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Abstract

Development and validation of Prediction models for Risks of complications in Early-onset Pre-eclampsia (PREP): a prospective cohort study

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Background: The prognosis of early-onset pre-eclampsia (before 34 weeks' gestation) is variable. Accurate prediction of complications is required to plan appropriate management in high-risk women.

Objective: To develop and validate prediction models for outcomes in early-onset pre-eclampsia.

Design: Prospective cohort for model development, with validation in two external data sets.

Setting: Model development: 53 obstetric units in the UK. Model transportability: PIERS (Pre-eclampsia Integrated Estimate of RiSk for mothers) and PETRA (Pre-Eclampsia TRial Amsterdam) studies.

Participants: Pregnant women with early-onset pre-eclampsia.

Sample size: Nine hundred and forty-six women in the model development data set and 850 women (634 in PIERS, 216 in PETRA) in the transportability (external validation) data sets.

Predictors: The predictors were identified from systematic reviews of tests to predict complications in pre-eclampsia and were prioritised by Delphi survey.

Main outcome measures: The primary outcome was the composite of adverse maternal outcomes established using Delphi surveys. The secondary outcome was the composite of fetal and neonatal complications.

Analysis: We developed two prediction models: a logistic regression model (PREP-L) to assess the overall risk of any maternal outcome until postnatal discharge and a survival analysis model (PREP-S) to obtain individual risk estimates at daily intervals from diagnosis until 34 weeks. Shrinkage was used to adjust for overoptimism of predictor effects. For internal validation (of the full models in the development data) and external validation (of the reduced models in the transportability data), we computed the ability of the models to discriminate between those with and without poor outcomes (*c*-statistic), and the agreement between predicted and observed risk (calibration slope).

Results: The PREP-L model included maternal age, gestational age at diagnosis, medical history, systolic blood pressure, urine protein-to-creatinine ratio, platelet count, serum urea concentration, oxygen saturation, baseline treatment with antihypertensive drugs and administration of magnesium sulphate. The PREP-S model additionally included exaggerated tendon reflexes and serum alanine aminotransaminase and creatinine concentration. Both models showed good discrimination for maternal complications, with an optimism-adjusted *c*-statistic of 0.82 [95% confidence interval (CI) 0.80 to 0.84] for PREP-L and 0.75 (95% CI 0.73 to 0.78) for the PREP-S model in the internal validation. External validation of the reduced PREP-L model showed good performance with a *c*-statistic of 0.81 (95% CI 0.77 to 0.85) in PIERS and 0.75 (95% CI 0.64 to 0.86) in PETRA cohorts for maternal complications, and calibrated well with slopes of 0.93 (95% CI 0.72 to 1.10) and 0.90 (95% CI 0.48 to 1.32), respectively. In the PIERS data set, the reduced PREP-S model had a *c*-statistic of 0.71 (95% CI 0.67 to 0.75) and a calibration slope of 0.67 (95% CI 0.56 to 0.79). Low gestational age at diagnosis, high urine protein-to-creatinine ratio, increased serum urea concentration, treatment with antihypertensive drugs, magnesium sulphate, abnormal uterine artery Doppler scan findings and estimated fetal weight below the 10th centile were associated with fetal complications.

Conclusions: The PREP-L model provided individualised risk estimates in early-onset pre-eclampsia to plan management of high- or low-risk individuals. The PREP-S model has the potential to be used as a triage tool for risk assessment. The impacts of the model use on outcomes need further evaluation.

Trial registration: Current Controlled Trials ISRCTN40384046.

Funding: The National Institute for Health Research Health Technology Assessment programme.

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AIC	Akaike information criterion
ALT	alanine aminotransaminase
APEC	Action on Pre-Eclampsia Charity
AST	aspartate transaminase
BIC	Bayesian information criterion
BP	blood pressure
CI	confidence interval
CTG	cardiotocography
FP	fractional polynomial
HELLP	haemolysis, elevated liver enzymes, low platelets
MFP	multivariable fractional polynomial
PCR	protein-to-creatinine ratio
PETRA	Pre-Eclampsia TRial Amsterdam
PIERS	Pre-eclampsia Integrated Estimate of RiSk
PREP	Prediction of Risks in Early-onset Pre-eclampsia
PREP-L	Prediction of Risks in Early-onset Pre-eclampsia – logistic model
PREP-S	Prediction of Risks in Early-onset Pre-eclampsia – survival model
rPREP-L	Prediction of Risks in Early-onset Pre-eclampsia – reduced logistic model
rPREP-S	Prediction of Risks in Early-onset Pre-eclampsia – reduced survival model
RR	relative risk
SD	standard deviation
SOGC	Society of Obstetricians and Gynaecologists in Canada
TRIPOD	Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis

Plain English summary

Pre-eclampsia is a disorder in pregnancy, characterised by raised blood pressure and protein in the urine. When it occurs before 34 weeks of pregnancy (early onset), it causes serious complications for the mother and baby. The only known cure for pre-eclampsia is delivery of the baby. There is a lack of sufficient evidence regarding the ability of tests to correctly predict complications to the mother or baby to inform management.

The PREP (Prediction of Risks in Early-onset Pre-eclampsia) study aims to provide estimates of risks faced by mothers, using tests that are routinely performed in the NHS.

We developed two models. The first model (PREP-L) provided overall individual risk estimates from diagnosis of early-onset pre-eclampsia until discharge. The second model (PREP-S) provided risk estimates at various time points from diagnosis until 34 weeks of pregnancy. The models' performance was assessed in populations outside the UK (Canada and the Netherlands).

A total of 946 women with early-onset pre-eclampsia from 53 hospitals in the UK participated in the study. For 82% of the women participating, the PREP-L model accurately predicted those mothers who will develop complications. The PREP-S model predicted accurately in 76% of women. The PREP-L model performed similarly in non-UK populations. Both models showed that the results could be generalised in an external population. Further studies are needed to assess the impact of the models' use in improving outcomes for the mother and baby.

Scientific summary

Background

Women with early-onset pre-eclampsia (before 34 weeks' gestation) are at high risk of maternal and fetal complications. Early identification of pregnancies at high risk is required to plan transfer of mothers to a tertiary care unit, commence intense monitoring and administer corticosteroids for fetal lung maturity.

Objectives

Primary

To develop prediction models to assess the overall risk of composite maternal outcomes in women with early-onset pre-eclampsia by postnatal discharge and at various time points after the diagnosis of the condition and to validate the performance of these prediction models in external data sets for assessment of transportability.

Secondary

To assess the predictive value of baseline maternal and fetal characteristics and tests for fetal and neonatal complications at birth and by discharge.

Methods

We developed and externally validated two prediction models: a logistic model (PREP-L) to assess the risk of any maternal complication until postnatal discharge and a survival analysis model (PREP-S) to predict the risk of composite maternal outcome at various time points after diagnosis and until 34 weeks' gestation.

Development of the models

Data source

We undertook a prospective observational study [Prediction of Risks in early-onset Pre-eclampsia (PREP)]. Consecutive eligible women with early-onset pre-eclampsia were recruited from 53 secondary and tertiary care maternity units in the UK. Pregnant women presenting with uncomplicated early-onset pre-eclampsia before 34 weeks' gestation were recruited to the study if they satisfied the following inclusion criteria:

- new-onset pre-eclampsia, defined as new-onset hypertension [systolic blood pressure (BP) of $\geq$ 140 mmHg or diastolic BP of $\geq$ 90 mmHg on two occasions between 4 and 6 hours apart] after 20 weeks of pregnancy and new-onset proteinuria (2+ or more on a urine dipstick or urine protein-to-creatinine ratio (PCR) of > 30 mg/mmol or 300 mg of protein excretion in 24 hours)
- superimposed pre-eclampsia diagnosed in women with chronic hypertension before 20 weeks' gestation and new-onset proteinuria. In women with significant proteinuria before 20 weeks' gestation, we defined superimposed pre-eclampsia as elevated serum alanine aminotransferase concentration (> 70 units per litre) or worsening hypertension (either two diastolic BP measurements of at least 110 mmHg 4 hours apart or one diastolic BP measurement of at least 110 mmHg if the woman had been treated with an antihypertensive drug) and one of the following: increasing proteinuria, persistent severe headaches or epigastric pain
- haemolysis, elevated liver enzymes, low platelets (HELLP) syndrome
- one episode of eclamptic seizures with no hypertension or proteinuria.

Additionally, we recruited women with suspected pre-eclampsia, with new-onset hypertension and 1+ proteinuria on a urine dipstick. Only those women whose diagnosis of pre-eclampsia was confirmed subsequently with significant proteinuria (PCR > 30 mg/mmol or 24-hour urine protein concentration > 300 mg) were included in the primary models.

Candidate predictors

We evaluated the predictive ability of tests that were routinely performed in women with pre-eclampsia. We identified 22 maternal and 27 fetal predictors a priori through systematic reviews and Delphi surveys for their association with adverse outcomes and their availability in the UK NHS.

We evaluated the following:

- maternal characteristics including age, gestation at diagnosis of pre-eclampsia and number of fetuses in pregnancy
- medical history including pre-existing hypertension, renal disease, diabetes mellitus, autoimmune disease and/or history of pre-eclampsia in previous pregnancies
- symptoms including headache and/or visual disturbance, epigastric pain, nausea and/or vomiting, chest pain and dyspnoea
- bedside examination findings and tests including BP, clonus, tendon reflex, oxygen saturation and urine dipstick
- laboratory investigations including haemoglobin levels, platelet counts, urine PCR serum and concentrations of alanine aminotransaminase (ALT), serum aspartate transaminase (AST), serum uric acid, serum urea and serum creatinine
- treatment measures including administration of antihypertensives and magnesium sulphate.

In addition, we considered estimated fetal weight and liquor volume by ultrasound, uterine artery Doppler, cardiotocography findings and administration of steroids for prediction of fetal outcomes.

Outcomes

The primary outcome, established using Delphi surveys of experts in the field, was a composite maternal outcome which included at least one of the following: eclamptic seizures, Glasgow Coma Scale score of < 13, stroke or reversible ischaemic neurological deficit (RIND), cortical blindness, retinal detachment, posterior reversible encephalopathy, Bell's palsy, hepatic dysfunction, liver haematoma or rupture, need for positive inotrope support, myocardial ischaemia or infarction, at least 50% fraction of inspired oxygen (FiO_2) for > 1 hour, intubation, pulmonary oedema, acute renal insufficiency, dialysis, transfusion of any blood product, abruptio placentae and postpartum haemorrhage and delivery before 34 weeks' gestation.

The secondary outcome was a composite fetal outcome, which included one or more of the following: perinatal or infant mortality, bronchopulmonary dysplasia, necrotising enterocolitis, grade III/IV intraventricular haemorrhage, cystic periventricular leukomalacia, stage 3–5 retinopathy of prematurity, hypoxic–ischaemic encephalopathy, stillbirth and admission to the neonatal intensive care unit.

Sample size

We aimed to evaluate 10 candidate predictors in our multivariable model, with at least 10 events per candidate predictor variable. We assumed that 20% of women with early-onset pre-eclampsia would have adverse maternal outcomes, with the objective to continue recruitment until 100 events were reached. Prior to the analysis, we included preterm delivery before 34 weeks as an outcome and we were able to study over 20 predictors.

Analysis

Candidate predictors that did not show a normal distribution were log-transformed to improve model fit. We dealt with missing data by multiple imputation for missing predictor values, except for oxygen saturation, missing values of which were assumed to be normal. The backward selection procedure was done to identify predictors for inclusion in the models. Non-linear terms were identified using fractional polynomials. PREP-L was used to predict risks of any adverse outcome by discharge, and a flexible parametric model censored at 34 weeks' gestation was used for PREP-S. The apparent model performance was evaluated for its ability to discriminate those with and without the outcome (Harrell's *c*-statistic for survival model and the *c*-statistic for the logistic model) and for calibration defined as the agreement between observed and predicted risks (by visual inspection of calibration plots).

We internally validated the model by using bootstrapping techniques that quantified the model's potential for overfitting, and the amount of optimism in the model's performance. We then calculated the optimism-adjusted *c*-statistic for each model and reduced the predictor effects in the final models by a uniform shrinkage factor to adjust for optimism.

External validation of the model

We assessed the performance of the models to predict adverse maternal outcomes in the two external cohorts from the Pre-eclampsia Integrated Estimate of RiSk for mothers (PIERS) and the Pre-Eclampsia TRial Amsterdam (PETRA) studies. Owing to the missing predictors in the PETRA and PIERS cohorts, it was necessary to reduce the number of predictor variables in the original PREP models, and the reduced logic model and survival model (rPREP-L and rPREP-S, respectively) were externally validated.

Results

Between December 2011 and April 2014, 1101 women with suspected or confirmed early-onset pre-eclampsia were recruited to the study. Of these, the diagnosis was confirmed and maternal outcomes were known in 946 women. Two-thirds (633/946, 66.9%) experienced at least one adverse maternal outcome by discharge and 584 (61.7%) experienced an adverse outcome before 34 weeks' gestation.

Prediction of adverse maternal outcomes

Apparent performance of the PREP-L model

The model included maternal age, gestational age at diagnosis, summary score for medical history (1 point for pre-existing chronic hypertension, renal disease, diabetes mellitus, autoimmune disease or previous history of pre-eclampsia), systolic BP, urine PCR, platelet count, serum urea concentration, baseline treatment with any antihypertensive drug and administration of magnesium sulphate. The apparent performance of the model showed an optimism-adjusted *c*-statistic of 0.82 [95% confidence interval (CI) 0.80 to 0.84] for composite adverse maternal outcomes.

Apparent performance of the PREP-S model

In addition to the predictors included in the PREP-L model, the PREP-S model included exaggerated tendon reflexes, and concentrations of serum ALT and serum creatinine. The model showed a discrimination (Harrell's *c*-statistic) of 0.75 (95% CI 0.73 to 0.78) for maternal complication after adjusting for optimism.

Performance of the models in external data sets

Data on exaggerated tendon reflexes, serum urea concentration and autoimmune disease in medical history were not available in the external cohorts. Therefore, we used reduced rPREP-L and rPREP-S models without these predictors for validation.

The rPREP-L model showed good discrimination in the PIERS and PETRA data sets, with a *c*-statistic of 0.81 (95% CI 0.77 to 0.85) and 0.75 (95% CI 0.64 to 0.86), respectively, for maternal complications. The calibration slope was 0.93 (95% CI 0.72 to 1.10) in the PIERS and 0.90 (95% CI 0.48 to 1.32) in the PETRA cohort.

The rPREP-S model showed a discrimination of 0.71 (95% CI 0.67 to 0.75) in the PIERS cohort, and a calibration slope of 0.67 (95% CI 0.56 to 0.79) for adverse maternal outcomes, which suggested large overprediction of the reduced PREP-S model. We did not validate the PREP-S model in the PETRA data set because of a lack of information on the timing of outcomes.

Prediction of fetal complications

Multivariable analysis of predictors showed that an increased gestational age at diagnosis of pre-eclampsia reduced the odds of fetal complications [odds ratio (OR) 0.09, 95% CI 0.01 to 0.61]. A medical history of pre-existing chronic hypertension, diabetes mellitus, autoimmune disease or renal disease or a history of pre-eclampsia in previous pregnancies reduced the odds of composite adverse fetal outcomes (OR 0.65, 95% CI 0.44 to 0.98) for one pre-existing medical condition and (OR 0.43, 95% CI 0.25 to 0.77) for two or more pre-existing medical conditions. The odds of fetal complications were significantly increased in women with raised urine PCR (OR 1.29, 95% CI 1.11 to 1.50) or serum urea concentration (OR 1.72, 95% CI 1.07 to 2.76), in women being treated with antihypertensive drugs (OR 1.56, 95% CI 1.04 to 2.37) or magnesium sulphate (OR 2.40, 95% CI 1.04 to 5.57), in women in whom uterine artery Doppler scanning was abnormal (OR 1.94, 95% CI 1.08 to 3.51) and when expected fetal weight was less than the 10th centile, as determined by ultrasound scanning (OR 2.54, 95% CI 1.46 to 4.40).

Conclusions

The PREP-L model provides accurate predictions of the overall severity of the disease, and will be crucial to plan subsequent care, such as regular follow-ups and admission of high-risk individuals and outpatient management of those at low risk. The reduced PREP-L model has excellent discrimination and calibration, even when transported to external validation data sets outside the UK. We expect the full PREP-L model to have similar, if not better, performance.

The PREP-S model can provide individual risk estimates for adverse maternal outcomes, at various time points after a diagnosis of early-onset pre-eclampsia to plan management. External validation of the reduced PREP-S model in a non-UK population shows similar discrimination, but recalibration may be required to improve the accuracy of predicted risks in populations outside the UK.

Future work recommendations

Further research may examine the impact of implementing the PREP-S and PREP-L models into clinical practice, in terms of their uptake by clinicians and their impact on patient outcomes.

Trial registration

This trial is registered as ISRCTN40384046.

Funding

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Chapter 1 Introduction

Burden of pre-eclampsia

Pre-eclampsia is a multisystem disorder in pregnancy associated with hypertension and proteinuria.[1–3] Hypertension is defined as systolic blood pressure (BP) of ≥ 140 mmHg and diastolic BP of ≥ 90 mmHg on two occasions between 4 and 6 hours apart.[1–3] Proteinuria is defined as ≥ 300 mg of protein in a 24-hour urine collection period or urine dipstick of 1+ or more in two samples collected 6 hours apart or a spot urine protein-to-creatinine ratio (PCR) of at least 30 mg/mmol.[2–4] Hypertensive diseases in pregnancy remain one of the leading causes of direct maternal deaths in the UK and account for 20% of all stillbirths.[5] In 1% of pregnant women, pre-eclampsia develops before 34 weeks' gestation and thus is called early-onset pre-eclampsia.[6,7]

Early-onset pre-eclampsia is considered to be a pathophysiologically different disease from late-onset pre-eclampsia, with considerably increased risk of maternal complications, including a 20-fold higher maternal mortality.[8–10] The only known cure for this condition is delivery of the baby and placenta. In women with early-onset pre-eclampsia, decisions on the timing of delivery can be difficult, as fetal and neonatal benefits from prolongation of pregnancy beyond preterm gestation need to be balanced against the risk of multisystem dysfunction in the mother. Preterm delivery accounts for 65% of neonatal deaths and 50% of neurological disability in childhood.[11] Many of the current practice guidelines do not consider gestational age at presentation as a criterion for diagnosis, severity or subclassification to stratify risk in women with pre-eclampsia.[2,12]

The complexity of the treatment in early-onset pre-eclampsia gives rise to high health-care costs.[6,7] Women are often admitted to a tertiary care facility, and one-third experience complications, which may necessitate admission to an intensive care facility.[13] Infants usually need prolonged intensive care treatment for the management of complications, including lifelong handicaps arising as a result of prematurity. The additional cost to the NHS of caring for a preterm baby born before 33 weeks' gestation is £61,509 and and of a baby born before 28 weeks' gestation is £94,190.[14] Each year, the care of preterm babies costs the NHS £939M, largely accounted for by neonatal care such as incubation and hospital readmissions.[14] Delaying premature births by a week could potentially save £260M a year.[14]

One of the key recommendations in the last Confidential Enquiries into Maternal and Child Health (CEMACH) report for policy-makers, service commissioners and providers, and health-care professionals (now known as the Centre for Maternal and Child Enquiries, CMACE) is the need to adopt an early-warning system to help in the timely recognition, referral and treatment of women who have or are developing critical conditions.[5] This applies to women with early-onset pre-eclampsia, as early recognition of women at risk of adverse outcomes will allow timely transfer from a secondary to a tertiary unit to enable care in a high-dependency unit or neonatal intensive care unit if needed.

Timely prediction of complications in women with early-onset pre-eclampsia involves the use of a combination of patients' characteristics, symptoms, physical signs and investigations;[15] these 'tests' are performed routinely in all obstetric units, but, in the absence of a structured approach, somewhat haphazardly. Gestational age is the most important determinant of perinatal outcome with more than half the chance of intact fetal survival when the gestational age is > 27 weeks and the birthweight is > 600 g.[16] Clinicians are hesitant to advocate expectant management because of uncertainties about the scale of maternal risk. Development of a prediction model for adverse maternal and fetal outcomes will help clinicians make appropriate decisions, after discussion with the parents.

Existing evidence

Evidence on assessment of risk of complications in early-onset pre-eclampsia

At present, it is difficult to identify those mothers with early-onset pre-eclampsia at increased risk of developing complications, and individual risk estimates for complications at various time points cannot be provided.[9] Current classification systems of pre-eclampsia [Royal College of Obstetricians and Gynaecologists (RCOG); Australia and New Zealand School of Government (ANZOG); International Society for the Study of Hypertension in Pregnancy (ISSHP); Community Health Partnerships (CHP); and the Society of Obstetricians and Gynaecologists in Canada (SOGC)] are based on the severity of the disease.[9,12,17–19] All of them include BP and proteinuria to dichotomise the severity but do not take into account gestational age to assess severity of pre-eclampsia, with the exception of the SOGC, which classifies all early-onset pre-eclampsia as severe.[19] However, in this subgroup the predictors that influence maternal and fetal outcomes are not well established.

Our systematic reviews on the accuracy of tests in predicting complications in women with pre-eclampsia were based on very few, poor-quality primary studies.[20–23] They did not take into account the predictive role of more than one test result on the outcome. Furthermore, there was no separate quantification of risks, especially in women with early-onset pre-eclampsia.

Prediction models, such as Pre-eclampsia Integrated Estimate of RiSk (PIERS), were developed in women with any onset pre-eclampsia and not particularly in those with early onset.[9] Furthermore, the PIERS model did not fully account for the treatment paradox, whereby a strong predictor of a common complication triggers an effective treatment, thereby preventing the occurrence of a certain proportion of adverse outcomes. In this situation, the predictor that triggered the treatment in the first place will look poorer in its predictive performance in a simple model.[24] Hence, tests such as BP and proteinuria were not identified to be significant in the PIERS model. This had a negative impact on the face validity of the model, as traditionally clinicians prioritise these tests and have a very low threshold for intervention when they are abnormal.

Management of early-onset pre-eclampsia

Currently, the only definitive treatment in pre-eclampsia is delivery. Antenatal corticosteroids are administered to improve fetal lung maturation whenever preterm delivery is anticipated. As steroids achieve their optimal effect after 48 hours,[25,26] clinicians tend to postpone delivery until this time unless complications have occurred or are anticipated. Neonatal morbidity from early preterm delivery could be reduced by stabilising the woman's condition and, if possible, by delaying delivery. Expectant management of early-onset pre-eclampsia has been shown to improve perinatal outcomes in randomised trials.[27,28] A Cochrane review[13] that compared early intervention with expectant management in women with early-onset severe pre-eclampsia[27,28] showed that babies born to mothers in the early intervention group had more hyaline membrane disease [relative risk (RR) 2.3, 95% confidence interval (CI) 1.4 to 3.8] and more necrotising enterocolitis (RR 5.50, 95% CI 1.04 to 29.60) and were more likely to be admitted to the neonatal intensive care unit (RR 1.3, 95% CI 1.1 to 1.6) than those allocated an expectant policy. Infants in the expectant group were delivered approximately 2 weeks later and were 300 g heavier at birth than infants in the early intervention group. A recent systematic review of observational studies suggested that expectant management in carefully selected cases of pre-eclampsia before 34 weeks' gestation was associated with few serious maternal complications (median < 5%), similar to interventionist care.[9,29] There is consensus that fetal outcome is poor before 24 weeks' gestation in women with early-onset pre-eclampsia.[27,30,31] However, many centres do not practise expectant management because of the poorly quantified maternal risk. Our study will establish a predictive rule to allow clinicians to confidently provide expectant care when risk of complications in early-onset pre-eclampsia is low.

Objectives

- To develop, and internally validate, a prediction model in women admitted with early-onset pre-eclampsia from 20^{+0} weeks to 33^{+6} weeks' gestation, for assessment of the risk of adverse maternal outcome by discharge and at various time points after diagnosis.
- To externally validate and update the model through two external data sets of patients with a diagnosis of early-onset pre-eclampsia.
- To assess the risk of adverse fetal and neonatal outcomes at birth and at any time until discharge, and to summarise the unadjusted and adjusted prognostic ability of a set of candidate predictor variables.

Chapter 2 Development and internal validation of the prediction model: PREP prospective observational study

Study methods

The study protocol was developed according to existing recommendations on prognostic research, model development and validation, and prediction rule development,[32–34] and reported in line with the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement.[35] The study received ethics approval from the National Research Ethics Service Committee West Midlands (approval number 11/WM/0248).

Study design and conduct

We undertook a prospective, observational cohort study to develop the prediction model(s). All consecutive women with suspected or confirmed diagnosis of early-onset pre-eclampsia were approached to take part in the study. Women were recruited from December 2011 to April 2014 based on a set of prespecified eligibility criteria and the follow-up of the last participant was completed in July 2014. Potential mothers were identified and recruited by research midwives and clinicians from the antenatal clinics, wards, day assessment units and delivery suites. We obtained information routinely collected as part of the antenatal booking process in the UK such as maternal age, ethnicity, smoking, alcohol intake and substance misuse. The ethnicity classification was applied using the NHS criteria.[36,37]

Setting

The multicentre study was conducted in 53 obstetric units within secondary and tertiary care hospitals in England and Wales.

Participants

Women with suspected or confirmed diagnosis of early-onset pre-eclampsia (before 34 weeks' gestation) were recruited to the study. Only women with confirmed early-onset pre-eclampsia were included in the final models.

