay - proportion	28%	Dirichlect (α = 7731)
Elective Inpatient - cost	£2,515.06	Gamma (SE=86, α = 853, β = 3)
Non-Elective Long Stay - cost	£3,302.55	Gamma (SE=6, α = 270853, β = 0.01)
Non-elective Short Stay - cost	£1,774.68	Gamma (SE=9, α = 37422, β = 0.05)
Caesarean Section without complications		
Elective Inpatient - proportion	6%	Dirichlect (α = 2702)
Non-Elective Long Stay - proportion	56%	Dirichlect (α = 23426)
Non-elective Short Stay - proportion	37%	Dirichlect (α = 15476)

Input	Mean value	PSA distribution
Elective Inpatient - cost	£3,493.86	Gamma (SE=20, α = 30400, β = 0.1)
Non-Elective Long Stay - cost	£3,497.43	Gamma (SE=6, α = 399606, β = 0.01)
Non-elective Short Stay - cost	£2,464.28	Gamma (SE=8, α = 92463, β = 0.03)
Caesarean Section with complications		
Elective Inpatient - proportion	6%	Dirichlect (α = 446)
Non-Elective Long Stay - proportion	75%	Dirichlect (α = 6024)
Non-elective Short Stay - proportion	19%	Dirichlect (α = 1550)
Elective Inpatient - cost	£5,558.95	Gamma (SE=45, α = 15157, β = 0.4)
Non-Elective Long Stay - cost	£4,758.08	Gamma (SE=18, α = 71528, β = 0.1)
Non-elective Short Stay - cost	£2,525.86	Gamma (SE=26, α = 9542, β = 0.3)
Adult critical care		
Adult Critical Care, 0 Organs Supported - proportion	51%	Dirichlect (α = 4828)
Adult Critical Care, 1 Organs Supported - proportion	49%	Dirichlect (α = 4684)
Adult Critical Care, 0 Organs Supported - cost	£660.05	Gamma (SE=6, α = 10630, β = 0.1)
Adult Critical Care, 1 Organs Supported - cost	£1,067.34	Gamma (SE=8, α = 17237, β = 0.01)
Neonatal critical care		
Neonatal critical care	£1,294.62	Gamma (SE=1, α = 1758597, β = 0.001)
QoL data		
Pregnant women with pre-eclampsia	0.053	Beta (α =5, β = 95)
Severe complications of pre-eclampsia	0.011	Beta (α =1, β = 132)

PSA, probabilistic sensitivity analysis; RR, relative risk; NICU, neonatal intensive care unit; QoL, quality of life

Results

Base-case results

The base case results of the analysis are shown in Table 26 and Table 27.

In Table 26, each strategy is compared against inpatient management (the strategy assumed to be the most likely to be used in clinical practice). It can be seen that all risk management strategies as well as a strategy of outpatient management for all women are much less costly and marginally less effective than inpatient management. This results in very high ICER values which indicate that large cost savings are made for each QALY that is lost (note that the ICER interpretation is non-standard because of negative costs and QALYs). Therefore,

the results indicate that all risk management strategies as well as outpatient management are cost-effective in comparison to inpatient management.

In Table 27, a 'dominance rank' approach is presented which allows all strategies to be compared against each other. This approach involves rank ordering strategies in terms of cost and then comparing each intervention in turn against the previous intervention that was found to be cost-effective.

A strategy of outpatient management was the least costly strategy overall. All other strategies were found to be more costly and more effective than outpatient management. Inpatient management if fullPIERS ≥ 30% was found to be cost-effective with an ICER value of £10,797 per QALY which is below the NICE threshold of £20,000 per QALY. All other strategies were not found to be cost-effective with ICERs well above the NICE threshold of £20,000 per QALY. Therefore the strategy of inpatient management if fullPIERS ≥ 30% was found to be the optimal strategy in cost-effectiveness terms.

Table 26: Base case results in comparison to inpatient management

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Inpatient management	£4,031	-	0.05164	-	-
Inpatient if fullPIERS ≥ 5%	£3,424	-£607	0.05159	-0.00005	£12,842,539
Inpatient if fullPIERS ≥ 10%	£3,243	-£788	0.05154	-0.00010	£7,847,220
Inpatient if fullPIERS ≥ 20%	£3,131	-£900	0.05148	-0.00017	£5,440,737
Inpatient if fullPIERS ≥ 30%	£3,064	-£966	0.05128	-0.00036	£2,681,636
Outpatient management	£3,047	-£983	0.04969	-0.00195	£503,502

QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio

Table 27: Base case results using dominance rank

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Outpatient management	£3,047	-	0.04969	-	-
Inpatient if fullPIERS ≥ 30%	£3,064	£17	0.05128	0.00159	£10,797
Inpatient if fullPIERS ≥ 20%	£3,131	£66	0.05148	0.00019	£340,580
Inpatient if fullPIERS ≥ 10%	£3,243	£178	0.05154	0.00026	£685,842
Inpatient if fullPIERS ≥ 5%	£3,424	£359	0.05159	0.00031	£1,147,915
Inpatient management	£4,031	£966	0.05164	0.00036	£2,681,636

QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio

Deterministic sensitivity analysis results

The results of the deterministic sensitivity analysis are presented in Table 28. It can be seen that the conclusion of the analysis changes in numerous scenarios with outpatient management found to be cost-effective in certain scenarios. Notably this includes numerous plausible scenarios such as where variations in the RR for adverse outcomes is applied or when the cost of adverse outcomes is changed.

