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Development and validation of a Prediction model for Risk of complications in Early onset Pre-eclampsia

Short title/Acronym:	**PREP (Prediction of Risks in Early Onset Pre-eclampsia)**
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Chief Investigator Agreement Page

The clinical study as detailed within this research protocol **(Version 3.0, dated 25th May 2012)**, or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Chief Investigator Name: Khalid S Khan

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Signature and Date: **25th May 2012**

Statistician Agreement Page

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Principal Investigator Agreement Page

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STUDY SUMMARY/SYNOPSIS

TITLE	**Development and validation of a Prediction model for Risk of complications in Early onset Pre-eclampsia**
SHORT TITLE	**PREP**
Protocol Version Number and Date	**Version 3.0, dated 25th May 2012**
Methodology	Prospective cohort study of development and validation of prediction model for risk of adverse outcomes in women with early onset pre-eclampsia.
Study Duration	30 months
Study Centre	**Multicentre.**
Objectives	*Primary Objectives* To develop and internally validate a prediction model in women with early onset pre-eclampsia from 20+0 and 33+6 weeks of gestation for timely assessment of the risk of adverse maternal outcome at 48 hours and by discharge. To externally validate and update the model through two external datasets of patients with a diagnosis of early onset pre-eclampsia in: a) PIERS (Pre-eclampsia Integrated Estimate of RiSk for mothers) study in Canada b) PETRA (The Pre-eclampsia Eclampsia TRial Amsterdam) study in Netherlands. *Secondary Objectives* To assess the risk of adverse fetal and neonatal outcomes at birth and by discharge.
Target sample size	500 women with confirmed diagnosis of pre-eclampsia
Main Inclusion Criteria	To be eligible for the PREP study, the women must meet the following criteria: 1. Aged 16 or over 2. Gestational age between 20+0 weeks' and 33+6 weeks 3. Pre-eclampsia defined as new onset hypertension (systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg on 2 occasions 4 -6 hours apart in women) after 20 weeks of pregnancy and new onset proteinuria (≥ 2+ in urine dipstick or PCR ratio of greater than 30mg/mmol or 300 mg of

	protein excretion in 24 hours)[51] OR Women with suspected pre-eclampsia defined as new onset hypertension (systolic bp ≥ 140 mm hg or diastolic bp ≥ 90 mm hg on 2 occasions 4 -6 hours apart in women) after 20 weeks of pregnancy and 1+ proteinuria on urine dipstick OR Women with the diagnosis of 'superimposed pre-eclampsia'. - This was defined as new-onset proteinuria (as defined previously) in women with chronic hypertension and no proteinuria at base line. - In women who had proteinuria at base line, the diagnosis of preeclampsia required an elevated serum alanine aminotransferase concentration (>70 U per litre) or worsening hypertension (either two diastolic BP of at least 110 mm Hg four hours apart or one diastolic measurement of at least 110 mm Hg if the woman had been treated with an antihypertensive drug), plus one of the following: increasing proteinuria, persistent severe headaches, or epigastric pain.[44] OR Women with diagnosis of HELLP syndrome with no proteinuria or hypertension[45;46] OR Women with one episode of eclamptic seizures with no hypertension or proteinuria[47] 4. Be capable of understanding the information provided, with use of an interpreter if required 5. Give written informed consent
Statistical Methodology and Analysis	The primary outcome will be maternal adverse outcome by 48 hours and maternal adverse outcome by discharge; in secondary analyses adverse fetal and neonatal outcomes at birth and by discharge will also be considered. The dataset assembled will be used to develop the prediction models. The performance of the model will be validated internally and externally using external data from two relevant studies (PIERS and PETRA).

Glossary of Terms and Abbreviations

ASR	Annual Safety Report
BP	Blood Pressure
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DAU	Day Assessment Unit
DMC	Data Monitoring Committee
EC	European Commission
GAfREC	Governance Arrangements for NHS Research Ethics Committees
HELLP	Haemolysis, Elevated Liver enzymes, Low platelets
ICF	Informed Consent Form
ISSHP	International Society for Study of Hypertension in Pregnancy
JRO	Joint Research and Development Office
MA	Marketing Authorisation
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
PCR	Protein Creatinine Ratio
PI	Principle Investigator
QA	Quality Assurance
QC	Quality Control
Participant	An individual who takes part in a clinical trial
PETRA	The Pre-eclampsia Eclampsia TRial Amsterdam
PIERS	Pre-eclampsia Integrated Estimate of RiSk for mothers
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SDV	Source Document Verification
SMG	Study Management Group
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
SSC	Study Steering Committee