Patient and public involvement

The Action on Pre-Eclampsia Charity (APEC) was vital in providing important input. The charity was involved from the very start with the development and design of the study protocol and will help with the dissemination of findings from the study. A member of the organisation sat as an independent member of the study steering committee and contributed to the overall supervision and management of the research project. They were also involved with the development of study materials, including the informed consent forms and patient information sheets. The APEC was involved in promoting the study to midwives and clinicians, attending the study days and meetings.

Inclusion criteria

The inclusion criteria were gestational age between 20^{+0} and 33^{+6} weeks; maternal age of ≥ 16 years; and a diagnosis of new-onset or superimposed pre-eclampsia. We also included women with a diagnosis of haemolysis, elevated liver enzymes, low platelets (HELLP) syndrome with no proteinuria or hypertension and those with one episode of eclamptic seizures but no hypertension or proteinuria.[9,38] All women provided written informed consent and were capable of understanding the information provided. We used an interpreter if required.

The definitions for diagnosis of pre-eclampsia are provided in *Table 1*.

Exclusion criteria

Women were excluded if the outcome (including recurrent eclamptic seizures) occurred prior to the tests or if there was insufficient time for gaining informed consent or if the mother did not comprehend spoken and written English adequately. A flow chart of study conduct is shown in *Figure 1*.

TABLE 1 Definitions of the inclusion criteria for women recruited in the Prediction of Risks in Early-onset Pre-eclampsia (PREP) study

Condition	Definition
New-onset pre-eclampsia	New-onset hypertension (systolic BP of ≥ 140 mmHg or diastolic BP of ≥ 90 mmHg on two occasions between 4 and 6 hours apart in women) after 20 weeks of pregnancy and new-onset proteinuria (≥ 2+ on urine dipstick or PCR of > 30 mg/mmol or 300 mg of protein excretion in 24 hours)[39]
Suspected pre-eclampsia	New-onset hypertension (systolic BP of ≥ 140 mmHg or diastolic BP of ≥ 90 mmHg on two occasions between 4 and 6 hours apart in women) after 20 weeks of pregnancy, and 1+ proteinuria on urine dipstick
Superimposed pre-eclampsia	
In women with chronic hypertension and no proteinuria before 20 weeks' gestation	New-onset proteinuria (as defined previously)
In women with significant proteinuria before 20 weeks' gestation	Elevated serum alanine aminotransferase concentration (> 70 units per litre) or worsening hypertension (either two diastolic BP measurements of at least 110 mmHg 4 hours apart or one diastolic BP measurement of at least 110 mmHg if the woman had been treated with an antihypertensive drug), plus one of the following: increasing proteinuria, persistent severe headaches or epigastric pain
HELLP syndrome	HELLP syndrome: presence of haemolysis based on examination of the peripheral smear, elevated indirect bilirubin levels, or low serum haptoglobin levels in association with significant elevation in liver enzymes and a platelet count below 100,000/mm^3 after ruling out other causes of haemolysis and thrombocytopenia
One episode of eclamptic seizures without hypertension or proteinuria[9,38]	Other neurological conditions of seizures have been excluded

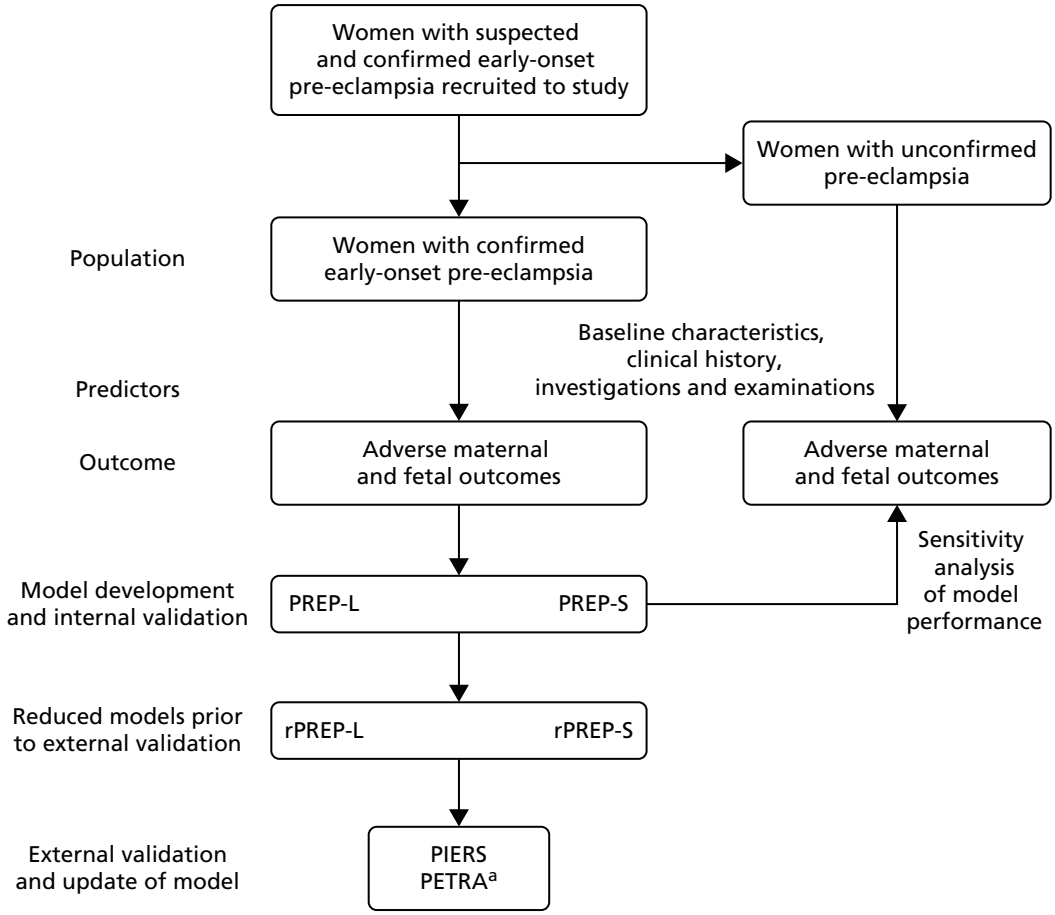

FIGURE 1 Flow chart of the Prediction of Risks in Early-onset Pre-eclampsia (PREP) study conduct. a, Only reduced PREP logistic model validated.

Predictors

Identification of predictors

Our previous Delphi survey of international experts on pre-eclampsia prioritised the tests that were considered to be clinically important in women with pre-eclampsia.[15,41] Additional predictors were identified from our systematic reviews on the accuracy of tests for complications in pre-eclampsia and other relevant studies.[9] This provided face validity to the choice of tests evaluated in the development of the Prediction of Risks in Early-onset Pre-eclampsia (PREP) model.

The list of preselected candidate predictor variables evaluated in the PREP study is provided in *Box 1* and the list of predictor variables for fetal complications in the study is shown in *Box 2*. In addition, we included management strategies that had the potential to reduce risk of complications to minimise bias from treatment paradox.[24] This included administration of antihypertensive drugs (oral and/or parenteral) and/or magnesium sulphate if women were on them at the time of diagnosis of early-onset pre-eclampsia, or if they were commenced within a day of diagnosis. We forced maternal age and gestational age at diagnosis into the model.

BOX 1 List of candidate predictor variables evaluated in the PREP study

Maternal characteristics

Maternal age at diagnosis (years).

Gestational age at diagnosis (weeks).

Number of fetuses in pregnancy at time of consent (1, 2 or 3).

History

Summary score for medical history – 1 point for each of the following: pre-existing hypertension, renal disease, diabetes mellitus, autoimmune disease, previous history of pre-eclampsia (0, 1, 2 or more).

Symptoms

Headache and/or visual disturbance (yes/no).

Epigastric pain, nausea and/or vomiting (yes/no).

Chest pain and dyspnoea (yes/no).

Bedside examination and tests

Systolic BP (mmHg, highest measurement over 6 hours).

Diastolic BP (mmHg, highest measurement over 6 hours).

Clonus (yes/no).

Exaggerated tendon reflexes (yes/no).

Abnormal oxygen saturation (< 95% on air) (yes/no).

Urine dipstick (0, 1+, 2+, 3+, 4+ or more).

Laboratory tests

Haemoglobin (g/l).

Platelet count ($\times 10^9$/l).

ALT concentration (IU/l).

Serum uric acid concentration (μmol/l).

Serum urea concentration (mmol/l).

Serum creatinine concentration (μmol/l).

Urine PCR (mg/mmol).

BOX 1 List of candidate predictor variables evaluated in the PREP study (*continued*)

Management at baseline

Administration of oral and/or parenteral antihypertensives (ongoing or commenced within 1 day of diagnosis) (yes/no).

Administration of magnesium sulphate (commenced before or within 1 day of diagnosis) (yes/no).

ALT, alanine aminotransaminase; IU, international unit.

BOX 2 List of predictor variables for fetal complications in the PREP study

Maternal characteristics

Maternal age at diagnosis (years).

Gestational age at diagnosis (weeks).

Number of fetuses in pregnancy at time of consent (1, 2 or 3).

History

Summary score for history, for example 1 point for each of pre-existing hypertension, renal disease, diabetes mellitus, autoimmune disease, previous history of pre-eclampsia (0, 1, 2 or more).

Symptoms

Headache and/or visual disturbance (yes/no).

Epigastric pain, nausea and/or vomiting (yes/no).

Chest pain and dyspnoea (yes/no).

Bedside examination and tests

Systolic BP (mmHg, highest measurement over 6 hours).

Diastolic BP (mmHg, highest measurement over 6 hours).

Clonus (yes/no).

Exaggerated tendon reflexes (yes/no).

Abnormal oxygen saturation (< 94% on air) (yes/no).

Urine dipstick (0, 1+, 2+, 3+, 4+ or more).

BOX 2 List of predictor variables for fetal complications in the PREP study (*continued*)

Laboratory tests

Haemoglobin (g/l).

Platelet count (× 10^9/l).

ALT concentration (IU/l).

Serum uric acid concentration (μmol/l).

Serum urea concentration (mmol/l).

Serum creatinine concentration (μmol/l).

Urine PCR in 24 hours (mg/mmol).

Ultrasound and cardiotocography

Uterine artery Doppler at 20–24 weeks' gestation (normal/abnormal).

CTG findings (normal/abnormal).

Estimated fetal weight by ultrasound (< 10th centile).

Liquor volume (normal/abnormal).

Management at baseline

Administration of oral and/or parenteral antihypertensives (ongoing or commenced within 1 day of diagnosis) (yes/no).

Administration of magnesium sulphate (commenced within 1 day of diagnosis) (yes/no).

Administration of corticosteroids (commenced within 1 day of diagnosis) (yes/no).

ALT, alanine aminotransaminase; CTG, cardiotocography; IU, international unit.

Outcome

The primary outcome was composite adverse maternal outcome that included at least one of the components in *Table 2*. In addition to maternal complications, prior to the analysis, we added delivery before 34 weeks' gestation as an additional component to the composite maternal adverse outcome to minimise bias caused by treatment paradox. The components of the composite outcome were developed through Delphic consensus and had previously undergone piloting and validation in the Canadian cohort of patients in the PIERS (Pre-eclampsia Integrated Estimate of RiSk) study.[9] A composite measure for fetal outcome was also developed by the Delphi consensus[9] (*Table 3*).

TABLE 2 Definitions of the individual components of the maternal composite outcome evaluated in the PREP study

Outcome	Definition
Mortality	Maternal death attributable to complications of pre-eclampsia
Hepatic dysfunction	INR > 1.2 indicative of disseminated intravascular coagulation (DIC) in the absence of treatment with warfarin. DIC is defined as having both abnormal bleeding and consumptive coagulopathy (i.e. low platelets, abnormal peripheral blood film or one or more of the following: increased INR, increased PTT, low fibrinogen, of increased fibrin degradation products that are outside normal non-pregnancy ranges)
Hepatic haematoma or rupture	Blood collection under the hepatic capsule as confirmed by ultrasound or laparotomy
Glasgow Coma Scale score of < 13	Based on the Glasgow Coma Scale score system[42]
Stroke	Acute neurological event, with deficits lasting > 48 hours
Cortical blindness	Loss of visual acuity in the presence of intact papillary response to light
Reversible ischaemic neurological deficit	Cerebral ischaemia lasting > 24 hours but < 48 hours revealed through clinical examination
Retinal detachment	Separation of the inner layers of the retina from the underlying retinal pigment epithelium (choroid) and is diagnosed by ophthalmological examination
Acute renal insufficiency	For women with an underlying history of renal disease defined as a creatinine concentration of > 200 µM; for patients with no underlying renal disease defined as a creatinine concentration of > 150 µM
Dialysis	Including haemodialysis and peritoneal dialysis
Transfusion of blood products	Includes transfusion of any units of blood products: fresh-frozen plasma, platelets, red blood cells, cryoprecipitate or whole blood
Positive ionotropic support	The use of vasopressors to maintain a systolic BP of > 90 mmHg or mean arterial pressure of > 70 mmHg
Myocardial ischaemia/infarction	ECG changes (ST segment elevation or depression) without enzyme changes and/or any one of the following: 1. development of new pathological Q waves on serial ECGs. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalised, depending on the length of time that has passed since the infarct developed 2. pathological findings of an acute, healed or healing myocardial infarction 3. typical rise and gradual fall (troponin) or more rapid rise and fall (creatine kinase–MB isoenzyme) of biochemical markers of myocardial necrosis with at least one of the following: ischaemic symptoms i. development of pathologic Q waves on the ECG; ii. ECG changes indicative of ischaemia (ST segment elevation or depression) iii. coronary artery intervention (e.g. coronary angioplasty)
Require > 50% oxygen for > 1 hour	Oxygen given at greater than 50% concentration based on local criteria for > 1 hour
Intubation other than for caesarean section	Intubation may be by ventilation, electrical impedance tomography or continuous positive airway pressure
Pulmonary oedema	Clinical diagnosis with radiographic confirmation or requirement of diuretic treatment and SaO_2 < 94%
Postpartum haemorrhage	Blood loss of > 1 l after delivery
Early preterm delivery	Delivery at a gestational age of < 34 weeks

ECG, electrocardiography; INR, international normalised ratio; PTT, partial thromboplastin time; SaO_2, saturation of oxygen.
Reproduced from Thangaratinam S, Allotey J, Marlin N, Dodds J, Cheong-See F, von Dadelszen P, *et al.* Prediction of complications in early-onset pre-eclampsia (PREP): development and external multinational validation of prognostic models. *BMC Med* 2017;**15**:68. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution and reproduction in any medium, provided that appropriate credit to the original authors and the source is given.[40]

TABLE 3 Definitions of the individual components of the fetal composite outcome evaluated in the PREP study

Outcome	Definition
Perinatal or infant mortality	Death of a fetus or neonate. Infant mortality is the death of a child < 1 year of age
Bronchopulmonary dysplasia	Oxygen requirement at 36 weeks corrected gestational age unrelated to an acute respiratory episode
Necrotising enterocolitis including only Bell's stage 2 or 3	Evidence of pneumatosis intestinalis on an abdominal radiography and/or surgical intervention
Grade III/IV intraventricular haemorrhage	Bleeding into the brain's ventricular system, where ventricles are enlarged by the accumulated blood or bleeding extends into the brain tissue around the ventricles
Cystic periventricular leukomalacia	Softening and necrosis in the hemispheric white matter in newborns that may result from impaired perfusion at the interface between ventriculopetal and ventriculofugal arteries
Stages 3–5 retinopathy of prematurity	Abnormal blood vessel development in the retina of the eye, where blood vessel growth is severely abnormal, where there is a partially or totally detached retina
Hypoxic–ischaemic encephalopathy	Apgar score of ≤ 5 at 10 minutes and/or pH 7.00 in first 60 minutes of life and/or base deficit ≥ -16 in first 60 minutes of life associated with abnormal consciousness level (lethargy, stupor or coma) and seizures and/or poor/weak suck and/or hypotonia and/or abnormal reflexes

When more than one outcome occurred in the same woman, we chose the adverse outcome that occurred first for the purpose of the survival model. A panel of clinicians with expertise in pre-eclampsia and prognosis research ranked the maternal outcomes for their importance to clinical care (see *Appendix 1*).

Sample size

We aimed to examine about 10 candidate predictor variables for inclusion in the model(s). Simulation studies examining predictor variables for inclusion in logistic regression models suggest that approximately 10 events are necessary for each candidate predictor to avoid overfitting.[43–45] Therefore, to examine 10 candidate predictors, we required at least 100 women with adverse maternal outcomes in our cohort. From our systematic reviews,[20–23] 20% of women (100 of 500) with early-onset pre-eclampsia were expected to have adverse maternal outcomes at any time before discharge. Thus, the original target sample size was 500 women with confirmed pre-eclampsia. As the event rate was lower than predicted, we revised the sample size to continue recruitment until 100 women had experienced adverse events. *Appendix 2* lists the changes compared to the original protocol submitted to the National Institute for Health Research Health Technology Assessment programme.

Prior to analysis, after discussion with the steering committee, the study group additionally classified delivery before 34 weeks' gestational age as an adverse maternal outcome to avoid treatment paradox from delivery. The sample size criteria remained the same. With the increased number of outcomes, we were able to consider about 20 candidate predictors but we maintained at least 10 events per predictor in the modelling process.

Data sets for external validation: PIERS and PETRA studies

The PREP model was externally validated in two external independent data sets from the PIERS[9] and the Pre-Eclampsia TRial Amsterdam (PETRA)[46] studies.

PIERS study

The aim of this prospective observational study was to develop a prediction model for adverse maternal outcomes in women with pre-eclampsia of any onset (both early and late).[9] Two thousand and twenty-three women were recruited from tertiary perinatal units in Canada, New Zealand, the UK and Australia between 1 September 2003 and 31 January 2010. Women were included if they were admitted with pre-eclampsia or had developed pre-eclampsia after admission. Women were excluded if they were admitted in spontaneous labour or had achieved any component of the maternal outcome before either fulfilling eligibility criteria or collection of predictor data. The primary outcome was a composite maternal outcome. The combined adverse maternal outcome included one or more of the following: maternal mortality or a serious central nervous system, cardiorespiratory, hepatic, renal, or haematological morbidity. We used the anonymised data set of women with early-onset pre-eclampsia in the PIERS study to validate the PREP model.

PETRA study

The PETRA study was a randomised controlled trial evaluating the effectiveness of plasma expansion in expectant management of early-onset hypertensive disease in pregnancy, including pre-eclampsia.[46] Women were recruited from two university hospitals, the Department of Obstetrics at the Academic Medical Centre and the Vrije University Medical Centre Amsterdam, between April 2000 and May 2003. Patients across the spectrum of severe hypertensive disorders of pregnancy were included in the trial. Patients were excluded if severe fetal distress or lethal fetal congenital abnormalities were diagnosed, if language difficulties prevented informed consent-taking, or if plasma volume expansion had already been given. A total of 216 women were randomised, 111 to plasma volume expansion and 105 to no plasma volume expansion (the control group). The primary outcomes were neonatal neurological development at term age (Prechtl score),[47] perinatal death, neonatal morbidity and maternal morbidity. The intervention showed no significant difference in outcomes between the two groups. Data from the entire study cohort were used in the external validation of the PREP model.

Analysis plan development

We convened a panel of 24 experts in the field of pre-eclampsia and prognostic research, to explore the challenges and potential solutions in the development of a prediction model. The panel focused its discussion on methods to reduce the risk of bias in the PREP models as a result of treatment paradox.[24] After consideration of various methods, it was decided to include effective treatments such as antihypertensive drugs and magnesium sulphate as predictors to avoid bias. The appropriateness of the population, predictors and outcomes was discussed. The methodological issues pertinent to the analysis, such as the choice of model (logistic or survival), were considered and the panel suggested the development of both models.

Statistical analysis

We used a transparent process with appropriate prognostic research methodology for our analysis, and reported using TRIPOD recommendations.[35] We developed and externally validated two models: a logistic model (PREP-L) for overall risk of any adverse outcome by discharge, and a survival model (PREP-S) to assess the risk of adverse outcomes at various time points from diagnosis of pre-eclampsia until 34 weeks' gestation.

Data preparation

We produced descriptive tables of baseline characteristics, candidate predictors and outcomes. Candidate predictors were checked for normality and log-transformed if applicable. We avoided dichotomisation of continuous variables to avoid loss of information. Only pulse oximetry findings were dichotomised because of the very small variations in values.

Methods for handling missing values

During model development, to deal with missing predictor values in some patients, multiple imputation was performed (under a missing at random assumption) using the user-written ICE package in Stata version 12 (StataCorp LP, College Station, TX, USA) with five imputations. We combined the estimates across imputed data sets using Rubin's rules to produce final parameter estimates for the model.[48]
All missing values of candidate predictor variables were multiply imputed except for pulse oximetry and previous occurrence of pre-eclampsia. Previous occurrence of pre-eclampsia was always classed as a 'no' in nulliparous women. Pulse oximetry was assumed normal if missing. The imputation of missing data was performed on the complete data set of all participants with suspected or confirmed pre-eclampsia. This was to allow as much information as possible into the imputation procedure. Apart from the eight women lost to follow-up after baseline, no outcome data were missing; therefore, no outcomes were imputed.

Selection of predictor variables

For both primary models, all 22 variables listed in *Box 1* were considered to be candidate predictor variables for inclusion in our maternal model. A backwards selection procedure was used to decide which of the candidate predictor variables should be included in the final prediction model (with a *p*-value of < 0.15 conservatively taken to warrant inclusion and prevent omission of important predictors). Gestational age and maternal age at diagnosis were forced into the model, to ensure clinical acceptability of the final model. For categorical variables, such as medical history and urine dipstick, we used the lowest *p*-value of any category (relative to the reference category) to indicate inclusion or exclusion.

Continuous variables were initially selected based on an assumed linear trend. After inclusion, non-linear trends were also evaluated using fractional polynomials (FPs), with a *p*-value of < 0.01 (for the change in model fit) used to justify the inclusion of non-linear trends. Any continuous variables that were originally dropped were double-checked for whether or not non-linear trends would alternatively suggest their inclusion.

Model development for adverse maternal outcomes

We applied the modelling process to women with confirmed diagnosis of early-onset pre-eclampsia and had complete outcome data (*Figure 2*).

Definition of survival time

For survival analysis, the end of follow-up was defined as the time of occurrence of the first adverse outcome or end of 34 weeks' gestation, whichever occurred first. A woman was considered to be at risk from the time of diagnosis of early-onset pre-eclampsia and the failure event was defined as maternal adverse outcome occurring before 34 weeks' gestation. The survival data information was described in the original data set and copied into all five imputed data sets. The survival information was independent of the multiple imputation, as no outcome was imputed and the time of diagnosis data were available for all women.

Survival model: flexible parametric model

A flexible parametric survival model was used via the Royston–Parmar approach,[49–51] with the cumulative baseline hazard scale modelled using restricted cubic splines (implemented as the stpm2 package in Stata12). We chose this approach over a Cox regression as it allowed us to explicitly model the baseline hazard rate allowing non-linear functions via cubic splines, which are very flexible and relatively simple to work with. Simpler parametric models may not be flexible enough to adequately represent the hazard function.

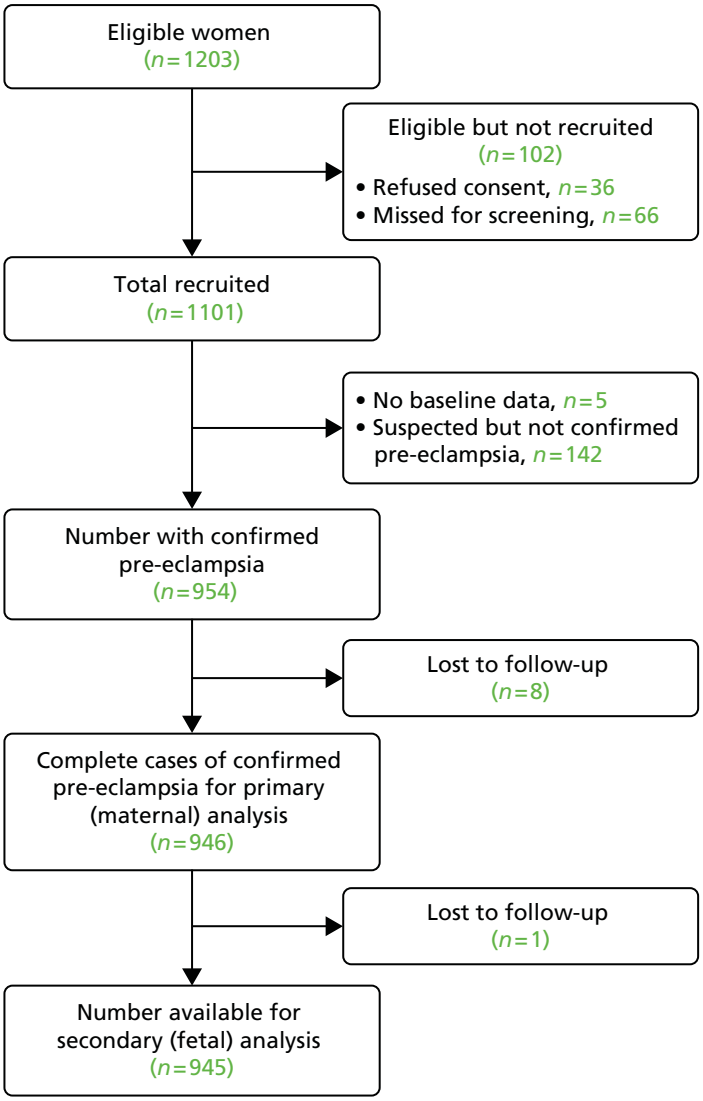

FIGURE 2 Flow of women recruited in the PREP study for development of the prediction model(s) for adverse maternal and fetal outcomes.