Table 28: Deterministic sensitivity analysis results

Modelled scenario	Optimal strategy
Base case	Inpatient if fullPIERS ≥ 30%
Prevalence of adverse outcomes 25% higher	Inpatient if fullPIERS ≥ 30%
Prevalence of adverse outcomes 25% lower	Inpatient if fullPIERS ≥ 30%
Accuracy based on initial 7 day test only	*Outpatient management*
Repeat test accuracy based on 7 day data	*Outpatient management*
Adverse outcomes – lower RR (0.12)	Inpatient if fullPIERS ≥ 30%
Adverse outcomes – upper RR (1.11)	*Outpatient management*
Adverse outcomes – RR = 1	*Outpatient management*
Adverse outcomes – RR = 0.75	*Outpatient management*
Adverse outcomes – RR = 0.50	Inpatient if fullPIERS ≥ 30%
Adverse outcomes – RR = 0.25	Inpatient if fullPIERS ≥ 30%
Adverse outcomes – RR = 0.00	Inpatient if fullPIERS ≥ 30%
All births via spontaneous delivery	*Outpatient management*
All births via induction of labour	Inpatient if fullPIERS ≥ 30%
All births via caesarean section	Inpatient if fullPIERS ≥ 30%
No NICU admissions	Inpatient if fullPIERS ≥ 30%
Inpatient and outpatient duration = 7 days	Inpatient if fullPIERS ≥ 30%
Inpatient and outpatient duration = 14 days	*Outpatient management*
No increased birth costs with adverse outcomes	*Outpatient management*
No admission to critical care with adverse outcomes	*Outpatient management*

RR, relative risk; NICU, neonatal intensive care unit

Threshold analysis results

A threshold analysis was conducted to determine the RR for adverse outcomes required for the inpatient management if fullPIERS ≥ 30% strategy to be cost-effective. It was found that a strategy of inpatient management if fullPIERS ≥ 30% was cost-effective with a RR of 0.395 or lower.

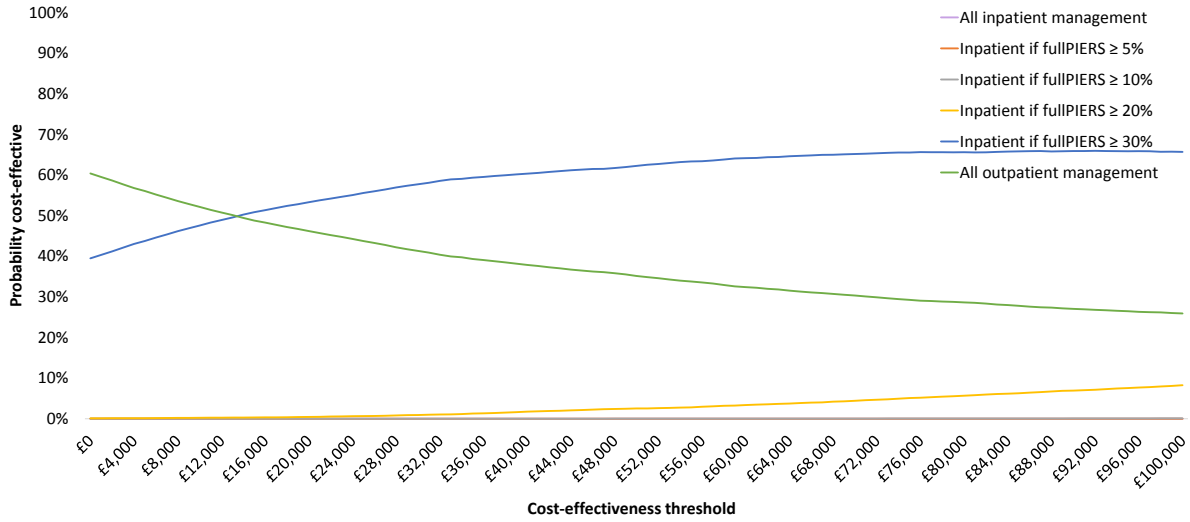
Probabilistic sensitivity analysis results

The results of 10,000 runs of the PSA are shown using cost-effectiveness acceptability curves (CEAC) Figure 2. The CEAC graph shows the probability of each strategy being considered cost-effective at various cost-effectiveness thresholds on the x axis.

It can be seen that outpatient management and a strategy of inpatient management if fullPIERS ≥ 30% have the highest probabilities of being cost-effective at all thresholds. Outpatient management is initially the preferred option with the strategy having the highest probability of being cost-effective at a threshold of £0 per QALY. As the threshold increases,

the strategy of inpatient management if fullPIERS ≥ 30% becomes the preferred option. At the threshold of £20,000 per QALY used by NICE, inpatient management if fullPIERS ≥ 30% has a 53% probability of being cost-effective while outpatient management has a 46% probability of being cost-effective. All other strategies were found to have a 0% probability of being cost-effective at the NICE threshold of £20,000 per QALY.