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1. Introduction

1.1 Background

Pre-eclampsia is a multisystem disorder in pregnancy associated with hypertension and proteinuria.[1-3] Hypertension is defined as systolic blood pressure of 140 mm Hg or more and diastolic blood pressure of 90 mm Hg or more on two occasions 4-6 hours apart.[1-3] Proteinuria is defined as 300 mg or more in 24 hour urine collection or urine dipstick of 1+ or more in 2 samples 6 hours apart or a spot urine protein/creatinine ratio 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 occurs before 34 weeks, so called early onset pre-eclampsia.[6;7]

Early onset pre-eclampsia is considered to be a pathophysiologically different disease than late onset pre-eclampsia with considerably increased risk of maternal complications with 20-fold higher maternal mortality.[8-10] The only known cure in this condition is delivery of the baby and placenta. In women with early onset pre-eclampsia, the decision about when is the best time to deliver can be difficult, as fetal and neonatal benefits from prolongation of pregnancy needs 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] Current practice guidelines do not consider gestational age at presentation as a criterion for diagnosis, severity, or sub classification to stratify risk in women with pre-eclampsia.[2;12] Pre-eclampsia is considered to manifest as two syndromes: Maternal, associated with hypertension and proteinuria, and fetal, manifested by intrauterine growth restriction (IUGR). The maternal syndrome the disease, and may persist, often deteriorating transiently, following delivery of the initiating agent, the imperfectly implanted placenta.[13]

Although the proportion of women with early onset pre-eclampsia is only 1% of all pregnancies, the complexity of the treatment gives rise to large health care costs.[6;7] Patients are often admitted in a tertiary care facility and 30% experience complications, which may necessitate an intensive care facility.[14] Infants usually need prolonged intensive care treatment for management of complications including lifelong handicaps arising as a result of pre maturity. The additional NHS costs to care for a preterm baby born before 33 weeks and 28 weeks are £61,509 and £94,190 respectively.[15] £939 million in extra costs for care of preterm babies per year in the NHS are linked to neo-natal care such as incubation, and hospital readmissions.[15] Delaying premature births by a week could potentially save £ 260 million a year.[15]

One of the key recommendations in the last CEMACH (Confidential Enquiries into Maternal and Child Health) report for policy makers, service commissioners and providers, and healthcare professionals 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 where early recognition of women at risk of adverse outcomes will allow timely transfer from secondary to 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 (Table 1);[16] these 'tests' are performed routinely in all units, but, in the absence of a structured approach, somewhat haphazardly.

One of the main reasons for the lack of confidence clinicians generally have in applying risk scores in practice is the lack of sufficient evidence to demonstrate the reproducibility and transportability of the model in a different population.[22] To be considered useful, a risk score should be clinically credible, accurate (well calibrated with good discriminative ability) and have generality (be externally validated).[22] The PREP study will quantify the performance of the prognostic model on a new series of patients in a different location (PIERS and PETRA), to enable confident application of the prediction rule in daily obstetric practice.

1.2 Summary of current evidence

1.2.1 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 who are at increased risk of developing complications, and this risk cannot be graded.[9] Current classification systems of pre-eclampsia (RCOG, ANZOG, ISSHP, CHP, SOGC) are based on the severity of the disease.[9;12;23-25] 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 SOGC (Society of Obstetricians and Gynaecologists in Canada) which classifies all early onset pre-eclampsia as severe.[25] However, in this group the predictors that influence maternal and fetal outcomes are not established.

We have conducted systematic reviews on the accuracy of tests in predicting complications in women with pre-eclampsia.[26-29] They are based on very few, poor quality primary studies (Section 1.3.2). They do not take into account the predictive role of more than one test result on the outcome. Furthermore, there is no separate quantification of risks especially in women with early onset pre-eclampsia. 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 more than 27 weeks and the birth weight is more than 600g.[30] Clinicians are hesitant to advocate expectant management due to uncertainties about the scale of maternal risk. Development of a risk score of adverse maternal and fetal outcomes will help clinicians make appropriate decisions after discussion with the parents.