Splines are flexible mathematical functions defined by piecewise polynomials, with some constraints to ensure that the overall curve is smooth. The points at which the polynomials join are called knots. Royston and Lambert[50] explain that the stpm2 uses restricted cubic splines which force the function to be linear before the first knot and after the final knot. Let s(x) be the restricted cubic spline function. Defining m interior knots, $k_1, \ldots, k_m$, and also two boundary knots, $k_{\min}$ and $k_{\max}s(x)$, can be written as a function of parameters γ and some newly created variables $z_1, \ldots, z_{m+1}$ giving:

$$s(x)=\gamma_0+\gamma_1 z_1+\gamma_2 z_2+\cdots+\gamma_{m+1}z_{m+1}. \quad (1)$$

The derived variables z_j (also known as the basis functions) can be calculated as follows:

$$\begin{aligned} z_1&=x \\ z_j&=(x-k_j)^3-\lambda_j(x-k_{\min})^3-(1-\lambda_j)(x-k_{\max})^3, \end{aligned} \quad (2)$$

where $j=2, \ldots, m+1$,

$$\lambda_j = \frac{k_{max} - k_j}{k_{max} - k_{min}}. \quad (3)$$

When choosing the location of the knots for the restricted cubic splines, it is useful to have some sensible default locations. In stpm2, the default knot locations are at the centiles of the distribution of uncensored log-event times.

Survival null model

We identified the number of knots to go into the model by fitting the null model with an increasing number of knots. The number of knots was chosen based on the lowest Akaike information criterion/ Bayesian information criterion (AIC/BIC) and visual inspection of the change in fitted shape, with preference for simplicity (i.e. fewer knots) to avoid overfitting. AIC and BIC are measurements of model fit.

Univariable model, full model and variable selection process

Univariable analyses were performed for both models on all 22 candidate predictors in their linear (log-transformed, if applicable) form. These were fitted in each imputed data set and combined using Rubin's rules.[48] Univariable analyses were performed only to summarise the unadjusted associations in the data, and were not used to inform the selection of predictors in the final multivariable models. Where applicable and computationally possible, all analyses were performed with the imputed data sets and the results were combined appropriately. A backwards selection procedure was applied to both full models as previously described. Maternal age and gestational age at diagnosis were forced into the model. The model was refitted after dropping each individual predictor.

Non-linear terms

We identified the non-linear terms using the multivariable FP (MFP) procedure in Stata, which selects the MFP model that best predicts the outcome variable. The MFP procedure allows the selection of non-linear terms for continuous variables and the procedure was applied to each of the five multiply imputed data sets separately, and the pattern that was identified by the majority of multiply imputed data sets was used (on consensus between the lead statisticians). In order to avoid overfitting, only non-linear terms that improved the model fit at a minimum significance level of 1% (test of deviance) were considered. The final models were refitted by including the FP terms and checked for dropping further predictors at a p-value of < 0.150. Such variables were dropped only if their exclusion did not change the FP terms already identified in the previous step. This step was performed only once and was not repeated if additional predictors had p-values of ≥ 0.150.

Sensitivity analyses

Logistic and survival model

We included treatment with any antihypertensive drug (oral and/or parenteral) within 1 day of diagnosis in the final models. As parenteral antihypertensive drugs are usually commenced in severe pre-eclampsia to prevent complications, the predictive values could be different for oral and parenteral antihypertensive drugs. A sensitivity analysis was conducted by including oral and parenteral antihypertensive drugs separately in the final models to check if model fitting is improved.

Survival model only

The full survival model needed to be fitted in each of the imputed data sets and the results combined using Rubin's rules. This procedure is not officially supported for use with the stpm2 command in Stata, although it does perform the estimation if forced. In order to confirm accuracy of the results, we fitted a Cox regression for the same model. The stcox command is supported for the combination of estimations using Rubin's rules. We also checked the final survival model for time-dependent effects.

Apparent performance

The apparent performance of the fitted models was examined by calculating discrimination performance using the *c*-statistic for the logistic model and Harrell's *c*-statistic for the survival model,[52] with a 95% confidence interval (CI), in the same data used to generate the model. A *c*-statistic close to 1 indicates excellent discrimination and 0.5 indicates no discrimination beyond chance. The calibration performance (fit of observed to expected risk across all individuals) was examined by checking that the calibration slope was 1. As the model was developed using the same data, we expected the calibration to show perfect agreement on average across the individuals.

Internal validation

To evaluate the potential for overfitting of our developed models, we used non-parametric bootstrapping. The variable selection procedure was repeated in 100 bootstrap data sets from each of the five multiple imputation data sets (thereby giving a total of 500 data sets). This led to a new final model being produced in each of the bootstrap samples. The performance of the models (in terms of *c*-statistic and calibration slope) in the bootstrap sample itself represents an estimation of the apparent performance, and their performance in the original sample represents test performance. The difference between these performances is an estimate of the optimism in the apparent performance. This difference was averaged to obtain a single estimate of optimism for the *c*-statistic and the calibration slope. This optimism was then subtracted from the original apparent performance statistics to produce optimism-adjusted performance statistics.

Production of the final models

The coefficients in the final models were adjusted for optimism. The optimism-adjusted calibration slope was taken as the uniform shrinkage factor, and the original predictor effects (beta coefficients) were multiplied by this value. Following this, the intercept (for the logistic model) or baseline hazard (for the survival model) were re-estimated to ensure that the overall calibration of the final model predictions to the observed data were maintained, that is, to ensure that calibration-in-the-large was zero. For the survival model, only the intercept term was modified in the baseline hazard function (i.e. the shape of the original baseline hazard was maintained). For sensitivity analysis, we applied these optimism-adjusted models to women with an unconfirmed diagnosis of pre-eclampsia.

After developing and validating the prediction model based on the final set of (close to) 20 predictors, we additionally investigated whether or not any of the candidate predictors we excluded would actually significantly improve the accuracy of the model; however, this was clearly noted as secondary analyses.

The models were available as Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) files (see *Appendices 3* and *4*) to allow clinicians to input the findings of their patients, and obtain estimates of overall risk of adverse outcomes (PREP-L) and risks at daily intervals after diagnosis (PREP-S).

External validation

The final models were externally validated using the PIERS and PETRA data. We compared the availability of predictors, missing values and the outcome components in the external data sets with the PREP data. If there were any missing predictors in the external cohorts, we planned to re-estimate a reduced version form of our model (using exactly the same process as above) using only those predictors that were available in the external data sets.

If predictors were centred in the PREP model, then predictors in the external data were centred by the same value. The reduced PREP models were used to estimate predicted risks (or risk scores) for women in the PIERS or PETRA population. To produce calibration plots, the risks were grouped into tenths (defined by centiles) of predicted risk in the PREP-L model and into four risk groups for the PREP-S model. As the predictions were not compatible with the Stata 12.1 facilities for combining results using Rubin's rules, we calculated the fitted values or predictions of risk within each imputed data set and then averaged them.

Secondary analysis of fetal outcomes

The analysis of fetal outcomes by discharge was done in the same way as for the logistic model described above, although non-linear terms were not considered. Analysis was performed on the level of the mother/pregnancy rather than on the fetal level. In multiple pregnancies with multiple sets of predictors and outcomes, we used the worst predictor and considered any outcome regardless of whether an outcome occurred in one of the babies or in both. A variable selection process on the full list of maternal and fetal candidate predictors provided the final fetal model. No adjustment for optimism, external validation or sensitivity analyses was performed for the fetal model.

All the above analyses were carried out using Stata version 12.0. Definitions of key terms are provided in *Table 4*.

TABLE 4 Definitions of key model performance terms

Terms	Definitions
Calibration	Calibration indicates the ability of the model to correctly estimate the absolute risks and was examined using calibration plots
Reproducibility (internal validation)	The process of determining internal validity. Internal validation assesses validity for the setting from which the development data originated
Generalisability/transportability (external validation)	The process of determining external validity of the prediction model to populations that are plausibly related
Discrimination	Discrimination describes the ability of the model to correctly distinguish those who will have an adverse outcome from those who will not
Calibration plot	In a calibration plot the predictive risk plotted against the observed incidence of the outcome. Ideally the predicted risk equals the observed incidence throughout the entire risk spectrum and the calibration plot follows the 45° line

Chapter 3 Maternal characteristics, predictors and outcomes in women with early-onset pre-eclampsia

Flow of participants in the study

Between December 2011 and April 2014, we screened 3302 pregnant women from 53 maternity units for inclusion in the PREP study. Of these, 2099 did not meet the inclusion criteria: 882 did not have raised proteinuria, 650 did not have raised BP readings, 457 were classed as other, 53 had underlying comorbidities, 36 were participating in a clinical trial of an investigational medicinal product and 21 did not understand English and an interpreter could not be used at the time of recruitment. Of the 1203 eligible women, 1101 were recruited to the study with a suspected or confirmed diagnosis of early-onset pre-eclampsia. Of those recruited, 954 women had confirmed pre-eclampsia, 142 women had a suspected diagnosis of pre-eclampsia that was not subsequently confirmed, baseline information data were not available in five participants and nine were lost to follow-up. The final maternal prediction models included data from 946 women and the fetal prediction model included data from 945 pregnancies (see *Figure 2*).

Baseline characteristics of women included in the PREP study

Table 5 shows the women recruited into the study according to the various inclusion criteria. Over 90% (866/954) of all participants had a diagnosis of new-onset pre-eclampsia, 75 women (75/954, 7.9%) had superimposed pre-eclampsia, 10 (10/954, 1.0%) had HELLP syndrome and three women (3/954, 0.3%) had a single episode of eclamptic seizure in the absence of raised BP or proteinuria.

The mean age of participants was 30.2 years [standard deviation (SD) 6.1 years] (*Table 6*). Two-thirds of women identified themselves as European (631/950, 66%), one-fifth as South or South-East Asian (18%, 172/950) and about one-tenth (81/950, 9%) as African. Around 3% of all women were from the Caribbean (31/950), 1% from the Far East (8/950) and 1% from the Middle East (6/950). Ninety-one per cent (866/954) of all pregnancies were singletons, while twins and triplets accounted for 9% (83/954) and 1% (5/954) of pregnancies, respectively. More than half of all women were nulliparous (551/954, 58%). Recurrent miscarriage (three or more) had occurred in 42 women (4.4%). About one-tenth (87/943, 9%) of women reported smoking in pregnancy at booking appointment and alcohol intake in pregnancy was reported by 5% (47/937) of all participants.

TABLE 5 Women recruited to the PREP study according to the various inclusion criteria

Inclusion criteria	Women, *n* (%)
New-onset pre-eclampsia	866 (91.0)
Superimposed pre-eclampsia	75 (7.9)
HELLP syndrome	10 (1.0)
Eclamptic seizures	3 (0.3)
Total	954

TABLE 6 Descriptive characteristics of women recruited in the PREP study

Maternal characteristics	Women with early-onset pre-eclampsia ($n = 954$) Mean (SD) or *n* (%)
Maternal age (years), mean (SD)	30.2 (6.1)
Alcohol intake	47 (5%)
Currently smoking	87 (9%)
Drug use	4 (0.4%)
Mother's ethnic group	
Europe	631 (66%)
Africa	81 (9%)
South and South East Asia	172 (18%)
Far East	8 (1%)
Middle East	6 (1%)
Caribbean	31 (3%)
Other	21 (2%)
Parity	
0	551 (58%)
1	207 (22%)
2	109 (11%)
3	55 (6%)
4	20 (2%)
5–9	12 (1%)
Total number of miscarriages	
0	607 (64%)
1	225 (24%)
2	72 (8%)
> 3	42 (4%)

Predictor characteristics in women with early-onset pre-eclampsia

The values of the various candidate predictors of women in the PREP study are shown in *Table 7*.
The mean gestational age at which the diagnosis of early-onset pre-eclampsia was made was 30.5 weeks (SD 2.9 weeks) and there were no missing values for gestational age at diagnosis.

Clinical history

One-quarter (251/953, 26%) of all women for whom data were available had at least one of the following risk factors: previous history of pre-eclampsia (169/396, 43%), chronic hypertension (139/944, 15%), diabetes mellitus (109/948, 11%), renal disease (30/944, 3%) and autoimmune disease (18/922, 2%). One-tenth (101/953, 11%) had two or more risk factors.

TABLE 7 Details of candidate predictors of women in the PREP study and the proportion with missing values

Candidate predictor	Women with early-onset pre-eclampsia ($N = 954$) Mean (SD) or *n* (%)	Women with missing data, *n* (%)
Maternal characteristics		
Maternal age (years), mean (SD)	30.2 (6.1)	2 (0.2)
Gestational age at diagnosis (weeks), mean (SD)	30.5 (2.9)	–
Number of fetuses in pregnancy[a]		
Singleton	866 (91%)	–
Twins	83 (9%)	–
Triplets	5 (1%)	–
History		
Summary score for medical history[b]		1 (0.1)
0	601 (63%)	–
1	251 (26%)	–
≥ 2	101 (11%)	–
Chronic hypertension	139 (15%)	10 (1.0)
Renal disease	30 (3%)	10 (1.0)
Previous history of pre-eclampsia	169 (43%)	558[c]
Autoimmune disease	18 (2%)	32 (3.4)
Pre-existing DM	109 (11%)	6 (0.6)
Type I DM	56 (51%)	–
Type II DM	16 (15%)	–
Gestational DM	37 (34%)	–
Symptoms		
Headache and/or visual disturbance	382 (40%)	28 (2.9)
Headache generalised	293 (31%)	36 (3.8)
Headache localised	121 (13%)	92 (9.6)
Visual disturbance	139 (15%)	56 (5.9)
Epigastric pain, nausea and/or vomiting	202 (22%)	47 (4.9)
Epigastric pain	131 (14%)	68 (7.1)
Nausea	111 (12%)	130 (13.6)
Vomiting	54 (6%)	120 (12.6)
Chest pain and/or breathlessness	60 (6%)	126 (13.2)
Chest pain	30 (3%)	164 (17.2)
Breathlessness	38 (4%)	162 (17.0)

continued

TABLE 7 Details of candidate predictors of women in the PREP study and the proportion with missing values (*continued*)

Candidate predictor	Women with early-onset pre-eclampsia ($N = 954$) Mean (SD) or *n* (%)	Women with missing data, *n* (%)
Bedside examination and tests		
Systolic BP (mmHg), mean (SD)	159 (19)	5 (0.5)
Diastolic BP (mmHg), mean (SD)	99 (12)	5 (0.5)
Clonus	95 (10%)	403 (42.2)
Exaggerated tendon reflexes	147 (15%)	353 (37.0)
Oxygen saturation by pulse oximetry (%), mean (SD)	98 (2)	521 (54.6)
Oxygen saturation abnormal (< 94%)	4 (≥ 1%)	521 (54.6)
Urine dipstick		
None/trace	39 (4%)	–
1+	170 (18%)	–
2+	314 (33%)	19 (2.0)
3+	306 (32%)	–
≥ 4	106 (11%)	–
Laboratory tests		
Haemoglobin (g/l), mean (SD)	11.9 (1.3)	37 (3.9)
Platelet count (× 10^9/l), mean (SD)	226 (78)	41 (4.3)
ALT concentration (U/l), mean (SD)	31.0 (71.0)	75 (7.9)
Serum uric acid concentration (μmol/l), mean (SD)	0.6 (2.7)	165 (17.3)
Serum urea concentration (mmol/l), mean (SD)	4.6 (4.4)	70 (7.3)
Serum creatinine concentration (μmol/l), mean (SD)	61.0 (17.8)	38 (4.0)
Urine PCR 24 hour (mg/mmol), mean (SD)	273 (492)	109 (11.4)
Treatment provided		
Any antihypertensive therapy[d]	753 (79%)	6 (0.6)
Oral antihypertensive therapy	734 (77%)	6 (0.6)
Parenteral antihypertensive therapy	111 (12%)	6 (0.6)
Intravenous magnesium sulphate[e]	144 (15%)	6 (0.6)

ALT, alanine aminotransaminase; DM, diabetes mellitus.
a Values represent the number of pregnancies.
b Each contributes to 1 point scored for medical history.
c All missing values are nulliparous women. Previous occurrence of pre-eclampsia is not applicable.
d Ongoing at diagnosis or introduced within 1 day of diagnosis.
e Administered any time before diagnosis or within 24 hours of diagnosis.

Symptoms

Symptoms such as headache and/or visual disturbances were experienced by 41% (382/926) of women, epigastric pain and/or vomiting by 22% (202/907) and chest pain and/or dyspnoea by 7% (60/828).

Bedside examination and tests

The mean systolic and diastolic BP at the time of diagnosis of early-onset pre-eclampsia was 159 mmHg (SD 19 mmHg) and 99 mmHg (SD 12 mmHg), respectively. Around two-thirds of women had demonstrable clonus (551/954, 58%) and exaggerated tendon reflexes (601/954, 63%). The oxygen saturation levels were ≤ 94% in only 1% (4/433) of women, and more than half of the women did not have documented results (521/954, 55%). There were no missing values for BP or proteinuria.

Laboratory tests

Serum alanine aminotransaminase (ALT) was measured more often than aspartate transaminase (AST) (in 93% of women vs. 30%); consequently, ALT was used in the analysis. Less than one-tenth of values were missing for haemoglobin level, platelet count and concentrations of serum urea and serum creatinine concentration. Furthermore, < 20% of values were missing for serum uric acid concentration.

Treatment provided

More than three-quarters (753/948, 79%) of women were previously on antihypertensive drugs or were started on them within the first 24 hours of diagnosis of pre-eclampsia. Three-quarters of women (734/948, 77%) were on oral antihypertensive therapy and 12% (111/948) were receiving parenteral antihypertensive therapy. Fifteen per cent (144/948) of women started magnesium sulphate treatment to prevent or treat eclamptic seizures in the first 24 hours after diagnosis.

Additional fetal predictors

For the analysis of fetal outcomes, five additional predictors were included, as shown in *Table 8*. Around one-quarter (91/342, 27%) of women had an abnormal uterine artery Doppler at 20–24 weeks' gestation. Only 6% of women had abnormal liquor volume (57/898) and 5% had abnormal cardiotocography (CTG) findings (46/713). Over 40% (291/717) of pregnancies had an estimated fetal weight < 10th centile. More than half (430/783, 55%) of the women received treatment with corticosteroids at baseline.

Maternal and fetal adverse outcomes in women with early-onset pre-eclampsia

Outcome data were available for 99% (946/954) of all participants in the PREP study. The rates of individual components of the composite adverse maternal and fetal outcomes are provided in *Tables 9* and *10*, respectively.

TABLE 8 Details of fetal predictors in the PREP study and the proportion with missing values

Additional fetal predictors	Women with early-onset pre-eclampsia ($n = 954$), mean (SD) or *n* (%)	Women with missing data, *n* (%)
Abnormal uterine artery Doppler	91 (10%)	612 (64)
Abnormal liquor volume	57 (6%)	56 (6)
Abnormal CTG findings	46 (5%)	241 (25)
Estimated fetal weight < 10th centile	291 (31%)	237 (25)
Baseline treatment: steroids	430 (45%)	171 (18)

TABLE 9 Rates of individual maternal complications in women with early-onset pre-eclampsia in the PREP study

Adverse maternal outcome	Women with complications ($N = 946$), *n* (%)
Maternal death	–
Neurological	
Eclamptic seizures	12 (1.3)
Glasgow Coma Scale score of < 13	3 (0.3)
Stroke or RIND	–
Cortical blindness	–
Retinal detachment	–
Posterior reversible encephalopathy	2 (0.2)
Bell's palsy	–
Hepatic	
Hepatic dysfunction	12 (1.3)
Subcapsular haematoma	–
Hepatic capsule rupture	–
Cardiorespiratory	
Need for positive inotrope support	1 (0.1)
Myocardial ischaemia or infarction	–
At least 50% FiO_2 for > 1 hour	7 (0.7)
Intubation	9 (1.0)
Pulmonary oedema	6 (0.6)
Renal	
Acute renal insufficiency	5 (0.5)
Dialysis	5 (0.5)
Haematological	
Transfusion	51 (5.4)
Abruptions	25 (2.6)
Postpartum haemorrhage	74 (7.8)
Preterm delivery	
Delivery at < 34 weeks' gestational age	580 (61.3)
At least one of the above occurred by discharge	633 (66.9)
At least one occurred before 34 weeks' gestational age	584 (61.7)

FiO_2, fraction of inspired oxygen; RIND, reversible ischaemic neurological deficit.

TABLE 10 Rates of individual fetal and neonatal complications in the PREP study

Adverse fetal outcome	Pregnancies with complications ($N = 945^a$), *n* (%)
Neonatal death	23 (2.4)
Bronchopulmonary dysplasia	41 (4.3)
Necrotising enterocolitis	34 (3.6)
Grade III/IV intraventricular haemorrhage	11 (1.2)
Cystic periventricular leukomalacia	5 (0.5)
Stage 3–5 retinopathy	7 (0.7)
Hypoxic ischaemic encephalopathy	2 (0.2)
Stillbirth	16 (1.7)
Admission to NICU at any time	681 (72.1)
At least one of the above occurred by discharge	702 (74.3)

NICU, neonatal intensive care unit.
a Excludes one participant whose fetal outcome data were lost to follow-up.
Reproduced from Thangaratinam S, Allotey J, Marlin N, Dodds J, Cheong-See F, von Dadelszen P, *et al.* Prediction of complications in early-onset pre-eclampsia (PREP): development and external multinational validation of prognostic models. *BMC Med* 2017;**15**:68. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution and reproduction in any medium, provided that appropriate credit to the original authors and the source is given.[40]

Overall, 66.9% (633/946) of all women with early-onset pre-eclampsia experienced at least one adverse maternal outcome and 74.3% (702/945) had at least one adverse fetal outcome. The most frequently reported outcome was preterm delivery before 34 weeks' gestation, occurring in 61.3% (580/946) of women. The second most common outcome was postpartum haemorrhage (7.8%, 74/946), followed by transfusion of any blood products (5.4%, 51/946) and abruptio placentae (2.6%, 25/946). The least reported maternal complications were need for positive inotrope support (0.1%, 1/946), posterior reversible encephalopathy (0.2%, 2/946) and a Glasgow Coma Scale score of < 13 (0.3%, 3/946). When preterm delivery was excluded as a component of the composite outcome, 15.5% of all women (147/946) had at least one adverse maternal outcome.

Chapter 4 Prediction of overall risk of adverse maternal outcome by discharge in women with early-onset pre-eclampsia: PREP-L model

Of the 946 women for whom outcome data were available, 633 (67%) experienced at least one adverse maternal outcome at any time from diagnosis to discharge. The number of women who had experienced an adverse outcome was 228 (24%) at 48 hours, 410 (43%) at 1 week and 624 (66%) at 30 days after diagnosis.

Modelling continuous predictors

Maternal age, systolic and diastolic BPs, haemoglobin level and platelet count were normally distributed, and hence we did not apply any transformation. Concentrations of ALT, AST, serum uric acid, serum urea and serum creatinine and the PCR were strongly right skewed, and we log-transformed these values. As gestational age at diagnosis was an inclusion criterion and limited to 34 weeks, a log transformation was applied to decrease the range. We were not able to fully evaluate serum uric acid concentration as a predictor because of data coding issues in this variable at the time of model development. Subsequent to model development being completed, and after the data coding issues were resolved for this variable, we calculated how the *c*-statistic changed after adding log-transformed serum uric acid concentration to the final models to assess whether or not this variable improved model performance (see *Apparent performance and internal validation of the PREP-L model*).

Development of PREP-L model: predictor selection

Table 11 shows the univariable and multivariable analysis for association of predictors and adverse maternal outcomes. The models were fitted in each of the imputed data sets and the results combined using Rubin's rules. In the univariable analysis, lower gestational age at diagnosis, symptoms of epigastric pain and/or nausea and vomiting, clonus, exaggerated tendon reflexes, raised systolic and diastolic BPs, urine dipstick-detectable proteinuria, high levels of haemoglobin, low platelet counts, raised concentrations of ALT, serum urea, serum uric acid and creatinine, increased urine PCR, management with antihypertensives and use of magnesium sulphate were significantly associated with adverse maternal outcomes ($p < 0.05$). Relevant medical history of one or more conditions such as chronic hypertension, diabetes mellitus, renal disease, autoimmune disease and a history of pre-eclampsia in previous pregnancy were associated with a reduced risk of complications.

Predictor variables were dropped stepwise based on the largest *p*-value. The final list of predictors for the logistic model were maternal age, log-transformed gestational age at diagnosis, summary score for medical history, systolic BP, platelet count, log-transformed serum urea concentration, log-transformed PCR, baseline treatment with any antihypertensive and baseline treatment with magnesium sulphate.

Transformation of predictors for the final PREP-L model

We considered the following continuous variables for non-linear terms: maternal age, log-transformed gestational age at diagnosis, systolic BP, platelet count, log-transformed serum urea concentration and log-transformed PCR.