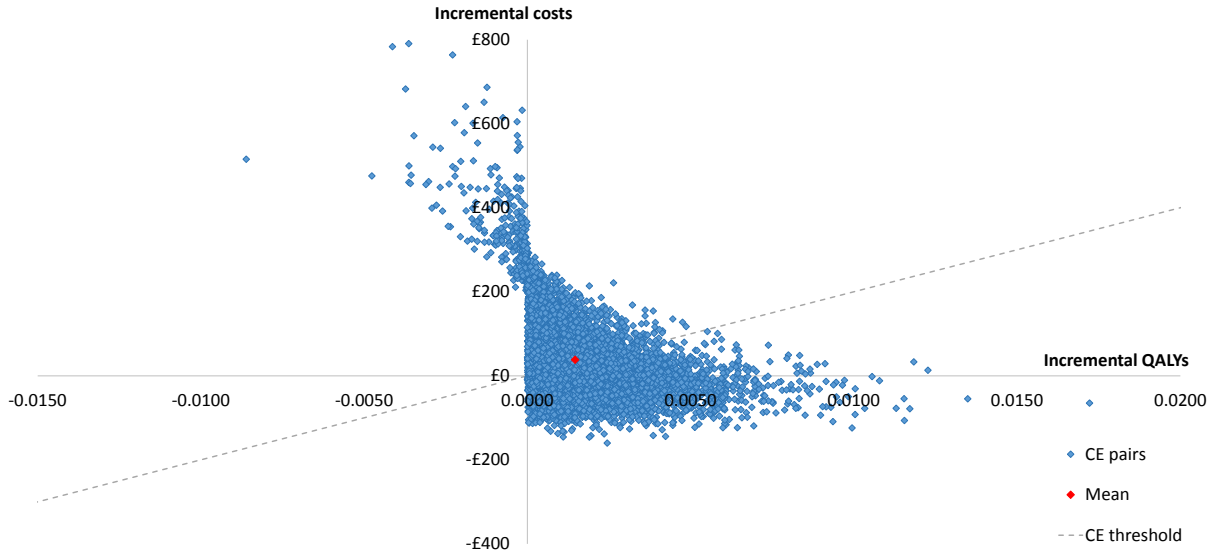
Figure 2: Cost-effectiveness acceptability curves (CEACs)



The results indicate that the comparison between outpatient management and a strategy of inpatient management if fullPIERS ≥ 30% is of the most importance from a cost-effectiveness standpoint. Therefore this comparison is further examined using the ICER scatterplot in Figure 3 which shows the incremental costs and QALYs for inpatient management if fullPIERS ≥ 30% compared to outpatient management for each of the 10,000 runs of the PSA along with the mean result.

From the ICER scatterplot, it can be seen that the vast majority of results reside on the East side of the graph, indicating that a strategy of inpatient management if fullPIERS ≥ 30% is more effective in the vast majority of modelled scenarios. Some of the results reside in the South East quadrant indicating that a strategy of inpatient management if fullPIERS ≥ 30% is more effective and less costly than outpatient management. The majority of the results appear to reside in the North East quadrant indicating that a strategy of inpatient management if fullPIERS ≥ 30% is more effective and more costly than outpatient management. Overall it can be seen that a marginal majority of results lie under the cost-effectiveness threshold line, indicating that a strategy of inpatient management if fullPIERS ≥ 30% is cost-effective more often than outpatient management (which is reflected in the CEAC result).

Figure 3: ICER scatterplot for fullPIERS ≥ 30% in comparison to outpatient management



Conclusion

The base case results of the analysis suggest that using the fullPIERS risk model with a threshold of 30% for inpatient management is cost-effective in women at 34-37 weeks of gestation. However, it should be noted that there are gaps in the clinical evidence base and therefore several assumptions have been made to run the analysis. Most notably, a speculative assumption was made around the reduction in the number of adverse maternal outcomes. Furthermore, deterministic sensitivity analysis suggested that differences in assumptions have the potential to change the conclusion of the analysis and probabilistic sensitivity analysis demonstrated some uncertainty around the result.