TABLE 11 Univariable and multivariable logistic analysis of candidate predictors and risk of adverse outcomes after multiple imputation

Candidate predictors	Women,[a] *n*	No adverse maternal outcome (*n* = 313), mean (SD) or *n* (%)	Adverse maternal outcome (*n* = 633), mean (SD) or *n* (%)	Univariable models after multiple imputation (*n* = 946)		Multivariable full model after multiple imputation (*n* = 946)	
				Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Maternal characteristics							
Maternal age (years)	944	30.7 (6.3)	30.0 (6.0)	0.981 (0.959 to 1.003)	0.088	0.978 (0.951 to 1.006)	0.123
Log-transformed gestational age at diagnosis	946	3.4 (0.1)	3.4 (0.1)	0.005 (0.001 to 0.028)	< 0.001	0.001 (0.000 to 0.009)	< 0.001
Multiple pregnancy							
Singleton (reference)	946	284 (91%)	579 (91%)				
Twins		28 (9%)	51 (8%)	0.893 (0.552 to 1.447)	0.647	1.381 (0.790 to 2.416)	0.257
Triplets		1 (< 1%)	3 (< 1%)	1.472 (0.152 to 14.209)	0.738	2.826 (0.257 to 31.104)	0.396
Global test					0.849		0.556
Medical history score							
0 (reference)	945	170 (54%)	425 (67%)				
1		98 (31%)	152 (24%)	0.622 (0.456 to 0.848)	0.003	0.708 (0.487 to 1.030)	0.071
≥ 2		45 (14%)	55 (9%)	0.488 (0.317 to 0.753)	0.001	0.515 (0.296 to 0.897)	0.019
Global test					< 0.001		0.032

Candidate predictors	Women,[a] *n*	No adverse maternal outcome (*n* = 313), mean (SD) or *n* (%)	Adverse maternal outcome (*n* = 633), mean (SD) or *n* (%)	Univariable models after multiple imputation (*n* = 946)		Multivariable full model after multiple imputation (*n* = 946)	
				Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Symptoms							
Headache and/or visual disturbance	920	128 (42%)	252 (41%)	0.967 (0.734 to 1.275)	0.813	0.839 (0.582 to 1.210)	0.349
Epigastric pain, nausea and/or vomiting	901	52 (18%)	148 (25%)	1.491 (1.035 to 2.147)	0.033	1.001 (0.610 to 1.643)	0.997
Chest pain and/or dyspnoea	822	17 (6%)	43 (8%)	1.254 (0.644 to 2.441)	0.510	1.074 (0.441 to 2.618)	0.876
Bedside examination and tests							
Clonus	545	19 (12%)	75 (19%)	1.976 (1.127 to 3.464)	0.029	1.157 (0.537 to 2.492)	0.716
Exaggerated tendon reflexes	594	25 (15%)	121 (29%)	2.244 (1.534 to 3.284)	< 0.001	1.037 (0.643 to 1.673)	0.881
Systolic BP (mmHg)	942	151 (15)	162 (20)	1.038 (1.029 to 1.047)	< 0.001	1.025 (1.013 to 1.038)	< 0.001
Diastolic BP (mmHg)	942	96 (10)	101 (12)	1.047 (1.032 to 1.061)	< 0.001	1.009 (0.989 to 1.029)	0.384
Oxygen saturation: abnormal (< 94%)	429	0 (0%)	4 (< 1%)	No abnormal values in women without outcome		No abnormal values in women without outcome	
Urine dipstick: none/ trace (reference)	928	16 (5%)	23 (4%)				
1+		80 (26%)	89 (14%)	0.780 (0.384 to 1.584)	0.491	0.884 (0.404 to 1.933)	0.757
2+		120 (39%)	193 (31%)	1.133 (0.575 to 2.233)	0.719	0.894 (0.420 to 1.905)	0.772
3+		71 (23%)	232 (37%)	2.243 (1.117 to 4.501)	0.023	1.171 (0.520 to 2.637)	0.703
≥ 4		19 (6%)	85 (14%)	3.035 (1.355 to 6.794)	0.007	1.233 (0.484 to 3.145)	0.661
Global test					< 0.001		0.712

continued

TABLE 11 Univariable and multivariable logistic analysis of candidate predictors and risk of adverse outcomes after multiple imputation (*continued*)

Candidate predictors	Women,[a] *n*	No adverse maternal outcome (*n* = 313), mean (SD) or *n* (%)	Adverse maternal outcome (*n* = 633), mean (SD) or *n* (%)	Univariable models after multiple imputation (*n* = 946)		Multivariable full model after multiple imputation (*n* = 946)	
				Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Laboratory tests							
Haemoglobin (g/l)	910	11.8 (1.2)	12.0 (1.4)	1.114 (1.004 to 1.237)	0.042	1.054 (0.917 to 1.212)	0.461
Platelet count (× 10^9/l)	906	245 (77)	217 (77)	0.995 (0.993 to 0.997)	< 0.001	0.996 (0.994 to 0.999)	0.001
Log-transformed ALT concentration	871	2.8 (0.6)	3.0 (0.8)	1.561 (1.257 to 1.937)	< 0.001	1.189 (0.914 to 1.548)	0.197
Log-transformed serum uric acid concentration	782	–1.3 (1.0)	–1.0 (0.7)	1.566 (1.210 to 2.028)	0.001		
Log-transformed serum urea concentration	877	1.2 (0.4)	1.5 (0.5)	3.812 (2.598 to 5.594)	< 0.001	2.634 (1.588 to 4.369)	< 0.001
Log-transformed serum creatinine concentration	909	4.0 (0.3)	4.1 (0.3)	3.120 (1.863 to 5.226)	< 0.001	1.157 (0.598 to 2.240)	0.665
Log-transformed PCR	838	4.2 (1.4)	4.9 (1.5)	1.369 (1.230 to 1.524)	< 0.001	1.111 (0.955 to 1.293)	0.173
Treatment provided							
Antihypertensive therapy	945	225 (72%)	526 (83%)	1.931 (1.398 to 2.667)	< 0.001	1.555 (1.055 to 2.292)	0.026
Administration of magnesium sulphate	945	8 (3%)	136 (22%)	10.433 (5.042 to 21.587)	< 0.001	3.886 (1.746 to 8.653)	0.001

a Descriptive of predictors are presented based on the original non-imputed data. *n* is the number of cases out of 946 where the predictor is observed.

Appendix 5 shows the FP terms identified within each multiply imputed data set and the *p*-value for the test of deviance comparing the FP model with the model including linear terms only. Non-linear terms were identified as significant at the 1% level for log-transformed gestational age at diagnosis and serum urea concentration.

Final PREP-L model before adjusting for optimism

Table 12 shows the final logistic model after multiple imputation, including FP terms, and prior to adjustment for optimism.

The final PREP-L model identified that maternal age, early gestational age at diagnosis of pre-eclampsia, raised systolic BP, high urine PCR, high serum urea concentration, low platelet counts, need for treatment with antihypertensive drugs and administration of magnesium sulphate were associated with increased risk of adverse maternal outcomes. A positive medical history for pre-existing medical conditions or a previous history of pre-eclampsia was associated with a reduced risk of complications.

Apparent performance and internal validation of the PREP-L model

The apparent *c*-statistic for the PREP-L model (averaged across all multiply imputed data sets) was 0.84 (95% CI 0.82 to 0.87) and after adjustment for optimism it was 0.82 (95% CI 0.80 to 0.84). A sensitivity analysis showed that when all predictors were added to the final model, the *c*-statistic increased by < 0.01. Another sensitivity analysis of the model using oral and parenteral antihypertensive drugs separately showed no change in the *c*-statistic; therefore, the combined antihypertensive variable was retained. The addition of log-transformed serum uric acid concentration increased the *c*-statistic by < 0.004.

The predicted risk was grouped into tenths defined by centiles of predicted risk. *Table 13* shows the proportions of outcomes observed within each centile of risk. *Figure 3* shows predicted versus observed risk in the model development data set PREP.

TABLE 12 Final PREP-L model including non-linear FP terms before optimism adjustment

Candidate predictors	Odds ratio (95% CI)	*p*-value
Maternal age (years)	0.977 (0.950 to 1.004)	0.099
FP (log-gestational age at diagnosis)^3	1,188,051.840 (29,739.511 to 47,461,008.565)	< 0.001
FP (log-gestational age at diagnosis)^3 × ln(log-gestational age at diagnosis)	0.000 (0.000 to 0.001)	< 0.001
Effect of one pre-existing condition	0.681 (0.467 to 0.994)	0.046
Effect of more than two pre-existing conditions	0.510 (0.295 to 0.884)	0.016
Systolic BP (mmHg)	1.028 (1.017 to 1.039)	< 0.001
Platelet count (× 10^9/l)	0.995 (0.993 to 0.997)	< 0.001
FP (log-serum urea concentration)$^{-1}$	0.332 (0.191 to 0.575)	< 0.001
Log-transformed PCR	1.185 (1.030 to 1.362)	0.019
Baseline treatment: any antihypertensive drug	1.607 (1.085 to 2.380)	0.018
Baseline treatment: magnesium sulphate	4.279 (1.963 to 9.325)	< 0.001
Constant	0.000 (0.000 to 0.000)	< 0.001

TABLE 13 Proportions of outcomes within groups of predicted risk in the PREP-L model

Centile of risk	Women, *n*	Outcomes observed, *n* (%)
< 10th centile	11	3 (27)
10–20th centile	35	11 (31)
20–30th centile	58	15 (26)
30–40th centile	78	20 (26)
40–50th centile	80	34 (43)
50–60th centile	92	47 (51)
60–70th centile	87	54 (62)
70–80th centile	122	86 (70)
80–90th centile	159	144 (91)
> 90th centile	224	219 (98)

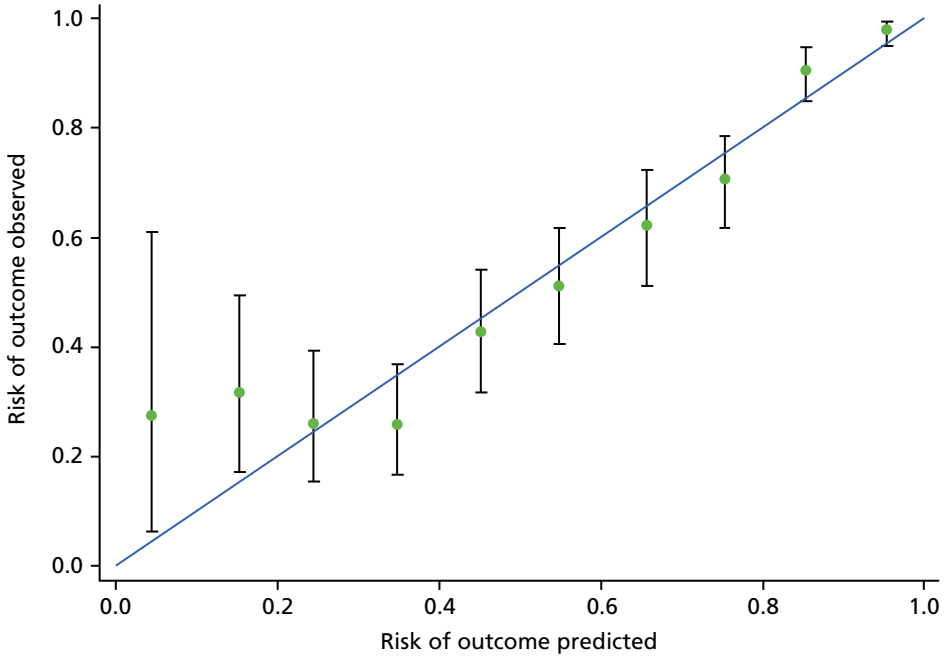

FIGURE 3 Predicted versus observed risk for maternal complications in the PREP-L model. Reproduced from Thangaratinam S, Allotey J, Marlin N, Dodds J, Cheong-See F, von Dadelszen P, *et al.* Prediction of complications in early-onset pre-eclampsia (PREP): development and external multinational validation of prognostic models. *BMC Med* 2017;**15**:68. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution and reproduction in any medium, provided that appropriate credit to the original authors and the source is given.[40]

Final adjusted PREP-L model for adverse maternal outcomes in women with early-onset pre-eclampsia

Based on the optimism in calibration, the predictor effect estimates of the developed model coefficient were reduced by the uniform shrinkage factor of 0.862. *Appendix 6* shows the coefficient for the final logistic model adjusted for optimism.

Based on the women's characteristics the probability of adverse outcome by discharge is:

$$\Pr(\text{outcome}) = \exp(X)/(1+\exp(X)), \quad (4)$$

where:

$$X = \beta_1 \times x_1 + \ldots + \beta_n \times x_n. \quad (5)$$

β_1–β_n are the coefficients for predictors in *Appendix 6*. Written formally, the equation used to derive individual risk predictions by discharge is as shown in *Box 3*.

The predicted probability of an outcome is $\exp(X)/(1 + \exp(X))$, where X is the predicted logit-p.

Application of the PREP-L model

We have shown examples of application of the PREP-L model below for two women recruited in the PREP study.

Scenario 1

BVH007, a 24-year-old woman with no relevant medical history, was admitted with a diagnosis of pre-eclampsia at 33 + 6 weeks' gestation. Her highest systolic BP was 200 mmHg and her urine PCR was 4907.6 mg/mmol. Her blood profile showed a platelet count of 75×10^9/l and a serum urea concentration of 9.5 mmol/l. She required parenteral antihypertensive therapy to manage her BP and was started on magnesium sulphate by her clinicians.

Applying the equation $\exp(3.649)/[1 + \exp(3.649)]$, her predicted risk of adverse maternal outcome by discharge was 97%. The mother was observed to need a blood transfusion following an emergency caesarean section as a result of worsening pre-eclampsia at 9 hours after diagnosis (*Table 14*).

BOX 3 Calculation of outcome risk by discharge

$$\begin{aligned} X = {} & -0.020 \times \text{maternal age} \\ & + 12.052 \times (\log(\text{GA}))^3 - 39.90241) \\ & - 7.930 \times ((\log(\text{GA}))^3 \times \log(\log(\text{GA}) - 49.08188) \\ & - 0.330 \text{ (if one pre-existing condition)} \\ & - 0.579 \text{ (if two or more pre-existing conditions)} \\ & + 0.146 \times \log(\text{PCR}) \\ & - 0.951 \times \left(\log(\text{serum urea concentration})^{-1}\right) \\ & - 0.004 \times \text{platelet count} \\ & + 0.024 \times \text{SBP} \\ & + 0.409 \text{ (if baseline treatment with antihypertensive drug)} \\ & + 1.252 \text{ (if baseline treatment with } MgSO_4) \\ & - 1.507 \\ & \Pr(\text{outcome}) = \exp(X)/(1+\exp(X)). \end{aligned}$$

GA, gestational age; $MgSO_4$, magnesium sulphate; SBP systolic BP.

TABLE 14 Examples of calculation of risk of adverse maternal outcome by discharge using the PREP-L model

	Example 1: BVH007			Example 2: BWH012		
Predictor variables	**Predictor values**	**Calculation**		**Predictor values**	**Calculation**	
Maternal age (years)	24	-0.020×24	–0.480	28	-0.020×28	–0.560
Summary score of medical history	0	+0	+0	1	+1	+1
Gestational age (weeks) at diagnosis	33.857	$+12.052 \times \{[\log(33.857)]^3 - 39.90241\} - 7.930 \times [\log(33.857)]^3 \times \log\{[\log(33.857)] - 49.08188\}$	–1.344	32.857	$+ 12.052 \times \{[\log(32.857)]^3 - 39.90241\} - 7.930 \times [\log(32.857)]^3 \times \log\{[\log(32.857)] - 49.08188\}$	–0.744
PCR (mg/mmol)	4907.6	$+0.146 \times \log(4907.6)$	+1.241	0.32	$+0.146 \times \log(0.32)$	–0.166
Serum urea concentration (mmol/l)	9.5	$-0.951 \times [\log(9.5) - 1]$	–0.422	3.5	$-0.951 \times [\log(3.5) - 1]$	–0.759
Platelet count ($\times 10^9$/l)	75	-0.004×75	–0.300	283	-0.004×283	–1.132
Systolic BP (mmHg)	200	$+0.024 \times 200$	+4.800	136	$+0.024 \times 136$	+3.264
Baseline treatment						
Any antihypertensive drug	1 ('yes')	+0.409	+0.409	1 ('yes')	+0.409	+0.409
Magnesium sulphate	1 ('yes')	+1.252	+1.252	0 ('no')	+0	+0
			– 1.507			–1.507
			= 3.649			= –1.525
Predicted risk by discharge			0.976			0.179
Adverse maternal outcomes		Blood transfusion within 9 hours of diagnosis			None	

Scenario 2

BWH012, a 28-year-old woman, was admitted with a diagnosis of pre-eclampsia at 32 + 6 weeks' gestation. She had a summary score of 1 for relevant medical history and her highest systolic BP was 136 mmHg. Her PCR was 0.32 mg/mmol and her blood profile showed a platelet count of 283×10^9/l and a serum urea concentration of 3.5 mmol/l. She was started on parenteral antihypertensives by her clinician to manage her BP.

Applying the equation, exp (–1.525)/[1 + exp(–1.525)], her predicted risk of adverse maternal outcome by discharge was 18%. The mother was discharged without having any adverse maternal outcome (see *Table 14*).

Sensitivity analysis of the PREP-L model in participants with unconfirmed diagnosis of pre-eclampsia

Of the 142 participants recruited with a suspected diagnosis of pre-eclampsia, 138 had a 1+ urine dipstick. There were two perfect predictions by baseline treatment with magnesium sulphate and these two observations were dropped. The optimism-adjusted logistic model, as described in *Appendix 6*, was applied to 136 women with an unconfirmed diagnosis of pre-eclampsia. The apparent *c*-statistic was 0.68 (95% CI 0.58 to 0.79) and the calibration slope was 0.64 (95% CI 0.25 to 1.04).

Chapter 5 Prediction of adverse maternal outcome in women with early-onset pre-eclampsia: PREP-S model

Overall, 946 women contributed towards 584 failures. Five of these failures occurred on the same day as diagnosis and were forced into the survival model by adding 10 minutes to the time of their occurrence. The total analysis time at risk was 10,923 days, the median analysis time per participant was 6 days (interquartile range 2–14 days) and the longest follow-up period is 98 days. The mean gestational age at delivery was 33.0 weeks (SD 3.2 weeks). For the survival model, the first adverse events are defined as the failure event and are shown in *Table 15*. Delivery before 34 weeks' gestation contributed the most (85%, 497/584) to failures.

Modelling continuous predictors

We modelled the continuous predictors as shown in *Chapter 4*, *Modelling continuous predictors*.

Development of the PREP-S model: predictor selection

Table 16 shows the hazard ratios for adverse pregnancy outcomes for various candidate predictors by univariable and by multivariable analysis summarised across using the multiply imputed data sets.

TABLE 15 Rates of failure defining adverse events for the survival model

Failure defining adverse event	Number of women ($N = 584$), *n* (%)
Eclamptic seizures after diagnosis	11 (1.9)
Glasgow Coma Scale score of < 13	1 (0.2)
Hepatic dysfunction	4 (0.7)
At least 50% FiO_2 for > 1 hour	1 (0.2)
Intubation	1 (0.2)
Pulmonary oedema	4 (0.7)
Transfusion of any blood product	12 (2.1)
Abruption	16 (2.7)
PPH	31 (5.3)
Delivery at < 34 weeks' gestational age	497 (85.1)
Combined events	
Acute renal insufficiency and preterm delivery (< 34 weeks' gestation)	1 (0.2)
Abruption and preterm delivery (34 weeks' gestation)	3 (0.5)
Intubation, PPH and transfusion of any blood product	1 (0.2)
Abruption and PPH	1 (0.2)

FiO_2, fraction of inspired oxygen; PPH, postpartum haemorrhage.

TABLE 16 Univariable and multivariable analysis of candidate predictors for adverse maternal outcomes in women with early-onset pre-eclampsia

Candidate predictors	Women,[a] *n*	No adverse maternal outcome (*n* = 374), mean (SD) or *n* (%)	Adverse maternal outcome (*n* = 572), mean (SD) or *n* (%)	Univariable analysis (*N* = 946)		Multivariable analysis (*N* = 946)	
				Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Maternal characteristics							
Maternal age (years)	944	30.9 (6.4)	29.8 (6.0)	0.972 (0.959 to 0.984)	< 0.001	0.968 (0.954 to 0.982)	< 0.001
Log-transformed gestational age (weeks) at diagnosis	946	3.45 (0.1)	3.40 (0.1)	10.198 (4.162 to 24.987)	< 0.001	22.425 (8.528 to 58.970)	< 0.001
Multiple pregnancy							
Singleton (reference)	946	319 (88%)	544 (93%)				
Twins		41 (11%)	38 (7%)	0.790 (0.568 to 1.098)	0.160	0.895 (0.631 to 1.270)	0.535
Triplets		2 (1%)	2 (< 1%)	0.816 (0.203 to 3.273)	0.774	1.194 (0.291 to 4.904)	0.806
Global test					0.360		0.794
Medical history score							
0 (reference)	945	195 (54%)	400 (69%)				
1		116 (32%)	134 (23%)	0.604 (0.496 to 0.736)	< 0.001	0.828 (0.671 to 1.022)	0.078
≥ 2		51 (14%)	49 (8%)	0.468 (0.347 to 0.631)	< 0.001	0.658 (0.479 to 0.905)	0.010
Global test					< 0.001		0.017
Symptoms							
Headache and/or visual disturbance	920	142 (40%)	238 (42%)	1.136 (0.962 to 1.341)	0.133	1.007 (0.835 to 1.215)	0.940
Epigastric pain, nausea and/or vomiting	901	61 (18%)	139 (25%)	1.495 (1.223 to 1.828)	< 0.001	0.943 (0.745 to 1.194)	0.627
Chest pain and/or dyspnoea	822	19 (6%)	41 (8%)	1.227 (0.844 to 1.785)	0.293	1.172 (0.766 to 1.793)	0.472

Candidate predictors	Women,[a] *n*	No adverse maternal outcome (*n* = 374), mean (SD) or *n* (%)	Adverse maternal outcome (*n* = 572), mean (SD) or *n* (%)	Univariable analysis (*N* = 946)		Multivariable analysis (*N* = 946)	
				Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Bedside examination and tests							
Clonus	545	24 (13%)	70 (19%)	1.622 (1.303 to 2.020)	< 0.001	0.763 (0.547 to 1.064)	0.129
Exaggerated tendon reflexes	594	28 (14%)	118 (30%)	1.966 (1.602 to 2.413)	< 0.001	1.249 (0.996 to 1.566)	0.055
Systolic BP (mmHg)	942	151 (14)	163 (20)	1.028 (1.023 to 1.032)	< 0.001	1.018 (1.012 to 1.024)	< 0.001
Diastolic BP (mmHg)	942	96 (10)	102 (12)	1.033 (1.026 to 1.040)	< 0.001	1.002 (0.993 to 1.011)	0.695
Oxygen saturation: abnormal (< 94%)	429	0 (0%)	4 (1%)	5.769 (2.154 to 15.449)	< 0.001	4.342 (1.496 to 12.607	0.007
Urine dipstick: none/ trace (reference)	928	18 (5%)	21 (4%)				
1+		95 (27%)	74 (13%)	0.731 (0.449 to 1.190)	0.208	0.864 (0.522 to 1.433)	0.572
2+		136 (38%)	177 (31%)	1.065 (0.676 to 1.679)	0.786	0.994 (0.619 to 1.597)	0.981
3+		84 (24%)	219 (38%)	1.853 (1.178 to 2.914)	0.008	1.293 (0.795 to 2.103)	0.300
≥ 4		21 (6%)	83 (14%)	2.487 (1.536 to 4.026)	< 0.001	1.216 (0.717 to 2.062)	0.469
Global test					< 0.001		0.076

continued

TABLE 16 Univariable and multivariable analysis of candidate predictors for adverse maternal outcomes in women with early-onset pre-eclampsia (*continued*)

Candidate predictors	Women,[a] *n*	No adverse maternal outcome (*n* = 374), mean (SD) or *n* (%)	Adverse maternal outcome (*n* = 572), mean (SD) or *n* (%)	Univariable analysis (*N* = 946)		Multivariable analysis (*N* = 946)	
				Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Laboratory tests							
Haemoglobin (g/l)	910	11.8 (1.2)	12.0 (1.4)	1.102 (1.032 to 1.176)	0.004	1.051 (0.984 to 1.121)	0.137
Platelet count (× 10^9/l)	906	242 (76)	217 (77)	0.995 (0.994 to 0.997)	< 0.001	0.997 (0.996 to 0.998)	< 0.001
Log-transformed ALT concentration	871	2.8 (0.6)	3.0 (0.8)	1.503 (1.338 to 1.689)	< 0.001	1.181 (1.040 to 1.341)	0.011
Log-transformed serum uric acid concentration	782	–1.3 (1.0)	–1.0 (0.7)	1.431 (1.280 to 1.600)	< 0.001		
Log-transformed serum urea concentration	877	1.2 (0.4)	1.5 (0.5)	1.985 (1.734 to 2.273)	< 0.001	1.555 (1.296 to 1.865)	< 0.001
Log-transformed serum creatinine concentration	909	4.0 (0.3)	4.1 (0.3)	3.381 (2.474 to 4.620)	< 0.001	1.549 (1.081 to 2.219)	0.017
Log-transformed PCR	838	4.2 (1.4)	5.0 (1.5)	1.405 (1.303 to 1.516)	< 0.001	1.082 (1.001 to 1.169)	0.049
Treatment provided							
Antihypertensive therapy	945	264 (73%)	487 (84%)	1.477 (1.187 to 1.838)	< 0.001	1.239 (0.983 to 1.562)	0.070
Magnesium sulphate administered	945	9 (2%)	135 (23%)	6.654 (5.442 to 8.137)	< 0.001	3.540 (2.708 to 4.627)	< 0.001

a Descriptions of predictors are presented based on the original non-imputed data. *n* is the number of cases out of 946 where the predictor is observed.

After dropping the candidate predictor variables stepwise based on the largest *p*-value, the following were included as the final list of predictors in the survival model: maternal age, log-transformed gestational age at diagnosis, summary score for medical history, systolic BP, clonus, exaggerated tendon reflexes, oxygen saturation, platelet count, log-transformed ALT concentration, log-transformed serum urea concentration, log-transformed serum creatinine concentration, log-transformed PCR, baseline treatment with any antihypertensive drug and baseline treatment with magnesium sulphate.

We identified non-linear terms for log-transformed gestational age at diagnosis and serum urea concentration using FPs. We chose terms with a *p*-value of > 0.001 to avoid overfitting. After including non-linear terms for gestational age at diagnosis and serum urea concentration, clonus then filled the criterion for exclusion at a *p*-value of > 0.150 and was therefore removed. Running the multivariable FP procedure without clonus confirmed that the FP terms identified originally were still valid (results not shown).

In the full multivariable model, the risk of adverse maternal outcomes were significantly increased at the 5% level with lower maternal age, greater gestational age at diagnosis, lower number of components of medical history, raised systolic BP, lower platelet count, raised ALT concentration, raised serum urea concentration, increased urine PCR and administration of magnesium sulphate.

We applied the variable selection process and included the non-linear terms for gestational age at diagnosis and serum urea concentration. The PREP-S survival model prior to adjustment for optimism is shown in *Table 17*.

Apparent performance of the PREP-S model

The apparent *c*-statistic of the developed survival model was 0.78 (95% CI 0.76 to 0.80). Estimation of risks in the five groups defined by the 10th, 25th, 75th and 90th centiles of predicted risk showed that the probability of adverse outcome was around 52% in the highest risk group at 48 hours after diagnosis, 95% by 1 week, and 100% by 1 month. Ninety-seven per cent (91/94) of women in the > 90th centile group experienced an adverse maternal outcome, with a mean follow-up time of 1.2 days (SD 1.3 days). In the lowest risk group (≤ 10th centile), the probability of outcome-free survival was around 97% at 48 hours after diagnosis, 87% by 1 week, and 56% by 1 month. In this group, 24% (23/95) had an adverse outcome, with a mean follow-up time of 28.9 days (SD 23.1 days) (*Table 18*).

In women in the groups defined by the highest centiles of predicted risk, there was good agreement between those with observed and predicted adverse outcomes. About 97% (91/94) of women with risks above the 90th centile had an adverse outcome; 83% (118/143) of women with predicted risks between the 75th and 90th centiles had complications; and 61% (289/471) with risks between the 25th and 75th centiles experience an adverse outcome.

Figure 4 shows the model-based mean survival curves for the five prognostic groups compared with their observed Kaplan–Meier survival curves, for 1 month after diagnosis-days. Agreement is generally excellent, perhaps with the exception of the lowest risk group, although this has fewest events and so more uncertainty about the mean predicted curve. CIs are not shown on the figure for aesthetic reasons.

Sensitivity analysis

Inclusion of all candidate predictors in the model only improved the Harrell's *c*-statistic by < 0.001. Comparison of the Cox regression model with our flexible parametric model yielded similar hazard ratios, as expected. The full models are presented in *Appendix 7*. Time-dependent effects on the model were not significant for all covariates except baseline medication. Inclusion of this effect for baseline medication into the model improved Harrell's *c*-statistic by 0.005 (results not shown). In order to avoid overfitting and achieve simplicity, we considered this improvement too small to include a time-dependent effect into our final model. Another sensitivity analysis of the model using oral and parenteral antihypertensive therapy separately showed no change in the *c*-statistic; therefore, the combined antihypertensive variable was retained. Addition of log-transformed uric acid concentration changed the Harrell's *c*-statistic by < 0.001.

TABLE 17 Final PREP-S model including non-linear FP terms before adjustment for optimism

Flexible parametric model after multiple imputation	Hazard ratio	95% CI	*p*-value
Maternal age (years)	0.964	0.951 to 0.978	< 0.001
FP [log(GA at diagnosis/10)]$^{-2}$ centred at 0.8345136	5.794	0.299 to 112.276	0.245
[a]FP [log(GA at diagnosis/10)]$^{-2}$ ln[log(GA at diagnosis/10)] centred at 0.0652155	750.276	2.380 to 236561.167	0.024
Exaggerated tendon reflexes	1.152	0.935 to 1.420	0.185
Number of pre-existing conditions			
0			
Effect of a medical history score of 1	0.822	0.668 to 1.010	0.062
Effect of a medical history score of ≥ 2	0.640	0.464 to 0.883	0.007
Systolic BP (mmHg)	1.018	1.013 to 1.023	< 0.001
Oxygen saturation < 94%	2.520	0.870 to 7.298	0.089
Platelet count (× 10^9/l)	0.997	0.996 to 0.998	< 0.001
Log-transformed ALT concentration	1.157	1.031 to 1.299	0.013
FP (log-serum urea concentration)^2	2.017	1.611 to 2.526	< 0.001
FP (log-serum urea concentration)^3	0.846	0.795 to 0.900	< 0.001
Log-transformed serum creatinine concentration centred at 4.067578	1.361	0.952 to 1.944	0.091
Log-transformed PCR	1.097	1.025 to 1.173	0.007
Baseline treatment			
Any antihypertensive drug	1.227	0.976 to 1.543	0.080
Magnesium sulphate	3.445	2.675 to 4.437	< 0.001

GA, gestational age.
a Spline basis functions not shown.

TABLE 18 Survival time within groups of predicted risk

Centile of predicted risk	Number of women, *n*	Adverse maternal outcome, *n* (%)	Follow-up time (days), mean (SD)	
			Adverse outcome	No adverse outcome
≤ 10th	95	22 (23)	28.2 (23.3)	40.2 (29.8)
10–25th	143	64 (45)	16.1 (12.7)	15.9 (13.7)
25–75th	471	289 (61)	8.6 (8.4)	10.1 (9.4)
75–90th	143	118 (83)	3.9 (4.4)	6.3 (5.9)
> 90th	94	91 (97)	1.2 (1.3)	3.7 (4.6)

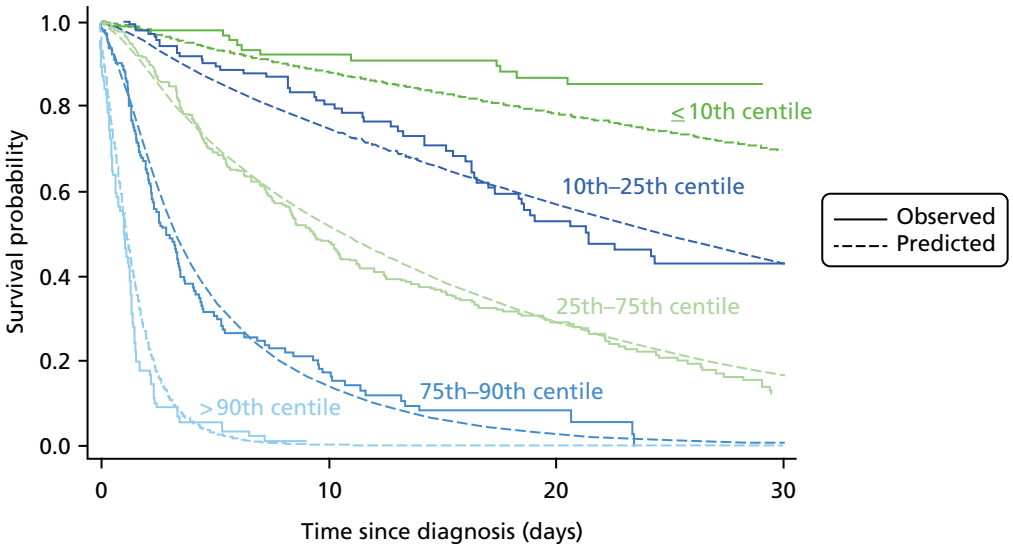

FIGURE 4 Mean survival curves for groups of prognostic index compared with their observed Kaplan–Meier survival curves up to 30 days from diagnosis. Reproduced from Thangaratinam S, Allotey J, Marlin N, Dodds J, Cheong-See F, von Dadelszen P, *et al.* Prediction of complications in early-onset pre-eclampsia (PREP): development and external multinational validation of prognostic models. *BMC Med* 2017;**15**:68. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution and reproduction in any medium, provided that appropriate credit to the original authors and the source is given.[40]

Internal validation and shrinkage of estimates for the final PREP-S model

The bootstrap approach showed an optimism of 0.019 (SD 0.010) in the *c*-statistic and 0.138 (SD 0.002) in the calibration slope. Based on the optimism in calibration, the predictor effect estimates of the developed model coefficient were reduced by the uniform shrinkage factor: $1 - 0.138 = 0.862$. The intercept of the baseline spline term was re-estimated to ensure perfect calibration-in-the-large. The optimism-adjusted Harrell's *c*-statistic of the survival model was 0.75 (95% CI 0.73 to 0.78).

Appendix 8 shows the coefficients of the final PREP-S model and the baseline hazard after adjusting for optimism. *Table 19* gives the baseline survival at various time points to calculate the predicted survival probability for a woman diagnosed with early-onset pre-eclampsia.

Based on the woman's characteristics, the survival probability at time point *t* is:

$$S_{(t)} = S_0(t)^{\exp}\,[(\beta_1 \times X_1 + \ldots + \beta_n \times X_n)], \quad (6)$$

where β_1–β_n are the coefficients for predictors shown in *Appendix 8*, and X_1–X_n are the predictor values for the patient. Written formally, the equation used to derive individual risk predictions over time is shown in *Box 4*.

Positive regression coefficients suggest an increase in the risk of adverse maternal outcome with increasing values of continuous predictors or the presence of dichotomous predictor variables, and vice versa for negative coefficients.

Application of the PREP-S model

We have provided examples of calculating the individual risk of adverse maternal outcomes at 48 hours using the PREP-S model. The predictor values of two women are provided in *Table 20*. The calculation of risk can easily be amended to a different time point by replacing the value for baseline survival with the baseline survival for the desired time point from *Table 18*.

TABLE 19 Baseline survival adjusted for optimism at various time points for women diagnosed with early-onset pre-eclampsia

Time point (days)	Baseline survival, $S_0(t)$
2	0.99142
3	0.98542
4	0.97973
5	0.97452
6	0.96962
7	0.96492
14	0.93404
21	0.90373
28	0.87377
35	0.84432
42	0.81549

BOX 4 Calculation of risk predictions over time

$$
\begin{aligned}
S(t) = \; & S_0(t)^{\exp(-0.031 \times \text{maternal age})} \\
& + 1.514 \times ((\log(\text{GA at diagnosis}/10))^{-2} - 0.8345136) \\
& + 5.707 \times (\log(\text{GA at diagnosis}/10))^{-2} \times \ln(\log(\text{GA at diagnosis}/10)) - 0.0652155) \\
& + 0.122 \text{ (if exaggerated tendon reflexes} = 1) \\
& - 0.169 \text{ (if one pre-existing condition)} \\
& - 0.384 \text{ (if} \geq 2 \text{ pre-existing conditions)} \\
& + 0.016 \times \text{systolic BP} \\
& + 0.797 \text{ (if pulse oximetry} < 94\%) \\
& - 0.002 \times \text{platelet count} \\
& + 0.126 \times \log(\text{ALT concentration}) \\
& + 0.605 \times \log(\text{serum urea concentration})^2 \\
& - 0.144 \times \log(\text{serum urea concentration})^3 \\
& + 0.265 \times \log(\text{serum creatinine concentration}) \\
& + 0.080 \times \log(\text{PCR}) \\
& + 0.176 \text{ (if baseline treatment with any antihypertensive drug)} \\
& + 1.066 \text{ (if baseline treatment with magnesium sulphate).}
\end{aligned}
$$

where $S_0(t)$ is the value of the baseline survival function at time t (see *Table 19*).

Sensitivity analysis of survival model in participants with unconfirmed diagnosis of pre-eclampsia

Of the 142 participants recruited with a suspected diagnosis of pre-eclampsia, 138 had a 1+ urine dipstick. For one woman the time of outcome was missing. The optimism-adjusted survival model, as described in *Appendix 8,* was applied to this population. The apparent *c*-statistic was 0.64 (95% CI 0.53 to 0.76) and the calibration scope was 0.88 (95% CI 0.17 to 1.58).

TABLE 20 Calculations of risk of adverse maternal outcome by 48 hours using the PREP-S model

	Example 1: BVH007			Example 2: BWH012		
Candidate predictors	**Predictor values**	**Calculation**		**Predictor values**	**Calculation**	
Time point	**48 hours**			**48 hours**		
Baseline survival		$= 0.99142^{exp}(...$			$= 0.99142^{exp}(...$	
Maternal age (years)	24	-0.031×24	–0.744	28	-0.031×28	–0.868
Gestational age (weeks) at diagnosis	33.857	$+ 1.514 \times (\log(33.857/10)^{-2} - 0.8345136) + 5.707 \times (\log(33.857/10)^{-2} \times \log(\log(33.857/10)) - 0.0652155)$	+0.144	32.857	$+ 1.514 \times (\log(32.857/10)^{-2} - 0.8345136) + 5.707 \times (\log(32.857/10)^{-2} \times \log(\log(32.857/10)) - 0.0652155)$	+0.134
Exaggerated tendon reflexes	0 ('no')	+0	+0	0 ('no')	+0	+0
Summary score for medical history	0	+0	+0	1	– 0.169	–0.169
Systolic BP (mmHg)	200	$+0.016 \times 200$	+3.200	136	$+0.016 \times 136$	+2.176
ALT concentration (U/l)	72	$+0.126 \times \log(72)$	+0.539	11	$+0.126 \times \log(11)$	+0.302
PCR (mg/mmol)	4907.6	$+0.080 \times \log(4907.6)$	+0.680	0.32	$+0.080 \times \log(0.32)$	–0.091
Serum urea concentration (mmol/l)	9.5	$+0.605 \times \log(9.5)^2 - 0.144 \times \log(9.5)^3$	+1.423	3.5	$+0.605 \times \log(3.5)^2 - 0.144 \times \log(3.5)^3$	+0.666
Serum creatinine concentration (μmol/l)	74	$+0.265 \times \log(74)$	+1.141	33	$+0.265 \times \log(33)$	+0.927
Platelet count ($\times 10^9$/l)	75	-0.002×75	–0.150	283	-0.002×283	–0.566
Oxygen saturation < 94%	99	+0	+0	Assumed normal	+0	+0
Baseline treatment						
Any antihypertensive drug	1 ('yes')	+0.176	+0.176	1 ('yes')	+0.176	+0.176
Magnesium sulphate	1 ('yes')	+1.066	+1.066	0 ('no')	+0	+0
			= 7.475			= 2.687
Predicted survival by 48 hours			= 0.00000025			= 0.881
Adverse maternal outcomes		Blood transfusion within 9 hours of diagnosis			None	

Chapter 6 External validation of the prediction models for complications in women with early-onset pre-eclampsia

Inclusion criteria and availability of data in external data sets

The PIERS study

The PIERS study evaluated the effects of 48 predictors in 2023 women with pre-eclampsia of any onset. Of these, 636 (31%) were diagnosed with early-onset pre-eclampsia and 634 had available data for external validation of the PREP models. The majority of women with early-onset pre-eclampsia were classified as having new-onset disease (519/636, 82%), followed by those with superimposed pre-eclampsia (95/636, 15%) and HELLP syndrome (22/636, 3%) (*Table 21*).

Of the 13 predictors in the PREP models, 10 were also evaluated in the PIERS study. Exaggerated tendon reflexes, serum urea concentration and autoimmune diseases (one element of the medical history) were assessed in the PREP study, but were not available in the PIERS data set.

The PETRA study

The PETRA study evaluated the effect of plasma volume expansion in 111 patients with severe hypertensive disorders of pregnancy compared with a control group of 105 patients with severe hypertensive disorders of pregnancy. All patients ($n = 216$) had a diagnosis of early-onset pre-eclampsia and had available data for external validation of the PREP-L model only. The majority of women with early-onset pre-eclampsia were those classified as having fetal growth restriction or pregnancy-induced hypertension (125/216, 58%), followed by those with new-onset pre-eclampsia (96/216, 44%), HELLP syndrome (54/216, 25%) and eclampsia (5/216, 2.3%) (see *Table 21*).

TABLE 21 Inclusion criteria for women with early-onset pre-eclampsia recruited to the PIERS and PETRA studies compared with the PREP cohort

Inclusion criteria	Study		
	Women in the PREP cohort ($N = 954$), *n* (%)	Women in the PIERS cohort ($N = 636$), *n* (%)	Women in the PETRA cohort ($N = 216$), *n* (%)
New-onset pre-eclampsia	866 (91.0)	519 (82)	96 (44)[a]
Chronic hypertension	75 (7.9)		
Superimposed pre-eclampsia	10 (1.0)	95 (15)	
HELLP syndrome	3 (0.3)	22 (3)	54 (25)[a]
Eclampsia			5 (2.3)[a]
Fetal growth restriction or pregnancy-induced hypertension			125 (58)[a]

a Some patients matched more than one inclusion diagnosis.

Characteristics of women with early-onset pre-eclampsia in the PIERS and PETRA studies

There were no significant differences in the mean gestational age at diagnosis of pre-eclampsia, which was around 30 weeks. The PETRA study included only singleton pregnancies, while around 91% (870/954) of pregnancies in the PREP study and 85% (542/634) in the PIERS study were singletons. Two-thirds (601/953, 63%) of women in the PREP study did not have any significant medical history, such as pre-existing medical conditions or previous history of pre-eclampsia, compared with 45% (284/634) and 84% (182/216) in the PIERS and PETRA studies, respectively.

The PETRA study did not have any data on symptoms or examination findings such as deep-tendon reflexes or clonus. In addition, the study did not report any tests for proteinuria, oxygen saturation and serum creatinine concentration that were reported in the other two cohorts. *Table 22* compares patient characteristics and candidate predictor variables in the PREP development data set and the PIERS and PETRA validation data sets.

Risk of adverse outcomes in the PIERS and PETRA cohorts

Overall, 67% (633/946) of women with early-onset pre-eclampsia in the PREP study had adverse maternal outcomes by discharge, compared with 77% (489/634) and 86% (185/216) in the PIERS and PETRA cohorts, respectively. The date and time of occurrence of adverse maternal outcomes was consistently reported in the PIERS data set and not in the PETRA study. Maternal and fetal composite outcomes not reported in the PIERS and PETRA data sets are provided in *Tables 23* and *24*.

External validation of the models

As not all predictors in the PREP models were available in the PIERS and PETRA data sets, we externally validated a slightly reduced version of our final models, with the model parameters re-estimated with a reduced set of predictors. We re-estimated the coefficients and intercept terms of the model, and then adjusted for optimism as before. We validated the survival model in only the PIERS data set, because of the non-availability of time of outcome occurrence in the PETRA cohort.

External validation of the PREP-L model in the PIERS data set

Complete records on the predictors considered were available for 437 of 654 women in whom pre-eclampsia was diagnosed at < 34 weeks' gestation.

Obtaining the reduced PREP-L model

Serum urea concentration was identified as a predictor in the PREP data, but it was not recorded in the PIERS data set. We obtained the reduced PREP-L (rPREP-L) model and adjusted for optimism after excluding serum urea concentration (see *Appendix 9*). The calibration slope for this optimism-adjusted rPREP-L model was 1.01 (95% CI 0.86 to 1.15) when averaged across all imputed data sets. The apparent *c*-statistic was 0.82 (95% CI 0.80 to 0.85).

Application of the reduced PREP-L model in the PIERS data set

The optimism-adjusted *c*-statistic of the rPREP-L model was 0.81 (95% CI 0.77 to 0.85), indicating a good discrimination in the external validation data set. The calibration slope was 0.93 (95% CI 0.72 to 1.13), indicating very good calibration and model fit in the PIERS data on average across all individuals (*Figure 5*).

The predicted risk was grouped into centiles of predicted risk. *Table 25* shows the risk of outcome for each centile of predicted risk. When the intercept term was recalibrated to the PIERS data, the calibration slope and *c*-statistic remained the same.

TABLE 22 Characteristics of women with early-onset pre-eclampsia in the PREP study and external validation cohorts (PIERS and PETRA)

Characteristics of women	Study					
	PREP		PIERS		PETRA	
	Women for whom data were available (*n*)	Mean (SD) or *n* (%)	Women for whom data were available (*n*)	Mean (SD) or *n* (%)	Women for whom data were available (*n*)	Mean (SD) or *n* (%)
Gestational age at diagnosis (weeks), mean (SD)	954	30.5 (2.9)	634	30.2 (3.0)	216	29.4 (2.6)
Maternal characteristics						
Maternal age (years), mean SD	952	30.2 (6.1)	634	31.2 (6.3)	216	30.0 (5.0)
Number of fetuses in pregnancy	954		634		216	
Singleton		866 (91%)		542 (85%)		216 (100%)
Twins		83 (9%)		88 (14%)		–
Triplets		5 (1%)		4 (1%)		–
History						
Summary score for medical history	953		634		216	
0		601 (63%)		284 (45%)		182 (84%)
1		251 (26%)		251 (40%)		30 (14%)
≥ 2		101 (11%)		99 (15%)		4 (2%)
Symptoms						
Headache and/or visual disturbance, present	926	382 (41%)	634	319 (50%)	–	–
Epigastric pain, nausea and/or vomiting, present	907	202 (22%)	634	220 (35%)	–	–
Chest pain and/or dyspnoea, present	828	60 (7%)	634	42 (7%)	–	–
Examination						
Clonus[a]	551	95 (17%)	–	–	–	–
Exaggerated tendon reflexes,[a] mean (SD)	601	139 (15%)	–	–	–	–
Systolic BP, mean (SD)	949	159 (19)	634	168 (20)	216	157 (18)
Diastolic BP, mean (SD)	949	99 (12)	634	105 (11)	216	104 (11)
Oxygen saturation by pulse oximetry (%), mean (SD)	433	98.1 (1.6)	474	96 (2)	–	–
Oxygen saturation abnormal (< 94%), present	433	4 (1%)	474	72 (15%)	–	–

continued

TABLE 22 Characteristics of women with early-onset pre-eclampsia in the PREP study and external validation cohorts (PIERS and PETRA) (*continued*)

Characteristics of women	Study					
	PREP		PIERS		PETRA	
	Women for whom data were available (*n*)	Mean (SD) or *n* (%)	Women for whom data were available (*n*)	Mean (SD) or *n* (%)	Women for whom data were available (*n*)	Mean (SD) or *n* (%)
Laboratory tests						
Haemoglobin (g/l), mean (SD)	917	11.9 (1.3)	–	–	–	–
Platelet count (× 10^9/l), mean (SD)	913	226 (78)	630	204 (77)	215	172 (87)
ALT concentration (U/l), mean (SD)	879	31.0 (71.0)	630	65.5 (157.6)	207	79.9 (139.3)
AST concentration (U/l), mean (SD)	275	36.9 (61.1)	600	74.3 (196.5)	212	91.9 (160.7)
Serum uric acid concentration (μmol/l), mean (SD)	789	0.6 (2.7)	–	–	–	–
Serum urea concentration (mmol/l), mean (SD)	884	4.6 (4.4)	–	–	–	–
Serum creatinine concentration (μmol/l), mean (SD)	916	61.9 (17.8)	626	69.3 (20.5)	214	67.8 (16.8)
Urine dipstick						
None/trace	935	39 (4%)	613	129 (21%)	–	–
1+		170 (18%)		69 (11%)	–	–
2+		314 (34%)		111 (18%)	–	–
3+		306 (33%)		141 (23%)	–	–
≥ 4		106 (11%)		163 (27%)	–	–
Urine PCR 24 hour (mg/mmol), mean (SD)	433	98.1 (1.6)	437	276 (437)	–	–
Baseline treatment						
Antihypertensive therapy, present	948	753 (79%)	634	551 (87%)	216	123 (57%)
Magnesium sulphate administration, present	948	144 (15%)	634	325 (51%)	216	34 (16%)

a Predictor is part of the survival model only and used as a component of the final PREP model.

TABLE 23 Comparison of the maternal outcome measures in the PIERS and PETRA data sets compared with the PREP study

Components of adverse maternal outcome evaluated in the PREP study	PIERS	PETRA
Maternal death	✓	✓
Eclamptic seizures	✓	✓
Glasgow Coma Scale score of < 13	✓	✓
Stroke or RIND	✓	✓
Cortical blindness	✓	✓
Retinal detachment	–	–
Posterior reversible encephalopathy	–	✓
Bell's palsy	✓	–
Hepatic dysfunction	✓	✓
Subcapsular haematoma	–	–
Hepatic rupture	✓	✓
Need for positive inotrope support	✓	–
Myocardial ischaemia or infarction	✓	–
At least 50% FiO_2 for > 1 hour	✓	✓
Intubation	✓	✓
Pulmonary oedema	✓	✓
Acute renal insufficiency (creatinine concentration of > 200 uM)	✓	✓
Dialysis	✓	✓
Transfusion of any blood product	✓	✓
Abruptions	–	✓
Postpartum haemorrhage	–	✓
Delivery at < 34 weeks' gestational age	✓	✓

FiO_2, fraction of inspired oxygen; RIND, reversible ischaemic neurological deficit.

TABLE 24 Comparison of the fetal outcome measures in the PIERS and PETRA data sets

Components of adverse fetal outcome evaluated in the PREP study	PIERS	PETRA
Neonatal death	✓	✓
Bronchopulmonary dysplasia	✓	✓
Necrotising enterocolitis	✓	✓
Grade III/IV intraventricular haemorrhage	✓	✓
Cystic periventricular leukomalacia	✓	✓
Stage 3–5 retinopathy	✓	–
Hypoxic–ischaemic encephalopathy	–	✓
Stillbirth	✓	✓
Admission to NICU at any time	✓	✓

NICU, neonatal intensive care unit.