Appendix K – Excluded studies

Clinical studies

Table 29: Clinical excluded studies with reasons for exclusion

Study	Reason for Exclusion
AbdelHalim, Radwa Marawan, Ramadan, Dalia Ibrahim, Zeyada, Reham, Nasr, Ahmed Soliman, Mandour, Iman Atef, Circulating Maternal Total Cell-Free DNA, Cell-Free Fetal DNA and Soluble Endoglin Levels in Preeclampsia: Predictors of Adverse Fetal Outcome? A Cohort Study, Molecular diagnosis & therapy, 20, 135-49, 2016	Fewer than 200 participants included
Allotey, J., Thangaratinam, S., Marlin, N., Mol, B., Von Dadelszen, P., Ganzevoort, W., Akkermans, J., Ahmed, A., Daniels, J., Deeks, J., Ismail, K., Barnard, A. M., Dodds, J., Kerry, S., Moons, C., Riley, R. D., Khan, K. S., Development and validation of a prediction model for the risk of adverse outcomes in women with early onset preeclampsia (PREP): Prospective cohort study, American Journal of Obstetrics and Gynecology, 214, S409, 2016	Abstract
Bouzari, Z., Javadiankutenai, M., Darzi, A., Barat, S., Does proteinura in preeclampsia have enough value to predict pregnancy outcome?, Clinical & Experimental Obstetrics & Gynecology, 41, 163-8, 2014	Only individual outcomes have been included
Chaiworapongsa, T, Romero, R, Korzeniewski, Sj, Cortez, Jm, Pappas, A, Tarca, Al, Chaemsaithong, P, Dong, Z, Yeo, L, Hassan, Ss, Plasma concentrations of angiogenic/anti-angiogenic factors have prognostic value in women presenting with suspected preeclampsia to the obstetrical triage area: a prospective study, Journal of maternal-fetal & neonatal medicine, 27, 132-144, 2014	Fewer than 200 participants included
Chaiworapongsa, Tinnakorn, Romero, Roberto, Korzeniewski, Steven J., Kusanovic, Juan Pedro, Soto, Eleazar, Lam, Jennifer, Dong, Zhong, Than, Nandor G., Yeo, Lami, Hernandez-Andrade, Edgar, Conde-Agudelo, Agustin, Hassan, Sonia S., Maternal plasma concentrations of angiogenic/antiangiogenic factors in the third trimester of pregnancy to identify the patient at risk for stillbirth at or near term and severe late preeclampsia, American Journal of Obstetrics and Gynecology, 208, 287.e1-287.e15, 2013	Women with pre-eclampsia were excluded from the study
Chaiworapongsa, Tinnakorn, Romero, Roberto, Savasan, Zeynep Alpay, Kusanovic, Juan Pedro, Ogge, Giovanna, Soto, Eleazar, Dong,	Fewer than 200 participants included

Study	Reason for Exclusion
Zhong, Tarca, Adi, Gaurav, Bhatti, Hassan, Sonia S., Maternal plasma concentrations of angiogenic/anti-angiogenic factors are of prognostic value in patients presenting to the obstetrical triage area with the suspicion of preeclampsia, The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians, 24, 1187-207, 2011	
De Oliveira, L., Peracoli, J. C., Peracoli, M. T., Korkes, H., Zampieri, G., Moron, A. F., Sass, N., SFlt-1/PlGF ratio as a prognostic marker of adverse outcomes in women with early-onset preeclampsia, Pregnancy Hypertension, 3, 191-195, 2013	Fewer than 200 participants have been included
Duckworth, S., Chappell, L. C., Griffin, M., Seed, P. T., Redman, C. W., Shennan, A. H., Plasma Placental Growth Factor (PlGF) in the diagnosis of women with pre-eclampsia requiring delivery within 14 days: The PELICAN study, BJOG: An International Journal of Obstetrics and Gynaecology, 120, e1-e2, 2013	Abstract
Ebrashy, Alaa, Azmy, Osama, Ibrahim, Magdy, Waly, Mohamed, Edris, Amira, Middle cerebral/umbilical artery resistance index ratio as sensitive parameter for fetal well-being and neonatal outcome in patients with preeclampsia: case-control study, Croatian medical journal, 46, 821-5, 2005	Fewer than 200 participants included
Elia, Eleni G., Robb, Amy O., Hemming, Karla, Price, Malcolm J., Riley, Richard D., French-Constant, Anna, Denison, Fiona C., Kilby, Mark D., Morris, Rachel K., Stock, Sarah J., Is the first urinary albumin/creatinine ratio (ACR) in women with suspected preeclampsia a prognostic factor for maternal and neonatal adverse outcome? A retrospective cohort study, Acta Obstetricia et Gynecologica Scandinavica, 96, 580-588, 2017	Not externally validated
Gangaram, Rajesh, Naicker, Manogaran, Moodley, Jagidesa, Comparison of pregnancy outcomes in women with hypertensive disorders of pregnancy using 24-hour urinary protein and urinary microalbumin to creatinine ratio, International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics, 107, 19-22, 2009	Fewer than 200 participants included
Geerts,L., Odendaal,H.J., Severe early onset pre-eclampsia: prognostic value of ultrasound and Doppler assessment, Journal of Perinatology, 27, 335-342, 2007	Fewer than 200 participants included