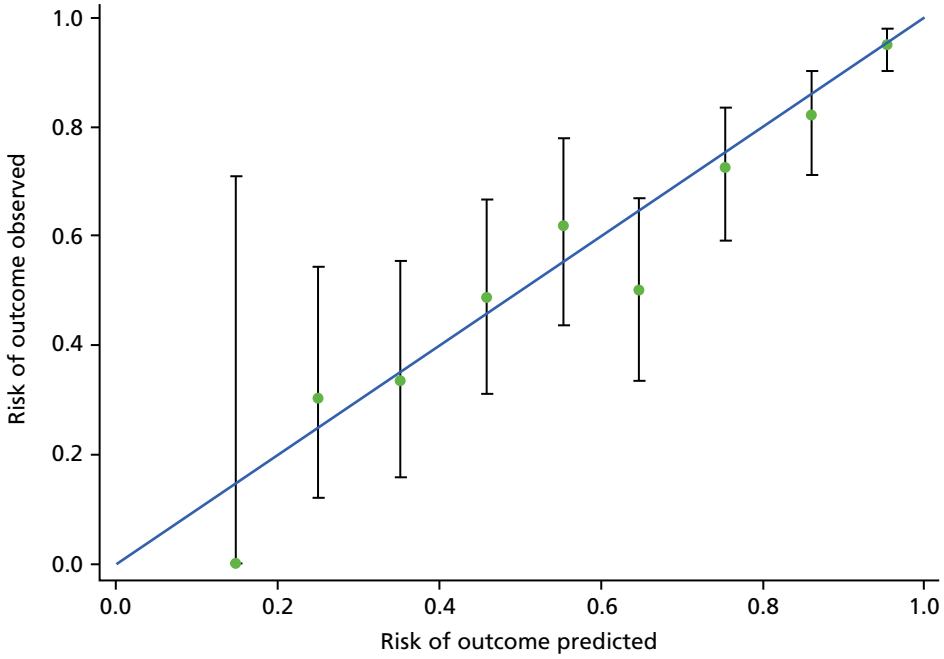

FIGURE 5 Validation plot of the predicted vs. observed risk for adverse maternal outcome using the rPREP-L model in the PIERS cohort. Reproduced from Thangaratinam S, Allotey J, Marlin N, Dodds J, Cheong-See F, von Dadelszen P, *et al.* Prediction of complications in early-onset pre-eclampsia (PREP): development and external multinational validation of prognostic models. *BMC Med* 2017;**15**:68. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution and reproduction in any medium, provided that appropriate credit to the original authors and the source is given.[40]

TABLE 25 Comparison of the predicted vs. observed risk for adverse maternal outcome using the rPREP-L model in the PIERS cohort

Groups of predicted risk	Women with predicted outcomes, *n*	Women with observed outcomes, *n* (%)
< 10th centile	0	–
10–20th centile	3	0 (0)
20–30th centile	20	6 (30)
30–40th centile	24	8 (33)
40–50th centile	33	16 (48)
50–60th centile	34	21 (62)
60–70th centile	38	19 (50)
70–80th centile	58	42 (72)
80–90th centile	72	59 (82)
> 90th centile	155	147 (95)

External validation of the reduced PREP-L model in the PETRA cohort

Complete records on the predictors considered were available for 211 of 216 women in whom pre-eclampsia was diagnosed at < 34 weeks' gestation .

Harrell's *c*-statistic was 0.75 (95% CI 0.64 to 0.86), indicating a moderate discrimination in the external validation data set. The calibration slope was 0.90 (95% CI 0.48 to 1.3), indicating some slight

miscalibration, with observed risk generally higher than predicted. However, predictions showed reasonably close agreement at predicted risks above 0.7 (*Figure 6*). *Table 26* shows the risk of outcome for groups defined by tenths of predicted risk.

Recalibration of the intercept to the PETRA data did not improve the calibration slope. *Table 27* shows the performance of the reduced PREP models in the derivation cohorts and external validation data sets.

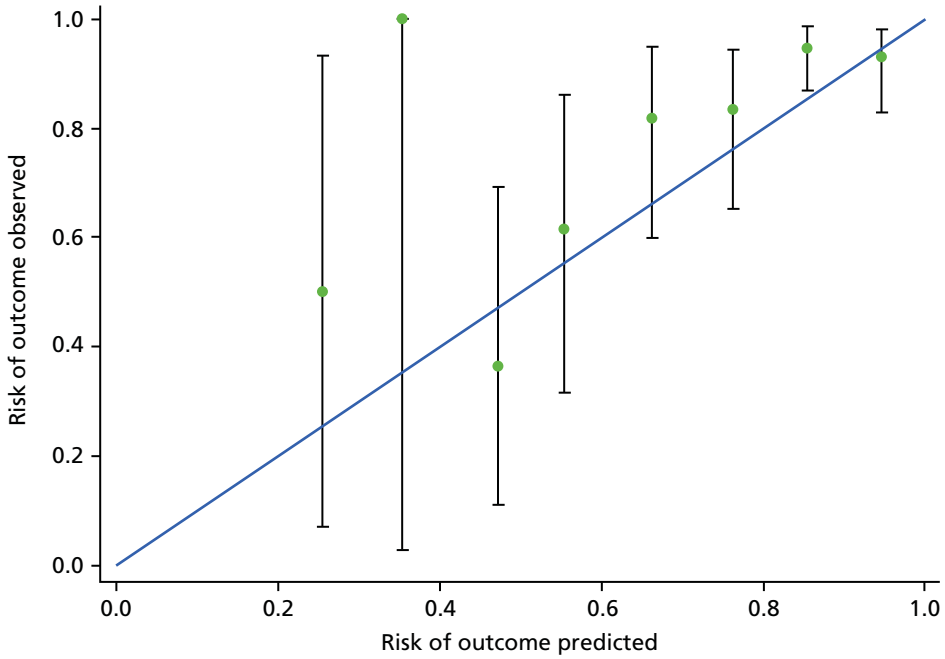

FIGURE 6 Validation plot of the predicted vs. observed risk for adverse maternal outcome using the rPREP-L model in the PETRA cohort. Reproduced from Thangaratinam S, Allotey J, Marlin N, Dodds J, Cheong-See F, von Dadelszen P, *et al.* Prediction of complications in early-onset pre-eclampsia (PREP): development and external multinational validation of prognostic models. *BMC Med* 2017;**15**:68. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution and reproduction in any medium, provided that appropriate credit to the original authors and the source is given.[40]

TABLE 26 Comparison of predicted vs. observed risk for adverse maternal outcome using the rPREP-L model in the PETRA cohort

Groups of predicted risk	Women with predicted outcomes, *n*	Women with observed outcomes, *n* (%)
< 10th centile	0	–
10–20th centile	0	–
20–30th centile	4	2 (50)
30–40th centile	1	1 (100)
40–50th centile	11	4 (36)
50–60th centile	13	8 (62)
60–70th centile	22	18 (82)
70–80th centile	30	25 (83)
80–90th centile	74	70 (95)
> 90th centile	56	52 (93)

TABLE 27 Performance of the rPREP-L and rPREP-S models in the derivation cohorts and external validation data sets

Model performance	PREP	rPREP (for PIERS)	PIERS	rPREP (for PETRA)	PETRA
PREP-L model					
Number analysed	946	946	437	946	211
Number of outcomes	633	633	318	633	180
Apparent *c*-statistic (95% CI)	0.84 (0.82 to 0.87)	0.82 (0.80 to 0.85)	0.81 (0.77 to 0.85)	0.81 (0.79 to 0.84)	0.75 (0.64 to 0.86)
Optimism-adjusted *c*-statistic (95% CI)	0.82 (0.80 to 0.84)	–	–	–	–
Calibration slope (95% CI)	1	1	0.93 (0.72 to 1.13)	1	0.90 (0.48 to 1.32)
PREP-S model					
Number analysed	946	946	339	–	–
Number of events	584	584	239	–	–
Apparent *c*-statistic (95% CI)	0.77 (0.75 to 0.79)	0.76 (0.74 to 0.78)	0.71 (0.67 to 0.75)	–	–
Optimism-adjusted *c*-statistic (95% CI)	0.75 (0.73 to 0.78)	–	–	–	–
Calibration slope (95% CI)	1	1	0.67 (0.56 to 0.79)	–	–

rPREP-S, reduced PREP-S.

External validation of the PREP-S model in the PIERS data set

In the PIERS data set, 634 women were diagnosed with pre-eclampsia before 34 weeks' gestation. Four hundred and sixty-one failures occurred during follow-up, six of which occurred on the same day as diagnosis and were included by adding a fraction of a day. One hundred and thirty-two had failures by 48 hours, 332 by 1 week and 458 by 30 days after diagnosis. We evaluated the reduced PREP-S (rPREP-S) model in 339 women with complete predictor value data. The total analysis time was 5425 days, with the last observed exit at 89 days of follow-up.

Obtaining the reduced PREP-S model

As serum urea concentration and exaggerated tendon reflexes were identified to be a predictor in the PREP-S model but were not recorded in the PIERS data set, we refitted the PREP-S model. *Appendix 10* shows the coefficients of the rPREP-S prediction model after excluding serum urea concentration and exaggerated tendon reflexes, adjusted for optimism. Harrell's *c*-statistic of the optimism-adjusted rPREP-S model was 0.76 (95% CI 0.74 to 0.78).

Applying the reduced PREP-S model in the PIERS data set

The rPREP-S model with coefficients as described in *Appendix 10* was fitted to the PIERS data set. *Figures 7* and *8* compare the predictions made by the PREP model in four prognostic groups of the PIERS data until 34 weeks' gestation up to 30 days after diagnosis, respectively.

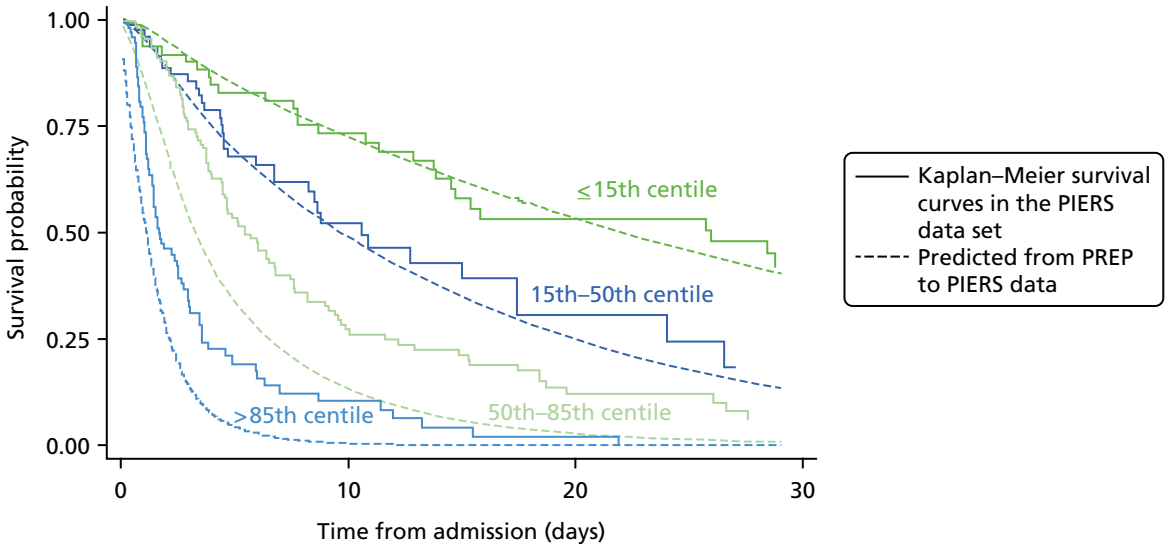

FIGURE 7 Validation of the PREP-S model in the PIERS data set up to 30 days from diagnosis.

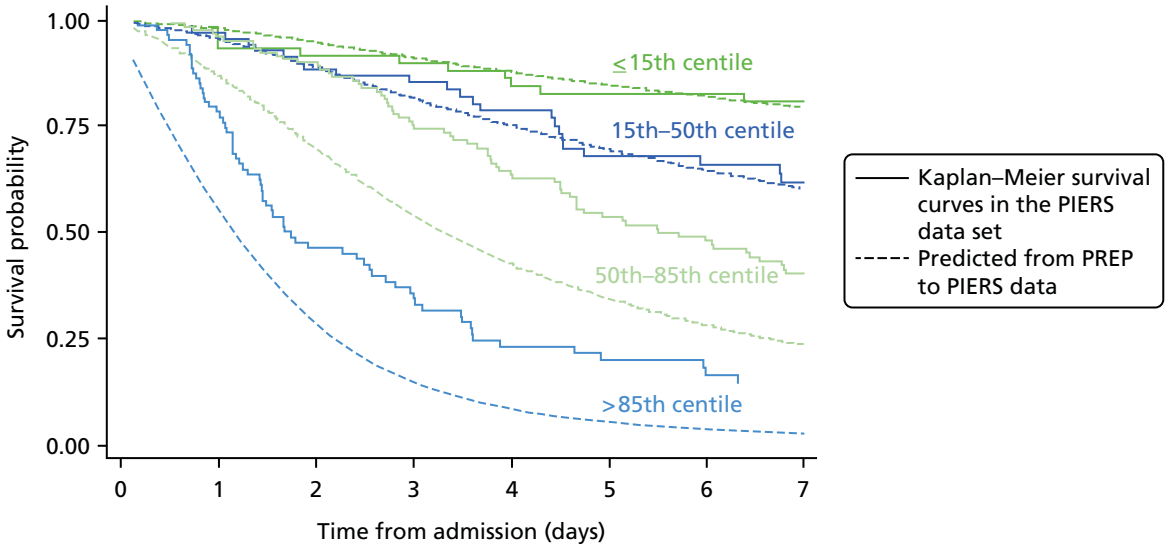

FIGURE 8 Validation of the PREP-S model in the PIERS data set up to 7 days from diagnosis.

The *c*-statistic in the PIERS cohort was 0.71 (95% CI 0.67 to 0.75), which was slightly lower than that of the rPREP-S model. However, the four risk groups are still noticeably distinct and ordered appropriately for the majority of the 30-day period, with the exception of the two intermediate-risk groups before 3 days. The calibration slope of the rPREP-S model in the PIERS data set was 0.67 (95% CI 0.56 to 0.79), suggesting large overprediction of the reduced PREP model, and this was observed predominantly in the third of four groups (which had the largest patient numbers), especially after 5 days. Importantly, those identified as 'high risk' by the PREP model were still in the high-risk category in the PIERS cohort, but the observed absolute risk values were lower than expected from the reduced PREP model.

Calibration slope for each of the four risk groups are:

- ≤ 15th centile ($n = 59$): 0.21 (95% CI –0.51 to 0.92)
- 15–50th centile ($n = 70$): 0.65 (95% CI –0.80 to 2.10)
- 50–85th centile ($n = 123$): 0.25 (95% CI –0.34 to 0.84)
- > 85th centile ($n = 87$) 0.73 (95% CI 0.42 to 1.00).

Recalibration of the intercept of the baseline hazard function in the rPREP-S model to the PIERS data set did not improve calibration. *Figure 9* shows that the agreement between observed and predicted survival was much improved in the high-risk group. However, it was noticeably worse in the other risk groups.

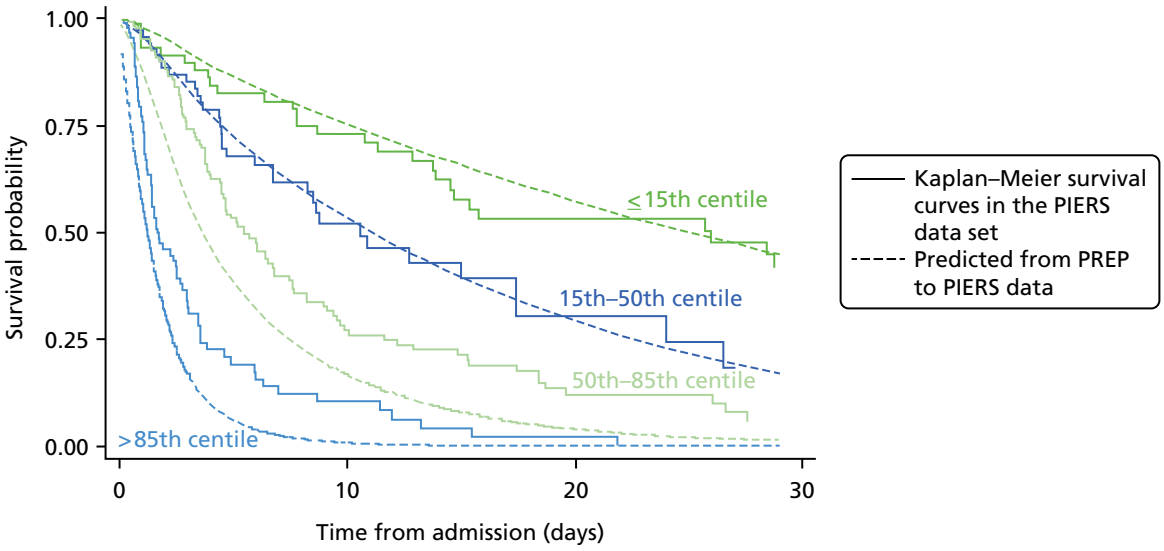

FIGURE 9 Validation of the rPREP-S model in the PIERS data set after recalibration up to 30 days from diagnosis. Reproduced from Thangaratinam S, Allotey J, Marlin N, Dodds J, Cheong-See F, von Dadelszen P, *et al.* Prediction of complications in early-onset pre-eclampsia (PREP): development and external multinational validation of prognostic models. *BMC Med* 2017;**15**:68. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution and reproduction in any medium, provided that appropriate credit to the original authors and the source is given.[40]

Chapter 7 Prediction of fetal complications in women with early-onset pre-eclampsia

We assessed the predictive value of individual tests on fetal outcomes in the 945 pregnancies for which outcome data were available. The rates of individual fetal and neonatal complications observed in women with early-onset pre-eclampsia can be seen in *Table 10*.

Performance of the PREP-L model for adverse fetal outcomes

We assessed the performance of the PREP-L model (see *Table 12*) for the fetal composite outcome, using the same predictors. *Table 28* and *Figure 10* show the proportions of outcomes observed within each centile of risk. The *c*-statistic was 0.76 (95% CI 0.73 to 0.79) and the calibration slope was 0.77 (95% CI 0.63 to 0.91), indicating overprediction of risk, especially for prediction of 0.6 or below. In women predicted to be at high risk (> 80th centile), around 90% had adverse fetal outcomes.

Predictive value of tests for adverse fetal and neonatal outcomes

We evaluated the prognostic value of all candidate predictors associated with maternal outcomes and the following five additional predictors: ultrasound (uterine artery Doppler in second trimester, expected fetal weight and liquor volume), CTG findings and use of steroids within or before 24 hours of diagnosis of pre-eclampsia. *Table 29* shows the descriptive values of the candidate predictors and their crude and multivariate association with adverse fetal outcomes.

Association of maternal and fetal characteristics with adverse fetal outcomes

In the multivariable analysis of predictors, increased gestational age at diagnosis of pre-eclampsia reduced the odds of fetal complications (OR 0.09, 95% CI 0.01 to 0.61). A medical history of pre-existing chronic

TABLE 28 Comparison of the number of women with observed adverse fetal outcomes in deciles of risk groups predicted by the PREP-L model

Decile of risk	Women with predicted outcomes, *n*	Women with observed outcomes, *n* (%)
< 10th centile	7	2 (29)
10–20th centile	23	8 (35)
20–30th centile	53	26 (49)
30–40th centile	73	35 (48)
40–50th centile	91	51 (56)
50–60th centile	101	69 (68)
60–70th centile	103	76 (74)
70–80th centile	140	109 (78)
80–90th centile	171	149 (87)
> 90th centile	183	177 (97)

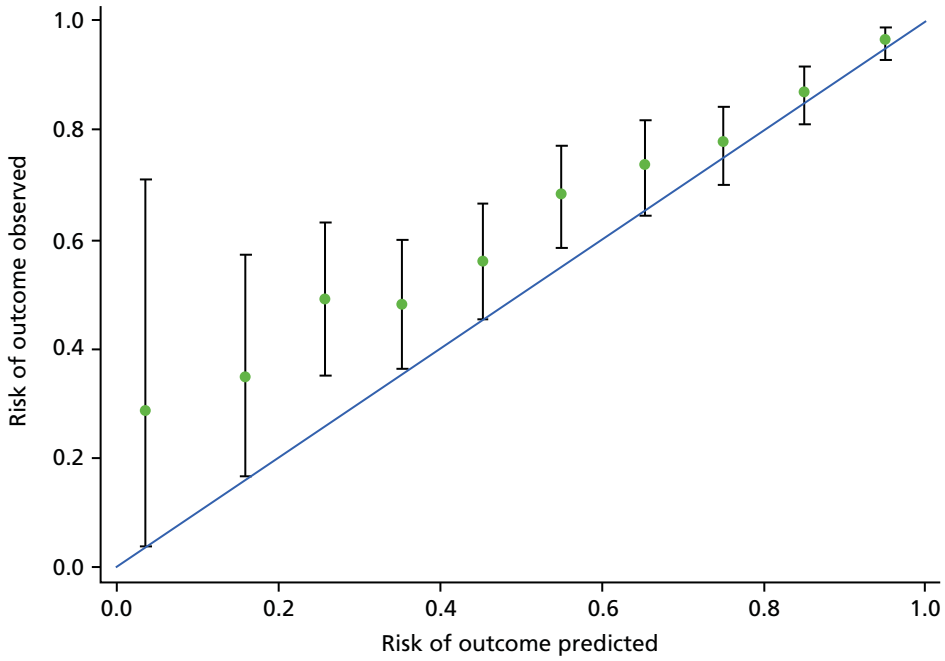

FIGURE 10 Calibration plot of the predicted vs. observed risk for adverse fetal outcome using the PREP-L model.