Study	Reason for Exclusion
Hadley, E. E., Poole, A., Herrera, S. R., Bradley, L., Dutta, E., Sukhavasi, N., Ayad, M., Costantine, M., Pacheco, L., Jain, S., Saade, G., External validation of the fullPIERS (Preeclampsia Integrated Estimate of RiSk) model, American Journal of Obstetrics and Gynecology, 214, S259-S260, 2016	Abstract
Koopmans, Corine M., van der Tuuk, Karin, Groen, Henk, Doornbos, Johannes P. R., de Graaf, Irene M., van der Salm, Pauline C. M., Porath, Martina M., Kuppens, Simone M. I., Wijnen, Ella J., Aardenburg, Robert, van Loon, Aren J., Akerboom, Bettina M. C., van der Lans, Peggy J. A., Mol, Ben W. J., van Pampus, Maria G., Hypitat study group, Prediction of postpartum hemorrhage in women with gestational hypertension or mild preeclampsia at term, Acta Obstetricia et Gynecologica Scandinavica, 93, 399-407, 2014	70% of participants presented with gestational hypertension
Koopmans, Corine M., van Pampus, Maria G., Groen, Henk, Aarnoudse, Jan G., van den Berg, Paul P., Mol, Ben W. J., Accuracy of serum uric acid as a predictive test for maternal complications in pre-eclampsia: bivariate meta-analysis and decision analysis, European journal of obstetrics, gynecology, and reproductive biology, 146, 8-14, 2009	Only individual outcomes have been reported
Kozic, J. R., Benton, S. J., Hutcheon, J. A., Payne, B. A., Magee, L. A., von Dadelszen, P., Ansermino, J. M., Cote, A. M., Cundiff, G., Gruslin, A., Hugo, D., Joseph, K. S., Lalji, S., Lee, S. K., Li, J., Lott, P., Menzies, J., Moutquin, J. M., Ouellet, A. B., Russell, J. A., Shaw, D., Smith, G. N., Still, D. K., Tawagi, G., Wagner, B., Walters, B. N., Mahajan, S., Noovao, A., Kyle, P. M., Moore, M. P., Hall, D., Wilhelm Steyn, D., Biryabarema, C., Mirembe, F., Nakimuli, A., Pipkin, F. B., Loughna, P., Walker, J. J., Grobman, W., Tsigas, E., Merialdi, M., Widmer, M., Abnormal Liver Function Tests as Predictors of Adverse Maternal Outcomes in Women With Preeclampsia, Journal of Obstetrics and Gynaecology Canada, 33, 995-1004, 2011	No sensitivity and specificity measures reported
Martin, J. N., Jr., May, W. L., Magann, E. F., Terrone, D. A., Rinehart, B. K., Blake, P. G., Taslimi, M. M., Witlin, A. G., Early risk assessment of severe preeclampsia: Admission battery of symptoms and laboratory tests to predict likelihood of subsequent significant maternal morbidity, American Journal of Obstetrics and Gynecology, 180, 1407-1414, 1999	Not externally validated

Study	Reason for Exclusion
Menzies, J., Magee, L. A., Macnab, Y. C., Ansermino, J. M., Li, J., Douglas, M. J., Gruslin, A., Kyle, P., Lee, S. K., Moore, M. P., Moutquin, J. M., Smith, G. N., Walker, J. J., Walley, K. R., Russell, J. A., von Dadelszen, P., Current CHS and NHBPEP criteria for severe preeclampsia do not uniformly predict adverse maternal or perinatal outcomes, Hypertension in Pregnancy, 26, 447-62, 2007	Prognostic accuracy data was not reported. Note that this study is included in Thangaratinam 2011, but only reported the predictive value for LDH and ALT/AST and not other maternal symptoms
Millman, A. L., Payne, B., Qu, Z., Joanne Douglas, M., Hutcheon, J. A., Lee, T., Magee, L. A., Walley, K. R., von Dadelszen, P., Walters, B. N., Ansermino, J. M., Benton, S., Cote, A. M., Cundiff, G., Gruslin, A., Hugo, D., Joseph, K. S., Lalji, S., Lee, S. K., Li, J., Lott, P., Menzies, J., Moutquin, J. M., Ouellet, A. B., Russell, J. A., Shaw, D., Smith, G. N., Still, D. K., Tawagi, G., Wagner, B., Mahajan, S., Noovao, A., Kyle, P. M., Moore, M. P., Hall, D., Steyn, D. W., Biryabarema, C., Mirembe, F., Nakimuli, A., Pipkin, F. B., Loughna, P., Walker, J. J., Grobman, W., Tsigas, E., Merialdi, M., Widmer, M., Oxygen Saturation as a Predictor of Adverse Maternal Outcomes in Women with Preeclampsia, Journal of Obstetrics and Gynaecology Canada, 33, 705-714, 2011	No sensitivity and specificity measures reported
Moore Simas, Tiffany A., Crawford, Sybil L., Solitro, Matthew J., Frost, Sara C., Meyer, Bruce A., Maynard, Sharon E., Angiogenic factors for the prediction of preeclampsia in high-risk women, American Journal of Obstetrics and Gynecology, 197, 244.e1-8, 2007	Included in Ukah 2017b
Moore, A., Young, H., Keller, J., Ojo, L., Yan, J., Simas, T. M., Maynard, S., Angiogenic biomarkers for the prediction of pregnancy complications in women with suspected preeclampsia, American Journal of Obstetrics and Gynecology, 206, S326-S327, 2012	Abstract
Moore, Andreea G., Young, Heather, Keller, Jennifer M., Ojo, Linda R., Yan, Jing, Simas, Tiffany A. Moore, Maynard, Sharon E., Angiogenic biomarkers for prediction of maternal and neonatal complications in suspected preeclampsia, The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians, 25, 2651-7, 2012	Women did not have a confirmed diagnosis of pre-eclampsia, less than 200 participants included
Orabona, Rossana, Gerosa, Vera, Gregorini, Maria Elena, Pagani, Giorgio, Prefumo, Federico, Valcamonico, Adriana, Frusca, Tiziana, The prognostic role of various indices	Less than 200 participants included

Study	Reason for Exclusion
and ratios of Doppler velocimetry in patients with pre-eclampsia, Clinical and experimental hypertension (New York, N.Y. : 1993), 37, 57-62, 2015	
Oztas, E., Ozler, S., Ersoy, A. O., Iskender, C. T., Sucak, A., Ergin, M., Uygur, D., Danisman, N., Increased levels of serum clusterin is associated with intrauterine growth restriction and adverse pregnancy outcomes in preeclampsia, Journal of Perinatal Medicine, 44, 269-275, 2016	Less than 200 participants included
Pagani, G., Gerosa, V., Gregorini, M. E., Rovida, P. L., Prefumo, F., Valcamonico, A., Frusca, T., Andrea, L., The role of doppler to predict adverse pregnancy outcome in patients with pre-eclampsia, Pregnancy Hypertension, 2, 298-299, 2012	Less than 200 participants included
Payne, B., Hodgson, S., Hutcheon, J. A., Joseph, K. S., Li, J., Lee, T., Magee, L. A., Qu, Z., Von Dadelszen, P., Performance of the fullPIERS model in predicting adverse maternal outcomes in pre-eclampsia using patient data from the PIERS (Pre-eclampsia Integrated Estimate of RiSk) cohort, collected on admission, BJOG: An International Journal of Obstetrics and Gynaecology, 120, 113-118, 2013	Not an external validation study
Payne, B., Hutcheon, J. A., Qu, Z., Haniff, F., Bhutta, Z., Biryabarema, C., Duan, T., Hall, D. R., Grobman, W. A., Groen, H., Magee, L. A., Merialdi, M., Mirembe, F., Nakimuli, A., Qureshi, R., Sass, N., Sikandar, R., Steyn, W., Widmer, M., Zhou, V., Von Dadelszen, P., Minipiers (pre-eclampsia integrated estimate of risk): Development of a clinical prediction model for use in low and middle income countries (LMIC), Pregnancy Hypertension, 2, 195-196, 2012	Abstract
Payne, B., Magee, L. A., Cote, A. M., Hutcheon, J. A., Li, J., Kyle, P. M., Menzies, J. M., Peter Moore, M., Parker, C., Pullar, B., von Dadelszen, P., Walters, B. N., Douglas, M. J., Walley, K. R., Russell, J. A., Lee, S. K., Gruslin, A., Smith, G. N., Moutquin, J. M., Brown, M. A., Davis, G., Sass, N., Duan, T., Zhou, J., Mahajan, S., Noovao, A., McCowan, L. A., Moore, M. P., Bhutta, S. Z., Bhutta, Z. A., Hall, D. R., Steyn, D. W., Broughton Pipkin, F., Loughna, P., Robson, S., de Swiet, M., Walker, J. J., Grobman, W. A., Lindheimer, M. D., Roberts, J. M., Mark Ansermino, J., Benton, S., Cundiff, G., Hugo, D., Joseph, K. S., Lalji, S., Lott, P., Ouellet, A. B., Shaw, D., Keith Still, D., Tawagi, G., Wagner, B., Biryabarema, C., Mirembe, F., Nakimuli, A., Tsigas, E., Merialdi,	No sensitivity and specificity measures reported

Study	Reason for Exclusion
M., Widmer, M., PIERS Proteinuria: Relationship With Adverse Maternal and Perinatal Outcome, Journal of Obstetrics and Gynaecology Canada, 33, 588-597, 2011	
Payne, Ba, Kyle, Pm, Lim, K, Lisonkova, S, Magee, La, Pullar, B, Qu, Z, Dadelszen, P, An assessment of predictive value of the biophysical profile in women with preeclampsia using data from the fullPIERS database, Pregnancy Hypertension, 3, 166-171, 2013	Less than 200 participants included
Rana, S., Powe, C. E., Salahuddin, S., Verlohren, S., Perschel, F. H., Levine, R. J., Lim, K. H., Wenger, J. B., Thadhani, R., Karumanchi, S. A., Angiogenic factors and the risk of adverse outcomes in women with suspected preeclampsia, Circulation, 125, 911-919, 2012	Included in Ukah 2017b
Saleh, L., Verdonk, K., Danser, A. H. J., Steegers, E. A. P., Russcher, H., Van Den Meiracker, A. H., Visser, W., The preratio study: Is the SFLT-1/PLGF ratio a suitable marker to diagnose preeclampsia and to predict adverse maternal/neonatal pregnancy outcome?, Journal of Hypertension, 33, e347-e348, 2015	Abstract
Saleh, L., Vergouwe, Y., Danser, A. H. J., Verdonk, K., Steegers, E. A. P., Russcher, H., Van Den Meiracker, A. H., Visser, W., The added value of the biomarkers SFLT-1, PLGF and their ratio on prediction of prolongation of pregnancy and maternal and foetal complications in (suspected) preeclampsia, Journal of Hypertension, 35, e177, 2017	Abstract
Saralaya, S., Do elevated serum uric acid levels lead to adverse outcomes in pregnancies with pre-eclampsia? Results from a tertiary hospital in South India, Journal of Obstetrics and Gynaecology Research, 43, 75, 2017	Less than 200 participants included
Tardif, C., Dumontet, E., Caillon, H., Misbert, E., Dochez, V., Masson, D., Winer, N., Angiogenic factors sFlt-1 and PlGF in preeclampsia: Prediction of risk and prognosis in a high-risk obstetric population, Journal of gynecology obstetrics and human reproduction, 47, 17-21, 2018	Less than 200 participants included
Thangaratinam, S., Datta, A., Ismail, K. M. K., Khan, K. S., What is the accuracy of blood pressure in predicting complications in pre-eclampsia?, Archives of Disease in Childhood: Fetal and Neonatal Edition, 96, 2011	Abstract
Thangaratinam, S., Gallos, I. D., Meah, N., Usman, S., Ismail, K. M. K., Khan, K. S., How accurate are maternal symptoms in predicting impending complications in women with preeclampsia? A systematic review and meta-	Only individual outcomes have been reported with the exception of 1 study (Menzies 1997), which was included separately in this evidence report.