TABLE 29 Crude univariable and multivariable analyses of candidate predictors and adverse fetal outcomes in women with early-onset pre-eclampsia

Candidate predictors	Women, *n*[a]	No adverse fetal outcomes (*n* = 243), mean (SD) or *n* (%)	Adverse fetal outcomes (*n* = 702), mean (SD) or *n* (%)	Univariable analysis (*N* = 945)		Multivariable analysis (*N* = 945)	
				OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Maternal characteristics							
Maternal age (years)	943	31.0 (6.1)	30.0 (6.1)	0.972 (0.949 to 0.995)	0.018	0.984 (0.954 to 1.015)	0.301
Log-transformed gestational age (weeks) at diagnosis	945	3.4 (0.1)	3.4 (0.1)	0.111 (0.022 to 0.554)	0.007	0.089 (0.013 to 0.607)	0.014
Multiple pregnancy							
Singleton (reference)	945	225 (93%)	637 (91%)				
Twins		17 (7%)	62 (9%)	1.288 (0.738 to 2.250)	0.373	1.676 (0.862 to 3.260)	0.128
Triplets		1 (0%)	3 (0%)	1.060 (0.110 to 10.239)	0.960	1.245 (0.112 to 13.774)	0.858
Global test					0.673		0.313
Medical history score							
0 (reference)	944	116 (48%)	478 (68%)				
1		83 (34%)	167 (24%)	0.490 (0.351 to 0.683)	< 0.001	0.654 (0.435 to 0.984)	0.041
≥ 2		44 (18%)	56 (8%)	0.309 (0.198 to 0.481)	< 0.001	0.434 (0.246 to 0.767)	0.004
Global test					< 0.001		0.009

TABLE 29 Crude univariable and multivariable analyses of candidate predictors and adverse fetal outcomes in women with early-onset pre-eclampsia (*continued*)

Candidate predictors	Women, *n*[a]	No adverse fetal outcomes (*n* = 243), mean (SD) or *n* (%)	Adverse fetal outcomes (*n* = 702), mean (SD) or *n* (%)	Univariable analysis (*N* = 945)		Multivariable analysis (*N* = 945)	
				OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Symptoms							
Headache and/or visual disturbance	919	102 (43%)	278 (41%)	0.891 (0.658 to 1.206)	0.456	0.812 (0.552 to 1.193)	0.289
Epigastric pain, nausea and/or vomiting	900	43 (19%)	157 (23%)	1.331 (0.906 to 1.955)	0.145	0.958 (0.578 to 1.590)	0.869
Chest pain and/or dyspnoea	821	12 (6%)	48 (8%)	1.340 (0.668 to 2.687)	0.410	1.190 (0.502 to 2.822)	0.693
Bedside examination and tests							
Clonus	545	10 (8%)	84 (20%)	2.399 (1.262 to 4.562)	0.008	1.487 (0.609 to 3.633)	0.384
Exaggerated tendon reflexes	594	20 (16%)	126 (27%)	2.063 (1.318 to 3.231)	0.002	0.852 (0.461 to 1.575)	0.610
Systolic BP (mmHg)	941	153 (16)	161 (20)	1.025 (1.016 to 1.034)	< 0.001	1.005 (0.992 to 1.019)	0.414
Diastolic BP (mmHg)	941	96 (11)	101 (11)	1.044 (1.029 to 1.059)	< 0.001	1.018 (0.996 to 1.039)	0.103
Oxygen saturation abnormal (< 94%)	428	1 (1%)	3 (1%)	1.039 (0.108 to 10.032)	0.974	0.107 (0.009 to 1.214)	0.071
Urine dipstick: none/trace (reference)	927	11 (5%)	28 (4%)				
1+		71 (30%)	98 (14%)	0.549 (0.256 to 1.179)	0.124	0.609 (0.259 to 1.435)	0.257
2+		100 (42%)	212 (31%)	0.840 (0.401 to 1.760)	0.644	0.781 (0.341 to 1.791)	0.560
3+		42 (18%)	261 (38%)	2.429 (1.117 to 5.284)	0.025	1.445 (0.587 to 3.555)	0.424
≥ 4		13 (5%)	91 (13%)	2.739 (1.111 to 6.751)	0.029	0.974 (0.334 to 2.840)	0.961
Global test					< 0.001		0.045
Laboratory tests							
Haemoglobin (g/l)	909	11.8 (1.1)	12.0 (1.4)	1.096 (0.983 to 1.223)	0.100	1.019 (0.885 to 1.173)	0.792
Platelet count (× 10^9/l)	905	244 (77)	220 (77)	0.996 (0.994 to 0.998)	< 0.001	0.998 (0.996 to 1.001)	0.128
Log-transformed ALT concentration	870	2.7 (0.6)	3.0 (0.8)	1.641 (1.244 to 2.165)	< 0.001	1.330 (0.958 to 1.848)	0.089
Log-transformed serum uric acid concentration	781	–1.3 (1.2)	–1.0 (0.7)	1.409 (1.135 to 1.750)	0.002		

continued

TABLE 29 Crude univariable and multivariable analyses of candidate predictors and adverse fetal outcomes in women with early-onset pre-eclampsia (*continued*)

Candidate predictors	Women, *n*[a]	No adverse fetal outcomes (*n* = 243), mean (SD) or *n* (%)	Adverse fetal outcomes (*n* = 702), mean (SD) or *n* (%)	Univariable analysis (*N* = 945)		Multivariable analysis (*N* = 945)	
				OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Log-transformed serum urea concentration	876	1.2 (0.4)	1.4 (0.5)	3.679 (2.482 to 5.452)	< 0.001	1.718 (1.068 to 2.764)	0.026
Log-transformed serum creatinine concentration	908	4.0 (0.3)	4.1 (0.3)	2.823 (1.662 to 4.795)	< 0.001	1.039 (0.506 to 2.135)	0.916
Log-transformed PCR	837	3.9 (1.4)	4.9 (1.4)	1.569 (1.397 to 1.762)	< 0.001	1.290 (1.111 to 1.497)	0.001
Treatment provided							
Antihypertensive therapy	944	177 (73%)	573 (82%)	1.663 (1.182 to 2.339)	0.004	1.558 (1.026 to 2.368)	0.038
Magnesium sulphate administered	944	9 (4%)	135 (19%)	6.190 (3.100 to 12.363)	< 0.001	2.402 (1.036 to 5.573)	0.041
Steroids administered	783	66 (41%)	364 (59%)	2.186 (1.549 to 3.085)	< 0.001	1.208 (0.795 to 1.835)	0.376
Ultrasound and CTG							
Uterine artery Doppler abnormal	339	12 (14%)	79 (31%)	2.365 (1.536 to 3.639)	< 0.001	1.944 (1.077 to 3.510)	0.027
CTG findings abnormal	710	10 (6%)	36 (7%)	1.395 (0.680 to 2.865)	0.364	0.625 (0.254 to 1.538)	0.306
Estimated fetal weight < 10th centile	712	27 (15%)	261 (49%)	3.835 (2.453 to 5.995)	< 0.001	2.538 (1.462 to 4.405)	0.001
Liquor volume abnormal	890	10 (4%)	46 (7%)	1.548 (0.776 to 3.087)	0.215	1.279 (0.519 to 3.152)	0.593

OR, odds ratio.

a Descriptive of predictors based on the original non-imputed data. *N* is the number of women with available data.

hypertension, diabetes mellitus, autoimmune disease, renal disease or a history of pre-eclampsia in previous pregnancies reduced the odds of composite adverse fetal outcomes for one pre-existing medical complication (OR 0.65 95% CI 0.44 to 0.98) and for two or more pre-existing medical complications (OR 0.43 95% CI 0.25 to 0.77).

The odds of fetal complications were significantly increased in women with raised urine PCR (OR 1.29, 95% CI 1.11 to 1.50), serum urea concentration (OR 1.72, 95% CI 1.07 to 2.76), treatment with antihypertensives (OR 1.56, 95% CI 1.04 to 2.37), treatment with magnesium sulphate (OR 2.40, 95% CI 1.04 to 5.57), abnormal uterine artery Doppler (OR 1.94, 95% CI 1.08 to 3.51) and when expected fetal weight was less than the 10th centile by ultrasound (OR 2.54, 95% CI 1.46 to 4.40).

Chapter 8 Discussion

In women with early-onset pre-eclampsia, the PREP prediction models provide robust estimates of the overall risk of adverse maternal outcomes by discharge, and the risks at various time points following diagnosis. The PREP-L model showed good discrimination and calibration and appeared to be useful in predicting risk of complications as a result of early-onset pre-eclampsia in pregnancy and until discharge for UK populations. Given that the rPREP-L model was easily transportable, with good performance in the non-UK populations, we expect the original PREP-L model to have similar performance externally. The PREP-S model showed good discrimination in external data sets, with reasonable calibration. The use of this model will be useful to health-care professionals in deciding on the appropriate setting for management and for commencement of interventions, such as steroids, if preterm delivery is anticipated.

Strengths and limitations

A well-performing prediction model is one that is relevant, accurate, validated in populations and data sets external to those used to develop the model and applicable to clinical practice. With these properties, it has the potential to improve clinical outcomes by helping clinicians and patients make more informed decisions.

The PREP models were developed in a sample of women with early-onset pre-eclampsia, a condition that is considered to be pathophysiologically different from late onset disease,[8–10] and with a high proportion of adverse outcomes. We used prospective cohorts with high-quality data for both model development and validation, and with standardised definitions of variables and outcomes. The model was developed with data from 53 units in the UK, making the results as generalisable as possible within the NHS.

We ensured that all routinely performed tests in clinical practice were evaluated. The choice of predictors and components of the composite outcome were made by using Delphi surveys of experts in the field.[9,15,41] We chose delivery before 34 weeks as an outcome to further minimise treatment paradox-related bias, as delivery is planned at this gestation only if there are concerns regarding the health of the mother.

Prediction models often evaluate a large number of predictors in a population with few events, making the findings less robust. We ensured that we had adequate sample size for the number of candidate predictors to avoid overfitting.[43–45] The rates of follow-up were very high in our PREP cohort and very few individuals had missing values for most predictors.

One of the main reasons why clinicians lack confidence in applying risk scores in practice is the lack of sufficient evidence to demonstrate the reproducibility and transportability of the model in an external data set.[32] Furthermore, they are less likely to accept the model if it does not include important predictors such as BP. Guided by an a priori expert workshop (see *Chapter 2*, *Analysis plan development*), we minimised bias due to treatment by the inclusion of management decisions such as use of antihypertensives and magnesium sulphate as predictors. We transparently reported the development of the model and have provided the regression coefficients to enable clinical use and future validation of the model.

Our prediction study used rigorous statistical methods to develop the model, to assess its accuracy and to formally validate its performance in external data sets.[32–35,39,48–51] We developed two prediction models for the dual purpose of obtaining overall complication risks arising from pre-eclampsia and risk estimates for complications at various time points after diagnosis. A logistic model alone would not have sufficient sample size to provide estimates of adverse outcomes at time points close to diagnosis, such as 48 hours after delivery, given the low rates of serious complications. However, the PREP-S model allowed us to overcome this problem, and is the first to provide individualised risks of adverse maternal outcomes at various time points after the diagnosis of early-onset pre-eclampsia.

We performed geographic, temporal and domain validation of the model. The external data sets of the PIERS and PETRA cohorts were geographically different (Canada and the Netherlands) and were conducted earlier than the PREP study. We validated reduced models in external data sets as fewer predictors were evaluated therein. However, the rPREP-L model validated with good discrimination and calibration for predicting overall risk, and we expect the original PREP-L model to have similar, if not better, performance if fully externally validated.

The aim of the model was to provide reliable, accurate and precise information of risks to the mother and baby based on tests done at the time of diagnosis of early-onset pre-eclampsia. We only evaluated the tests and variables measured routinely in clinical practice. The added value of biomarkers and ultrasound to the accuracy of the model is not known. We refrained from using predictors such as fetal weight estimated by ultrasound, which may have been a significant predictor, as access to ultrasound may not always be available close to the diagnosis of pre-eclampsia in most units. We arbitrarily chose the components of relevant medical history and scored them. Inclusion of a different set of medical conditions may have altered the results. Women with a medical history score appeared to have a reduction in the risk of complications. It is likely that specialists in joint obstetric specialist clinics closely monitor these mothers resulting in early diagnosis of pre-eclampsia. Targeted and intense follow-up of these women may have led to prolongation of pregnancy beyond 34 weeks and with low complications. When developing our PREP models, we were unable to properly examine serum uric acid concentration as a predictor because at the time of the model development there was a coding error in the data for this variable. However, subsequent to the PREP models being developed and this coding error being corrected, we examined if the inclusion of serum uric acid concentration was important and found that the *c*-statistic barely changed for either the PREP-L or PREP-S model.

Women with earlier diagnosis of pre-eclampsia appeared to be at lower risk of maternal complications in the PREP-S model. This is likely, as the primary outcome is largely driven by delivery before 34 weeks. In women who were close to 34 weeks' gestation, clinicians may have a lower threshold for delivery in the next few days or weeks. However, if the diagnosis was made much earlier in the pregnancy, clinicians would aim to prolong gestation as long as possible, leading to a longer survival time.

Our primary outcome was a composite of maternal complications. A different choice of outcomes may have identified a different set of predictors. However, given the rarity of individual complications in women with early-onset pre-eclampsia, we felt that our approach to include delivery before 34 weeks is a close representative measure for the severity of the disease. However, we did not separately report iatrogenic preterm deliveries from spontaneous preterm deliveries. As it is difficult to accurately identify the cause of spontaneous preterm delivery, which could still be related to pre-eclampsia such as small abruption, we grouped them together as one outcome.

The external data sets were limited in the number of variables evaluated, and hence we were unable to validate our full PREP model in either of them. The reduced PREP models, especially rPREP-L, showed good performance in the development and validation data sets, although the rPREP-S model showed reduced performance. Although the overall values of predictors may be similar to the PREP cohort, the management of women with early-onset pre-eclampsia may be different in the various health-care systems of the external cohorts; for example, magnesium sulphate treatment was provided in 51% of all women with early-onset pre-eclampsia in the PIERS cohort, compared with only 15% in the PREP cohort. Furthermore, the variation in the proportion of women giving birth before 34 weeks' gestation, which was the major component of the composite outcome, may have contributed to the reduced performance of the model in the external data sets. The narrow spectrum of diseases in individuals in the PETRA cohort may have contributed to the reduced performance of the PREP model.

Comparison with existing evidence

So far, systematic reviews have not been able to produce robust estimates of accuracy of the individual tests.[20,22,23,39,53,54] Tests widely used in clinical practice, such as measurement of BP and proteinuria, suffered from treatment paradox and those such as clonus and deep-tendon reflexes were not studied in sufficient detail. This study is the first to address the above deficiencies.

The PREP study is the first to develop and validate the models for predicting adverse maternal outcomes specifically in women with early-onset disease. Previously, the PIERS and mini-PIERS models have provided estimates for overall risk of adverse outcomes in women with pre-eclampsia of any onset. Their sample sizes were too small to predict complications in women with early-onset pre-eclampsia. This is also the first study to provide individualised risk estimates for adverse outcomes at various time points after diagnosis of early-onset pre-eclampsia. Although the PIERS model included predictors such as gestational age at diagnosis, and concentrations of liver enzymes (AST) and serum creatinine to predict a composite maternal outcome, other important variables, such as BP and proteinuria, were not included.

The performance of any prediction model is influenced by effective treatment measures, such as antihypertensive drugs, magnesium sulphate and delivery, which reduces the probability of adverse outcomes. To avoid such bias, we included management strategies such as need for antihypertensive drugs and magnesium sulphate as predictors. Furthermore, as delivery is considered to be the cure for the condition, we incorporated preterm delivery before 34 weeks' gestation as a component of the maternal composite adverse outcome. We considered early preterm delivery to be indicative of the severity of the condition, as clinicians usually aim to prolong pregnancy beyond 34 weeks' gestation to reduce prematurity-related complications in the neonate unless there are overwhelming concerns about the health of the mother. This approach has led to the inclusion of important tests such as measurement of BP, proteinuria and the need for antihypertensives and magnesium sulphate as significant predictors in the final PREP models.

To ensure that the prediction model could be applied in clinical practice, the findings at the time of baseline (i.e. at diagnosis) should be used to assess the risk. Many models include the worst value of the predictor in the same time period used for outcome ascertainment. This is likely to overestimate the predictive performance of the model. Rule of thumb indicates that at least 10 events should be available per candidate predictor for model development. Compared with the PIERS model, that evaluated 34 predictors for 106 outcomes at 48 hours, the survival analysis approach taken with the PREP-S model allowed us to have sufficient sample size to predict complications accurately at various time points, including 48 hours after diagnosis. The PIERS model did not provide estimates of overall risk of complications in pregnancy and reported a discrimination index of just > 0.7 for prediction of adverse outcomes by 1 week. The PREP-L model showed good discrimination of > 0.8 to predict overall risk until discharge and the PREP-S model had an estimate of > 0.75. The performance validated well in the external data set with good discrimination and calibration. Given the potentially rapid changes in predictor values over time in pregnancy, these measures are impressive for their predictive power at the time of diagnosis of the condition.

Implications for clinical practice

The PREP models were developed with the explicit purpose of providing relevant information to mothers and clinicians on individualised risks at the time of diagnosis of pre-eclampsia. The Microsoft Excel file is user-friendly and easily accessible. It should be emphasised that the PREP models should not be used to choose between administration or non-administration of antihypertensives and magnesium sulphate, which are predictor variables. The risk estimates provided by the model are relevant to women who are managed as per the current clinical guidelines.[55] For example, when managing women admitted with very high BP, the clinicians are expected to manage the mother as per current guidelines with antihypertensives

and, if appropriate, magnesium sulphate, and not to base treatment on the probability of risk provided by the model. However, the PREP-S model will be useful in providing the mother's individualised risk of adverse outcomes at various time points, such as 48 hours after diagnosis, given the clinical characteristics and the choice of treatment.

The PREP-L model provides mothers with the overall risk of experiencing an adverse outcome by the time of discharge. The PREP-L model had high discrimination and calibration estimates in both development and validation data sets, and thus appears accurate and transportable to the non-UK populations examined. Clinicians and mothers should be informed that the model provides overall risks by discharge and should not be used to plan immediate management.

The calibration of the PREP-S model was good in the development data set, as expected, and reasonable in the validation cohort, especially for those with high risk, which suggests that women deemed to be at high risk of outcomes are also more likely to experience the outcome. The PREP-S model can be used as a tool for triaging mothers with a diagnosis of pre-eclampsia before 34 weeks' gestation to decide on the optimal place of delivery. In women identified as high risk by the model, efforts should be made for early transfer of the mother to a tertiary unit for neonatal care, in addition to care for the mother. As the tool provides risk estimates at various time points, resources can be mobilised appropriately when required for transfer of the mother. The risk estimates will identify mothers who require prophylactic corticosteroids when preterm delivery is anticipated. In addition, this tool will allow neonatologists to provide individualised prognostic estimates for the baby after delivery, depending on the predicted risk of complications and for that gestational age.

Research recommendations

The PREP models assessed the risk of composite adverse outcomes. Individual patient data meta-analysis of the studies evaluating the prediction of the accuracy of tests for complications would provide an increased sample size to assess the risk of individual outcomes or outcomes grouped by the organ system involvement. We have undertaken the first two stages (model development and external validation) in prognostic research aimed at improving patient care. A final evaluation of the impact of PREP models on clinical practice is required, especially in the improvement of health outcomes for the mother and baby, but is beyond the remit of this project. In other words, further research may examine the impact of implementing the PREP-S and PREP-L models into clinical practice, in terms of their uptake by clinicians and their impact on patient outcomes. This might be in the form of a cluster randomised trial, for example, with practices randomised to either using or not using the PREP-S and PREP-L models.

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John Allotey (Senior Trials Co-ordinator) oversaw the day-to-day management of the study, ensured the study protocol was followed at participating hospitals and assisted in preparing the draft and final version of the manuscript.

Nadine Marlin (Statistician) performed the statistical analysis of the study and contributed to *Chapter 2* of the final report.

Ben W Mol (Professor of Obstetrics and Gynaecology) provided clinical direction and edited the final version of the report.

Peter Von Dadelszen (Professor of Maternal Fetal Medicine) provided the PIERS data set used for validation of the PREP model.

Wessel Ganzevoort (Gynaecologist, Fellow of Perinatology) provided the PETRA data set used for validation of the PREP model.

Joost Akkermans (Research Physician, Resident Obstetrician and Gynaecologist) provided the PETRA data set used for validation of the PREP model.

Asif Ahmed (Pro-Vice-Chancellor for Health) contributed to the protocol and study development.

Jane Daniels (Deputy Director/Senior Research Fellow) contributed to the write-up of the final report.

Jon Deeks (Professor of Biostatistics, Joint School Research Lead) contributed to the protocol and study development.

Khaled Ismail (Professor of Obstetrics and Gynaecology) contributed to the protocol and study development.

Ann Marie Barnard (CEO Action on Pre-eclampsia Charity) helped draft and review the lay summary, contributing to the writing of the final report.

Julie Dodds (Senior Clinical Trials Manager) provided management direction by supervising the study co-ordinator (John Allotey), ensuring the implementation of the protocol, preparing the data for analysis and editing the final report.

Sally Kerry (Reader in Medical Statistics) provided guidance and management to the statistician (Nadine Marlin), oversaw the statistical analysis and edited the final report.

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Data sharing statement

Study data can be obtained from the corresponding author on request.

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Appendix 1 Prioritisation of outcomes for inclusion in the composite adverse maternal outcome based on clinical importance by expert panel

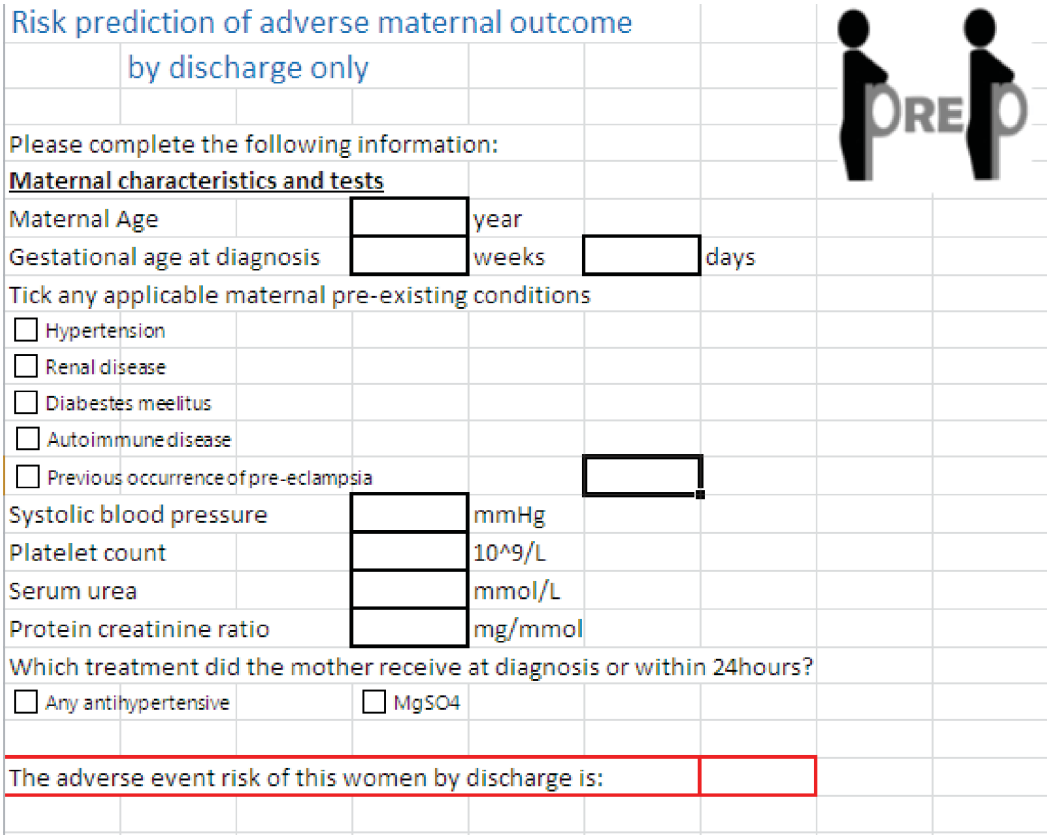
Outcome	Score	Median	Range	Ranking
Transfusion of blood products	11	1	1–2	Mild
Bell's palsy	12	1	1–2	Mild
Postpartum haemorrhage > 1 l	15	2	1–3	Moderate
Hepatic dysfunction	15.5	2	1–3	Moderate
Acute renal insufficiency	17	2	1–3	Moderate
Positive inotrope support	18	2	1–3	Moderate
Requirement for > 50% oxygen for > 1 hour	18	2	1–3	Moderate
Posterior reversible encephalopathy	20.5	2	2–3	Moderate
Reversible ischaemic neurological deficit	21	2	2–3	Moderate
Hepatic haematoma	22	2	2–3	Moderate
Intubation	22	3	2–3	Severe
Glasgow coma scale score of < 13	23	3	2–3	Severe
Pulmonary oedema	23	3	2–3	Severe
Abruptio placentae	23	3	1–3	Severe
Retinal detachment	24	3	2–3	Severe
Eclamptic seizures	25	3	2–3	Severe
Cortical blindness	26	3	3–3	Severe
Stroke	26.5	3	3–3	Severe
Maternal mortality	27	3	3–3	Severe
Hepatic rupture	27	3	3–3	Severe
Dialysis	27	3	3–3	Severe
Myocardial ischaemia/infarction	27	3	3–3	Severe

Appendix 2 Changes since original application

What was proposed in original grant application	What was done in the PREP study
The original target sample size was 500 women with confirmed diagnosis of pre-eclampsia	The sample size was revised so we continued recruitment until 100 women had experienced an adverse event. The population did not change
Update on maternal predictor variables	Chest pain and dyspnoea were added as candidate predictors. Gestational age, maternal age and platelet count were also added to the maternal prognostic factors
One general list of candidate prognostic factors	Candidate prognostic factors were split into maternal and fetal predictor variables and only the fetal predictor variables included ultrasound
Symptoms of headache, epigastric pain, nausea, chest pain, dyspnoea or visual disturbance were one variable	These were split and regrouped into: 1. symptoms of headache and visual disturbance 2. epigastric pain and nausea 3. chest pain and dyspnoea, forming three variables relating to a particular body system
BP was one variable	This was split into systolic BP and diastolic BP
Outcome assessment by 48 hours and by discharge	For the logistic model we had insufficient sample size to assess model performance at 48 hours. Therefore, we developed a second model, the survival model, to provide risks at various time points including 48 hours. However, we censored at 34 weeks, as one of the components of the outcome is delivery by 34 weeks
Develop the PREP model in the ASTRONAUT cohort of women	The ASTRONAUT study (gtr.rcuk.ac.uk/projects?ref=G0601295) did not commence and we were therefore unable to work on its data
Validate the PREP model in the PIERS and PETRA cohort	We validated the rPREP-L model in both external data sets. We were unable to validate the rPREP-S model in the PETRA data set; dates and times of outcome occurrence were not reported
Assess the added predictive contribution of biomarkers (sFlt1, sEng, PlGF) in maternal blood or urine	The ASTRONAUT study, planned to provide data on biomarkers, did not commence and we were therefore unable to work on its data
Update of maternal outcomes	Platelet count and infusion of any third parenteral antihypertensive removed as maternal outcomes. Preterm delivery < 34 weeks' gestation added as a maternal outcome

ASTRONAUT, Angiogenic biomarkerS as predictive Tests for early ONest pre-eclampsia: a population based sTudy; PlGF, placental growth factor; sEng, soluble endoglin; sFlt1, soluble fms-like tyrosine kinase-1.

Appendix 3 PREP-L model



Risk prediction of adverse maternal outcome by discharge only

Please complete the following information:

Maternal characteristics and tests

Maternal Age		year		
Gestational age at diagnosis		weeks		days

Tick any applicable maternal pre-existing conditions

- ☐ Hypertension
- ☐ Renal disease
- ☐ Diabestes meelitus
- ☐ Autoimmune disease
- ☐ Previous occurrence of pre-eclampsia

Systolic blood pressure		mmHg
Platelet count		10^9/L
Serum urea		mmol/L
Protein creatinine ratio		mg/mmol

Which treatment did the mother receive at diagnosis or within 24hours?