Study	Reason for Exclusion
analysis, Acta Obstetricia et Gynecologica Scandinavica, 90, 564-573, 2011	
Thangaratinam, S., Ismail, K. M. K., Sharp, S., Coomarasamy, A., Khan, K. S., Accuracy of serum uric acid in predicting complications of pre-eclampsia: A systematic review, BJOG: An International Journal of Obstetrics and Gynaecology, 113, 369-378, 2006	Only individual outcomes have been reported
Thangaratinam, S., Ismail, K., Sharp, S., Coomarasamy, A., O'Mahony, F., Khan, K. S., O'Brien, S., Prioritisation of tests for the prediction of preeclampsia complications: A Delphi survey, Hypertension in Pregnancy, 26, 131-138, 2007	Not externally validated
Thangaratinam, Shakila, Allotey, John, Marlin, Nadine, Mol, Ben W., Von Dadelszen, Peter, Ganzevoort, Wessel, Akkermans, Joost, Ahmed, Asif, Daniels, Jane, Deeks, Jon, Ismail, Khaled, Barnard, Ann Marie, Dodds, Julie, Kerry, Sally, Moons, Carl, Riley, Richard D., Khan, Khalid S., Development and validation of Prediction models for Risks of complications in Early-onset Pre-eclampsia (PREP): a prospective cohort study, Health technology assessment (Winchester, England), 21, 1-100, 2017	The same content was covered by Thangaratinam 2017
Thangaratinam, Shakila, Coomarasamy, Arri, O'Mahony, Fidelma, Sharp, Steve, Zamora, Javier, Khan, Khalid S., Ismail, Khaled M. K., Estimation of proteinuria as a predictor of complications of pre-eclampsia: a systematic review, BMC Medicine, 7, 10, 2009	Only individual outcomes have been reported
Thida, M., Latt, K., Mar, O., Swe, A. T., Yi, E. E. P. N., Shein, T. M. M., Role of red blood cell deformability and serum magnesium level in prediction of severity, maternal and fetal outcomes in preeclampsia at the Central Women's Hospital, Yangon, Journal of Obstetrics and Gynaecology Research, 43, 32-33, 2017	Fewer than 200 participants included
Ukah, U. Vivian, De Silva, Dane A., Payne, Beth, Magee, Laura A., Hutcheon, Jennifer A., Brown, Helen, Ansermino, J. Mark, Lee, Tang, von Dadelszen, Peter, Prediction of adverse maternal outcomes from pre-eclampsia and other hypertensive disorders of pregnancy: A systematic review, Pregnancy Hypertension, 2017	This systematic review included studies with women who did not present with pre-eclampsia
Von Dadelszen, P., Payne, B., Li, J., Ansermino, J. M., Pipkin, F. B., Cote, A. M., Douglas, M. J., Gruslin, A., Hutcheon, J. A., Joseph, K. S., Kyle, P. M., Lee, T., Loughna, P., Menzies, J. M., Merialdi, M., Millman, A. L., Moore, M. P., Moutquin, J. M., Ouellet, A. B., Smith, G. N.,	Not externally validated study

Study	Reason for Exclusion
Walker, J. J., Walley, K. R., Walters, B. N., Widmer, M., Lee, S. K., Russell, J. A., Magee, L. A., Prediction of adverse maternal outcomes in pre-eclampsia: Development and validation of the fullPIERS model, The Lancet, 377, 219-227, 2011	
von Dadelszen, Peter, Menzies, Jennifer M., Payne, Beth, Magee, Laura A., Piers Study Group, Predicting adverse outcomes in women with severe pre-eclampsia, Seminars in Perinatology, 33, 152-7, 2009	Narrative review
Waugh, Jason, Bell, Stephen C., Kilby, Mark D., Lambert, Paul, Shennan, Andrew, Halligan, Aidan, Urine protein estimation in hypertensive pregnancy: which thresholds and laboratory assay best predict clinical outcome?, Hypertension in Pregnancy, 24, 291-302, 2005	Fewer than 200 participants included
Woelkers, D. A., Von Dadelszen, P., Sibai, B., Diagnostic and prognostic performance of placenta growth factor (PLGF) in women with signs or symptoms of early preterm preeclampsia, American Journal of Obstetrics and Gynecology, 214, S264, 2016	Abstract
Woelkers, D. A., Von Dadelszen, P., Sibai, B., Placenta Growth Factor (PLGF) predicts time to delivery in women with signs or symptoms of early preterm preeclampsia, American Journal of Obstetrics and Gynecology, 214, S25-S26, 2016	Abstract
Wu, Pensee, van den Berg, Caroline, Alfirevic, Zarko, O'Brien, Shaughn, Rothlisberger, Maria, Baker, Philip Newton, Kenny, Louise C., Kublickiene, Karolina, Duvekot, Johannes J., Early Pregnancy Biomarkers in Pre-Eclampsia: A Systematic Review and Meta-Analysis, International Journal of Molecular Sciences, 16, 23035-56, 2015	This systematic review assessed predictors for detecting women at high risk of developing pre-eclampsia
Yen, T. W., Payne, B., Qu, Z., Hutcheon, J. A., Lee, T., Magee, L. A., Walters, B. N., von Dadelszen, P., Using Clinical Symptoms to Predict Adverse Maternal and Perinatal Outcomes in Women With Preeclampsia: Data From the PIERS (Pre-eclampsia Integrated Estimate of RiSk) Study, Journal of Obstetrics and Gynaecology Canada, 33, 803-809, 2011	No sensitivity and specificity measures reported
Zeisler, Harald, Llurba, Elisa, Chantraine, Frederic, Vatish, Manu, Staff, Anne Cathrine, Sennstrom, Maria, Olovsson, Matts, Brennecke, Shaun P., Stepan, Holger, Allegranza, Deirdre, Dinkel, Carina, Schoedl, Maria, Dilba, Peter, Hund, Martin, Verlohren, Stefan, Soluble fms-Like Tyrosine Kinase-1-to-Placental Growth Factor Ratio and Time to Delivery in Women	Correlational study, women had unconfirmed pre-eclampsia

Study	Reason for Exclusion
With Suspected Preeclampsia, Obstetrics and Gynecology, 128, 261-9, 2016	

Economic studies

Table 30: Economic excluded studies with reasons for exclusion

Study	Reason for Exclusion
Delahaije DH, van Kuijk SM, Dirksen CD, Sep SJ, Peeters LL, Spaanderman ME, Bruinse HW, de Wit-Zuurendonk LD, van der Post JA, Duvekot JJ, van Eyck J, van Pampus MG, van der Hoeven MA., Smits LJ. Cost-effectiveness of recurrence risk guided care versus care as usual in women who suffered from early-onset preeclampsia including HELLP syndrome in their previous pregnancy (the PreCare study). BMC pregnancy and childbirth, 10, 60. 2010	No results presented (study protocol only)
Frampton GK, Jones J, Rose M, Payne L. Placental growth factor (alone or in combination with soluble fms-like tyrosine kinase 1) as an aid to the assessment of women with suspected pre-eclampsia: systematic review and economic analysis. Health Technol Assess;20(87) 2016	Considers different population - women with suspected pre-eclampsia rather than women with pre-eclampsia
Frusca T, Gervasi MT, Paolini D, Dionisi M, Ferre F, Cetin I. Budget impact analysis of sFlt-1/PlGF ratio as prediction test in Italian women with suspected preeclampsia, The Journal of Maternal-Fetal & Neonatal Medicine, 30:18, 2166-2173 2017	Considers different population - women with suspected pre-eclampsia rather than women with pre-eclampsia
Hadker N, Garg S, Costanzo C, Miller JD, Foster T, Van der Helm W, Creeden J. Financial impact of a novel pre-eclampsia diagnostic test versus standard practice: a decision-analytic modeling analysis from a UK healthcare payer perspective, Journal of Medical Economics, 13:4, 728-737 2010	Considers different population - women with suspected pre-eclampsia rather than women with pre-eclampsia
Meads CA, Cnossen JS, Meher S, Juarez-Garcia A,ter Riet G, Duley L, Roberts TE, Mol BW, Van der Post JA, Leeflang MM, Barton PM, Hyde CJ, Gupta JK, Khan KS. Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling. Health Technol Assess;12(6). 2008	Considers different population - women with suspected pre-eclampsia rather than women with pre-eclampsia
Paolini D, Dionisi M, Frusca T, Gervasi MT, Cetin I. Value in Health 19(7) A688 2016.	Considers different population - women with suspected pre-eclampsia rather than women with pre-eclampsia

Study	Reason for Exclusion
Shmueli A, Meiri H, Gonen R. Economic assessment of screening for pre-eclampsia. Prenat Diagn, 32: 29-38 2012	Considers different population - women with suspected pre-eclampsia rather than women with pre-eclampsia

Appendix L – Research recommendations

No research recommendations were made for this review question.