☐ Any antihypertensive ☐ MgSO4

The adverse event risk of this women by discharge is:

Appendix 4 PREP-S model

Risk prediction of adverse maternal outcome before 34 weeks of gestational age

Please complete the following information:

Timepoint from baseline	Maternal characteristics and tests				
☐ 2 days	Maternal Age		year		
☐ 3 days	Gestational age at diagnosis		weeks		days
☐ 4 days	Does the mother have exaggerated tendon reflexes?				
☐ 5 days	☐ Yes she she exaggerated tendon reflexes		☐ No she does not		
☐ 6 days	Tick any applicable maternal pre-existing conditions				
☐ 7 days	☐ Hypertension				
☐ 14 days	☐ Renal disease				
☐ 21 days	☐ Diabestes meelitus				
☐ 28 days	☐ Autoimmune disease				
☐ 35 days	☐ Previous occurrence of pre-eclampsia				
☐ 42 days	Systolic blood pressure		mmHg		
	Pulse oximetry		%		
	Platelet count		10^9/L		
	ALT		U/L		
	Serum urea		mmol/L		
	Serum creatinine		µmol/L		
	Protein creatinine ratio		mg/mmol		
	Which treatment did the mother receive at diagnosis or within 24hours?				
	☐ Any antihypertensive	☐ MgSO4			

The adverse event risk of this women by the timepoint indicated is:

Appendix 5 Multivariable fractional polynomial terms that best predict outcome in the logistic model

Multiple imputation data set	Variables	Best powers identified	*p*-value
1	Maternal age (years)	1	0.782
	Log-transformed gestational age at diagnosis	3 3	< 0.001
	Systolic BP (mmHg)	1	0.788
	Platelet count (× 10^9/l)	1	0.250
	Log-transformed serum urea concentration	–1	0.002
	Log-transformed PCR	1	0.261
2	Maternal age (years)	1	0.835
	Log-transformed gestational age at diagnosis	3 3	< 0.001
	Systolic BP (mmHg)	1	0.761
	Platelet count (× 10^9/l)	1	0.176
	Log-transformed serum urea concentration	–1	0.003
	Log-transformed PCR	1	0.202
3	Maternal age (years)	1	0.821
	Log-transformed gestational age at diagnosis	3 3	< 0.001
	Systolic BP (mmHg)	1	0.682
	Platelet count (× 10^9/l)	1	0.177
	Log-transformed serum urea concentration	–1	0.002
	Log-transformed PCR	1	0.364
4	Maternal age (years)	1	0.799
	Log-transformed gestational age at diagnosis	3 3	< 0.001
	Systolic BP (mmHg)	1	0.653
	Platelet count (× 10^9/l)	1	0.219
	Log-transformed serum urea concentration	–1	0.001
	Log-transformed PCR	1	0.462
5	Maternal age (years)	1	0.958
	Log-transformed gestational age at diagnosis	3 3	< 0.001
	Systolic BP (mmHg)	1	0.684
	Platelet count (× 10^9/l)	1	0.288
	Log-transformed serum urea concentration	–1	0.007
	Log-transformed PCR	1	0.342

Appendix 6 Coefficients of the final multivariable logistic model after adjustment for optimism

Predictor	Coefficient
Maternal age (years)	–0.020
FP (log-GA at diagnosis)^3 centred at 39.90241	12.047
FP (log-GA at diagnosis)^3 × ln(log-GA at diagnosis) centred at 49.08188	–7.926
Effect of a medical history score of 1	–0.330
Effect of a medical history score of ≥ 2	–0.579
Systolic BP (mmHg)	0.024
Platelet count (× 10^9/l)	–0.004
FP (log-serum urea concentration)$^{-1}$	–0.950
Log-transformed PCR	0.146
Baseline treatment: any antihypertensive drug	0.409
Baseline treatment: magnesium sulphate	1.252
Constant	–1.507

GA, gestational age.

Appendix 7 Comparison of the flexible parametric approach with the Cox model for the full survival model

Candidate predictors	Flexible parametric model after multiple imputation		Cox regression after multiple imputation	
	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Maternal age (years)	0.968 (0.954 to 0.982)	< 0.001	0.967 (0.954 to 0.982)	< 0.001
Log-transformed gestational age (weeks) at diagnosis	22.425 (8.528 to 58.970)	< 0.001	21.552 (8.156 to 56.952)	< 0.001
Symptoms of headache and/or visual disturbance	1.007 (0.835 to 1.215)	0.940	1.004 (0.832 to 1.211)	0.968
Symptoms of epigastric pain, nausea and/or vomiting	0.943 (0.745 to 1.194)	0.627	0.942 (0.744 to 1.192)	0.618
Symptoms of chest pain and/or dyspnoea	1.172 (0.766 to 1.793)	0.465	1.183 (0.771 to 1.813)	0.442
Clonus	0.763 (0.547 to 1.064)	0.111	0.763 (0.545 to 1.068)	0.115
Exaggerated tendon reflexes	1.249 (0.996 to 1.566)	0.054	1.261(1.004 to 1.584)	0.046
Medical history score (reference 0)				
Effect of a medical history score of 1	0.828 (0.671 to 1.022)	0.078	0.831 (0.673 to 1.025)	0.084
Effect of a medical history score of 2	0.658 (0.479 to 0.905)	0.010	0.660 (0.480 to 0.908)	0.011
Twins vs. singleton	0.895 (0.631 to 1.270)	0.535	0.904 (0.637 to 1.283)	0.571
Triplets vs. singleton	1.194 (0.291 to 4.904)	0.806	1.177 (0.287 to 4.836)	0.821
Systolic BP (mmHg)	1.018 (1.012 to 1.024)	< 0.001	1.017 (1.012 to 1.023)	0.000
Diastolic BP (mmHg)	1.002 (0.993 to 1.011)	0.695	1.002 (0.993 to 1.011)	0.677
Oxygen saturation < 94%	4.342 (1.496 to 12.607)	0.007	4.514 (1.557 to 13.088)	0.006
Haemoglobin level (g/l)	1.051 (0.984 to 1.121)	0.137	1.053 (0.986 to 1.124)	0.123
Platelet count ($\times 10^9$/l)	0.997 (0.996 to 0.998)	< 0.001	0.997 (0.996 to 0.998)	< 0.001
Log-transformed ALT concentration	1.181 (1.040 to 1.341)	0.010	1.179 (1.038 to 1.340)	0.011
Log-transformed serum uric acid concentration	1.052 (0.957 to 1.157)	0.289	1.051 (0.956 to 1.155)	0.302
Log-transformed serum urea concentration	1.555 (1.296 to 1.865)	< 0.001	1.558 (1.300 to 1.868)	< 0.001
Log-transformed serum creatinine concentration	1.549 (1.081 to 2.219)	0.017	1.549 (1.080 to 2.220)	0.017
Urine dipstick (reference: none/trace)				
1+	0.864 (0.522 to 1.433)	0.572	0.855 (0.516 to 1.417)	0.544
2+	0.994 (0.619 to 1.597)	0.981	0.987 (0.614 to 1.585)	0.956
3+	1.293 (0.795 to 2.103)	0.300	1.282 (0.789 to 2.085)	0.316
≥ 4	1.216 (0.717 to 2.062)	0.469	1.200 (0.707 to 2.036)	0.499
Log-transformed PCR	1.082 (1.001 to 1.169)	0.047	1.084 (1.004 to 1.170)	0.040
Baseline treatment				
Any antihypertensive drug	1.239 (0.983 to 1.562)	0.070	1.231 (0.976 to 1.552)	0.079
Magnesium sulphate	3.540 (2.708 to 4.627)	< 0.001	3.523 (2.693 to 4.609)	< 0.001

Appendix 8 Coefficients of the survival model after adjusting for optimism

Predictor	Coefficient
Maternal age (years)	–0.031
FP (log(GA at diagnosis/10))$^{-2}$ centred at 0.8345136	1.514
FP (log(GA at diagnosis/10))$^{-2}$ × ln(log(GA at diagnosis/10)) centred at 0.0652155	5.707
Exaggerated tendon reflexes	0.122
Summary score of medical history	
Effect of a medical history score of 1	–0.169
Effect of a medical history score of ≥ 2	–0.385
Systolic BP (mmHg)	0.016
Pulse oximetry < 94%	0.797
Platelet count (× 10^9/l)	–0.002
Log-transformed ALT concentration	0.126
FP (log-serum urea concentration)^2	0.605
FP (log-serum urea concentration)^3	–0.144
Log-transformed serum creatinine concentration centred at 0.4067578	0.265
Log-transformed PCR	0.080
Baseline treatment	
Any antihypertensive	0.176
Magnesium sulphate	1.066
Baseline H(t) terms	
Spline basis function 1	1.500
Spline basis function 2	–0.116
Spline basis function 3	0.141
Spline basis function 4	–0.054
Spline basis function 5	–0.011
Constant	–3.724

GA, gestational age; H(t), hazards at time.

Appendix 9 Coefficients of the final adapted PREP-L model adjusted for optimism excluding serum urea concentration

Predictor variables	Coefficient
Maternal age (years)	–0.020
FP (log-GA at diagnosis)^3 centred at 39.90241	11.386
FP (log-GA at diagnosis)^3 × ln(log-GA at diagnosis) centred at 49.08188	–7.492
Summary score of medical history	
Effect of a medical history score of 1	–0.340
Effect of a medical history score of ≥ 2	–0.518
Systolic BP (mmHg)	0.023
Platelet count (× 10^9/l)	–0.005
Log-transformed PCR	0.203
Baseline treatment	
Any antihypertensive	0.453
Magnesium sulphate	1.287
Constant	–3.577

GA, gestational age.

Appendix 10 Coefficients of the final adapted PREP-S model adjusted for optimism and excluding serum urea concentration, clonus and exaggerated tendon reflexes

Predictor variables	Coefficient
Maternal age (years)	–0.029
FP (log(GA at diagnosis/10))$^{-2}$ centred at 0.8345136	1.076
FP (log(GA at diagnosis/10))$^{-2}$ × ln(log(GA at diagnosis/10)) centred at 0.0652155	4.635
Effect of a medical history score of 1	–0.188
Effect of a medical history score of ≥ 2	–0.339
Systolic BP (mmHg)	0.016
Oxygen saturation < 94%	1.587
Platelet count (× 10^9/l)	–0.003
Log-transformed ALT concentration	0.141
Log-transformed serum creatinine concentration centred at 4.067578	0.669
Log-transformed PCR	0.138
Baseline treatment: any antihypertensive	0.178
Baseline treatment: magnesium sulphate	1.083
Spline basis function 1	1.455
Spline basis function 2	–0.090
Spline basis function 3	0.148
Spline basis function 4	–0.052
Spline basis function 5	–0.009
Constant	–6.009

GA, gestational age.

Appendix 11 PREP study data collection forms

PREP CLINICIANS MANAGEMENT PLAN (CMP) Hospital No..... Name..... Gestational age .....wks.....days

CURRENT SYMPTOMS			
Headache – generalised	Yes ☐ No☐	Visual disturbances	Yes ☐ No☐
Headache – localised	Yes ☐ No☐	Epigastric pain	Yes ☐ No☐
Nausea	Yes ☐ No☐	Vomiting	Yes ☐ No☐
Chest pain	Yes ☐ No☐	Breathlessness	Yes ☐ No☐
Fetal movements	Felt☐	Other symptoms	Yes ☐ No☐
	Not Felt ☐	*If yes, please specify:*	
	Reduced ☐	_____	

EXAMINATION				
Blood Pressure (Highest reading)	_____ / _____ mmHg			
Urine dipstick	None ☐	Trace ☐		
	1+☐	2+☐	3+☐	>4+☐
Exaggerated tendon reflexes	Yes ☐	No ☐		
Clonus	1+☐	2+☐	≥3+☐	None☐
Papilloedema	Yes ☐	No ☐	Not done ☐	
Pulse Oximetry (SaO_2)on air	.....%			

TREATMENT / MANAGEMENT:	Decision	If yes, give reason(s) – please list all that apply (see INDICATION codes)	INDICATION code
Administration of steroids	Yes ☐ No ☐		1. Severe hypertension
Start/increase dose/number of oral anti-hypertensives	Yes ☐ No ☐		2. Abnormal blood results
Start parenteral anti-hypertensives	Yes ☐ No ☐		3. Pathological/suspicious CTG
Admission to HDU	Yes ☐ No ☐		4. Likely to be a preterm birth
Start Magnesium Sulphate	Yes ☐ No ☐		5. Fetal compromise on scan
Plan for delivery	Yes ☐ No ☐		6. Symptoms
Manage as outpatient	Yes ☐ No ☐		7. Significant proteinuria
Manage as inpatient/In utero Transfer	Yes ☐ No ☐		8. Exaggerated reflexes/ clonus
			9. Other, please specify .....

Date / *Time*	*Signature* / *PRINT NAME:*	*Your designation / grade*	*Bleep No.*
__/__/____ 00:00			

PREP clinicians management plan (CMP)_V3.0_11/MAY/2012

PREP CLINICIANS MANAGEMENT PLAN (CMP) Hospital No..... Name..... Gestational age .....wks.....days

CURRENT SYMPTOMS			
Headache – generalised	Yes ☐ No☐	Visual disturbances	Yes ☐ No☐
Headache – localised	Yes ☐ No☐	Epigastric pain	Yes ☐ No☐
Nausea	Yes ☐ No☐	Vomiting	Yes ☐ No☐
Chest pain	Yes ☐ No☐	Breathlessness	Yes ☐ No☐
Fetal movements	Felt☐	Other symptoms	Yes ☐ No☐
	Not Felt ☐	*If yes, please specify:*	
	Reduced ☐	_____	

EXAMINATION				
Blood Pressure (Highest reading)	_____ / _____ mmHg			
Urine dipstick	None ☐	Trace ☐		
	1+☐	2+☐	3+☐	>4+☐
Exaggerated tendon reflexes	Yes ☐	No ☐		
Clonus	1+☐	2+☐	≥3+☐	None☐
Papilloedema	Yes ☐	No ☐	Not done ☐	
Pulse Oximetry (SaO_2)on air	.....%			

TREATMENT / MANAGEMENT:	Decision	If yes, give reason(s) – please list all that apply (see INDICATION codes)	INDICATION code
Administration of steroids	Yes ☐ No ☐		1. Severe hypertension
Start/increase dose/number of oral anti-hypertensives	Yes ☐ No ☐		2. Abnormal blood results
Start parenteral anti-hypertensives	Yes ☐ No ☐		3. Pathological/suspicious CTG
Admission to HDU	Yes ☐ No ☐		4. Likely to be preterm a birth
Start Magnesium Sulphate	Yes ☐ No ☐		5. Fetal compromise on scan
Plan for delivery	Yes ☐ No ☐		6. Symptoms
Manage as outpatient	Yes ☐ No ☐		7. Significant proteinuria
Manage as inpatient/In utero Transfer	Yes ☐ No ☐		8. Exaggerated reflexes/ clonus
			9. Other, please specify .....

Date / *Time*	*Signature* / *PRINT NAME:*	*Your designation / grade*	*Bleep No.*
__/__/____ 00:00			

PREP clinicians management plan (CMP)_V3.0_1/MAY/2012

Participant UTIN

_ _ _/_ _ _ _

Development and validation of a **P**rediction model for **R**isk of complications in **E**arly onset **P**re-eclampsia

Data **C**ollection **F**orm

FORM A

Baseline

FORM B1
Clinical & Laboratory Assessment

DATE FORM FILLED DD /MMM /YYYY

Participant UTIN __ __ __/__ __ __

1. CLINICAL ASSESSMENT

Symptoms assessed Yes ☐ No ☐ *If yes, please specify below*

Date and time when symptoms assessed DD /MMM /YYYY HH:MM

1.1. Current symptoms

Headache – generalised	Yes ☐	No ☐	NK ☐	**Visual disturbances**	Yes ☐	No ☐	NK ☐	
Headache – localised	Yes ☐	No ☐	NK ☐	**Epigastric pain**	Yes ☐	No ☐	NK ☐	
Nausea	Yes ☐	No ☐	NK ☐	**Vomiting**	Yes ☐	No ☐	NK ☐	
Chest pain	Yes ☐	No ☐	NK ☐	**Breathlessness**	Yes ☐	No ☐	NK ☐	
Fetal movement	Felt ☐	Not Felt ☐	NK ☐ Reduced ☐	**Other symptoms** *If yes to Other symptoms, please specify*	Yes ☐	No ☐	NK ☐ _____	

1.2. Examination

Blood Pressure *If multiple readings use the highest reading*	Systolic BP _____mmHg Diastolic BP _____mmHg		
Papilloedema	Yes ☐	No ☐	Not done ☐
Pulse Oximetry (SaO_2) on air	_____%		NK ☐
Exaggerated tendon reflexes	Yes ☐	No ☐	NK ☐
Clonus	Yes ☐	No ☐	NK ☐
If yes, please select	1 beat ☐	2 beats ☐	≥ 3 beats ☐

2. LABORATORY ASSESSMENTS

2.1. Urine tests

Urine test done Yes ☐ No ☐ *If yes, please specify below*

Urine dipstick	None ☐ Trace ☐ 1+ ☐ 2+ ☐ 3+ ☐ ≥4+ ☐	**Date test performed**	DD /MMM /YYYY
24h urine protein	_____ g/24 hrs	**Date sample taken**	DD /MMM /YYYY
Protein Creatinine Ratio(PCR)	_____ mg/mmol	**Date sample taken**	DD /MMM /YYYY
Albumin Creatinine Ratio(ACR)	_____ mg/mmol	**Date sample taken**	DD /MMM /YYYY

2.2. Blood tests results - *Please provide units for those not specified*

Blood tests done Yes ☐ No ☐ *If yes, please specify* **Date sample taken** DD /MMM /YYYY

Haemoglobin	_____	**Serum bilirubin**	_____ µmol/l
White cell count	_____ x10⁹/l	**Alanine Transaminase**	_____ U/l
Platelet count	_____ x10⁹/l	**Aspartate Transaminase**	_____ U/l
Prothrombin time	_____ sec	**Serum albumin**	_____
Activated Plasma Thromboplastin Time	_____ sec	**Serum uric acid /Urate**	_____
Serum fibrinogen	_____ g/l	**Lactate dehydrogenase**	_____ U/l
Na	_____ mmol/l	**Serum urea**	_____
K	_____ mmol/l	**Serum creatinine**	_____ µmol/l
HCO3	_____ mmol/l	**Ca**	_____ mmol/l

After completing the form please sign below

Initials _____ **Signature** _____

FORM B2
Ultrasound & cardiotocography findings

DATE FORM FILLED DD / MMM / YYYY

Participant UTIN __ __ __/__ __ __

1. ULTRASOUND & CARDIOTOCOGRAPHY FINDINGS

Estimated delivery date by scan DD / MMM / YYYY

If more than <u>two</u> fetuses, please copy this form and fill fields as required.
In case of singleton pregnancy, please cross out irrelevant section.

1.1. Details

Fetus No.	**Liquor volume**	Excess ☐	Normal ☐	Reduced ☐	NK ☐	**Date of scan**	DD / MMM / YYYY
Umbilical artery Doppler End diastolic flow		Present ☐	Absent ☐	Reversed ☐	NK ☐	**Date of scan**	DD / MMM / YYYY
Any other abnormal Doppler? (eg MCA, DV)		Yes☐ No☐	*If yes, please specify*				
Fetal weight on ultrasound growth chart	_____ g	**Gestational Age**	_____wks ____days			**Date of scan**	DD / MMM / YYYY
Date of cardiotocography	DD / MMM / YYYY	**CTG findings**	Normal ☐	Suspicious ☐	Pathological ☐	NK ☐	

1.2. Details

Fetus No.	**Liquor volume**	Excess ☐	Normal ☐	Reduced ☐	NK ☐	**Date of scan**	DD / MMM / YYYY
Umbilical artery Doppler End diastolic flow		Present ☐	Absent ☐	Reversed ☐	NK ☐	**Date of scan**	DD / MMM / YYYY
Any other abnormal Doppler? (eg MCA, DV)		Yes☐ No☐	*If yes, please specify*				
Fetal weight on ultrasound growth chart	_____ g	**Gestational Age**	_____wks ____days			**Date of scan**	DD / MMM / YYYY
Date of cardiotocography	DD / MMM / YYYY	**CTG findings**	Normal ☐	Suspicious ☐	Pathological ☐	NK ☐	

After completing the form please sign below

Initials ____ ____ **Signature** _____

FORM B3

CLINICAL MANAGEMENT PLAN

DATE FORM FILLED DD /MMM /YYYY

Participant UTIN __ __ __/__ __ __

CLINICIAN'S MANAGEMENT PLAN AT DIAGNOSIS (*from PREP CMP Sticker*)

For use when a previously suspected diagnosis of pre-eclampsia is confirmed for a patient before 34/40

Action	Decision Yes	Decision No	Reason(s)	INDICATION code
A. Administration of steroids	☐	☐	_____	1. Severe hypertension
B. Start/Increase the dose or number of oral anti-hypertensives	☐	☐	_____	2. Abnormal blood results
C. Start parenteral anti-hypertensives	☐	☐	_____	3. Pathological/suspicious CTG
D. Admission to HDU	☐	☐	_____	4. Likely to be a preterm birth
E. Start Magnesium Sulphate	☐	☐	_____	5. Fetal compromise on scan
F. Plan for delivery	☐	☐	_____	6. Symptoms
G. Manage as outpatient	☐	☐	_____	7. Significant proteinuria
H. Manage as inpatient/In utero transfer	☐	☐	_____	8. Exaggerated reflexes (or) clonus
				9. Other – please specify reason _____

After completing the form please sign below

Initials	___ ___	Signature	_____	Date of assessment	DD /MMM /YYYY

PREP DCF Version 6.0 Date: 01/OCT/2013

FORM C
Management Provided in Pregnancy and Delivery Outcomes

DATE FORM FILLED DD /MMM /YYYY

Participant UTIN __ __ __/__ __ __

1. MANAGEMENT PROVIDED IN PREGNANCY SINCE DIAGNOSIS UNTIL DISCHARGE

Please specify only once

Steroids	Yes ☐ No ☐	***Start date and time***	DD /MMM /YYYY HH:MM	
Magnesium Sulphate (MgSO4)	Yes ☐ No ☐	***Start date and time***	DD /MMM /YYYY HH:MM	
Transferred out for care	Yes ☐ No ☐	**Date**	DD /MMM /YYYY	

*If **yes**, please complete forms B1, B2 and D with data from the unit transferred*

In case of multiple data please fill more than one form

Parenteral antihypertensive Yes ☐ No ☐ *If **yes**, specify below*

		Start date and time	***End date and time***	***On-going***
Labetalol	☐	DD /MMM /YYYY HH:MM	DD /MMM /YYYY HH:MM	☐
Hydralazine	☐	DD /MMM /YYYY HH:MM	DD /MMM /YYYY HH:MM	☐

		Date and time
Infusion of any third parenteral antihypertensive	Yes☐ No☐	DD /MMM /YYYY HH:MM

Oral antihypertensive Yes ☐ No ☐ *If **yes**, specify below*

	Max daily dose		***Start date***	***End date***	***On-going***	***Dose increased in pregnancy***
Labetalol	☐	***mg***	DD /MMM /YYYY	DD /MMM /YYYY	☐	Yes ☐ No ☐
Nifedipine	☐	***mg***	DD /MMM /YYYY	DD /MMM /YYYY	☐	Yes ☐ No ☐
Methyldopa	☐	***mg***	DD /MMM /YYYY	DD /MMM /YYYY	☐	Yes ☐ No ☐

Admission to HDU	Yes ☐ No ☐	***Total days spent***	_____
		Date and time of 1st admission	DD /MMM /YYYY HH:MM

FORM D
Maternal and Neonatal Outcomes

DATE FORM FILLED DD / MMM / YYYY

Participant UTIN _ _ _/_ _ _

1. MATERNAL OUTCOMES	Presence		Date and Time of outcome occurrence	
1.1. Mortality				
Maternal death	Yes ☐	No ☐	DD / MMM / YYYY	HH:MM
1.2. Central nervous system				
Eclamptic seizures	Yes ☐	No ☐	DD / MMM / YYYY	HH:MM
GCS (Glasgow Coma Scale) score<13	Yes ☐	No ☐	DD / MMM / YYYY	HH:MM
Stroke or RIND (Reversible Ischemic Neurological Deficit)	Yes ☐	No ☐	DD / MMM / YYYY	HH:MM
Cortical blindness	Yes ☐	No ☐	DD / MMM / YYYY	HH:MM
Retinal detachment	Yes ☐	No ☐	DD / MMM / YYYY	HH:MM
Posterior reversible encephalopathy	Yes ☐	No ☐	DD / MMM / YYYY	HH:MM
Bell's palsy	Yes ☐	No ☐	DD / MMM / YYYY	HH:MM
1.3. Hepatic				
Hepatic dysfunction	Yes ☐	No ☐	DD / MMM / YYYY	HH:MM
Subcapsular haematoma	Yes ☐	No ☐	DD / MMM / YYYY	HH:MM
Hepatic capsule rupture	Yes ☐	No ☐	DD / MMM / YYYY	HH:MM
1.4. Cardiorespiratory				
Need for positive inotrope support	Yes ☐	No ☐	DD / MMM / YYYY	HH:MM
Myocardial ischaemia or infarction	Yes ☐	No ☐	DD / MMM / YYYY	HH:MM
At least 50% FIO2 for greater than 1 hour	Yes ☐	No ☐	DD / MMM / YYYY	HH:MM
Intubation	Yes ☐	No ☐	DD / MMM / YYYY	HH:MM
Pulmonary oedema	Yes ☐	No ☐	DD / MMM / YYYY	HH:MM
1.5. Renal				
Acute renal insufficiency (creatinine >200uM)	Yes ☐	No ☐	DD / MMM / YYYY	HH:MM
Dialysis	Yes ☐	No ☐	DD / MMM / YYYY	HH:MM
1.6. Haematological				
Transfusion of any blood product	Yes ☐	No ☐	DD / MMM / YYYY	HH:MM
Abruption	Yes ☐	No ☐	DD / MMM / YYYY	HH:MM
Postpartum haemorrhage (PPH)	Yes ☐	No ☐	DD / MMM / YYYY	HH:MM
If yes to PPH occurrence, please select:		*Type*	Traumatic ☐	Atonic ☐
		Blood loss	1.0-1.5L ☐	>1.5L ☐
Date and time of mother's discharge	DD / MMM / YYYY HH:MM			

EME
HS&DR
HTA
PGfAR
PHR

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