1.2.2 Research on management of early onset pre-eclampsia

Currently, the only definitive treatment in pre-eclampsia is delivery. Delivery is achieved in women with severe pre-eclampsia by either induction of labour or caesarean section after corticosteroids have been given to improve fetal lung maturation. As steroids achieve their optimal effect after 48 hours,[32;33] clinicians tend to postpone delivery until this time unless complications have occurred or are considered imminent. Early preterm delivery to avoid risk to mother can be associated with significant neonatal morbidity. This can be reduced by stabilisation of the woman's condition and then, if possible, delaying delivery. Expectant management of early onset pre-eclampsia has been shown to improve perinatal outcomes in RCTs.[34;35] A recent Cochrane review[14] that compared early intervention with expectant management in women with early onset severe pre-eclampsia[35,34] showed that babies whose mothers had been allocated to the early intervention group had more hyaline membrane disease (RR 2.3, 95% CI 1.4 to 3.8), more necrotising enterocolitis (RR 5.5, 95% CI 1.04 to 29.6) and were more likely to need admission to neonatal intensive care (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 had 300 gram higher birth weight 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 <34 weeks, was associated with few serious maternal complications (median <5%), similar to interventionist care.[9;36] There is general consensus that the fetal outcome is poor before 24 weeks in women with early onset pre-eclampsia.[34;37;38] However, many centres do not practice expectant management due to 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.

1.3 Work leading to the proposal

1.3.1 Systematic review of tests that predict onset of pre-eclampsia

We have evaluated the accuracy of tests in predicting onset of pre-eclampsia by systematic review of literature through a NHS HTA funded project (HTA No. 01/64/04). The HTA report concluded that no current tests employed for screening pre-eclampsia were sufficiently accurate and no known preventive treatments were sufficiently effective to become part of routine care. One of the recommendations from that project was to evaluate prognostic/predictive features that are associated with maternal and fetal complications once pre-eclampsia has started. This is what we aim to do in this project.

1.3.2 Systematic reviews on the accuracy of tests to predict complications in pre-eclampsia - TIPPS (Tests in the Prediction of Pre-eclampsia Severity) project

We have conducted systematic reviews of literature to assess the predictive value of five of the commonly performed tests in pre-eclampsia.[16;26-29] We conducted electronic searches in MEDLINE, EMBASE, the Cochrane Library and the MEDION databases without any language restrictions. We analysed more than 25,000 citations and reviewed 60 relevant studies. The association between the tests in pre-eclampsia and maternal complications is provided in Table 1. The need for further evaluation of predictors in early onset pre-eclampsia has been published in over 20 online scientific journals and magazines.

The reviews identified the

- paucity of quality primary studies to evaluate the predictive accuracy of tests, especially in early onset pre-eclampsia (but not exclusively in this group).
- poor quality, such that studies varied in design and conduct, with lack of details about the tests and reference standards, the duration between tests and outcome, the effect of other risk factors and interventions on prediction of complications.
- lack of information to evaluate the accuracy of combination of tests
- inadequate sample size to precisely estimate accuracy measures.

Although we conducted good quality reviews,[26-28] it was hard to provide recommendations on the value of tests due to the above deficiencies in the primary studies. However the data collated give face validity of the choice of tests chosen for use in prediction model in our project.

Table 1. Likelihood ratios for maternal complications in women with pre-eclampsia for various tests

Test	Study Year	Test	cut off	Outcome	LR+ (95% CI)	LR- (95% CI)
Liver Function						
Test	Borglin 1958	AST/ALT	Increased	Eclampsia	2.6(0.70,9.4)	0.45(0.05,4.4)
	Crisp 1959	AST	70	Eclampsia	2.1(1.5,3)	0.12(0.01,1.8)
	Romero 1988	AST	2SD	Eclampsia	3.6(2.1,6.1)	0.36(0.11,1.2)
	Aali 2004	AST/ALT	500/300	Eclampsia	9.1(3.3,25.5)	0.75(0.61,0.93)
	Audibert 1996	LDH/AST/ALT	600/70/70	Eclampsia	1(0.49,2.0)	1.0(0.77,1.31)
	Abramovici 1999	AST	70	Eclampsia	0.94(0.37,2.4)	1(0.87,1.2)
	Haddad 2000	LDH/AST/ALT	600/70/70	Eclampsia	1.1(0.59,2.2)	0.87(0.40,1.90)
	Woldesellasie 2005	AST	43	Eclampsia	0.97(0.73,1.3)	1.2(0.31,4.3)
	Woldesellasie 2005	ALT	60	Eclampsia	1.3(0.07,23.4)	0.99(0.87,1.1)
	Woldesellasie 2005	LDH	180	Eclampsia	4.5(2.5,8)	0.36(0.14,0.92)
	Romero 1988	AST	2SD	Pulmonary oedema	3.2(1.4,7.5)	0.42(0.08,2.1)
	Audibert 1996	LDH/AST/ALT	600/70/70	Pulmonary oedema	1.9(0.97,3.6)	0.68(0.37,1.3)
	Haddad 2000	LDH/AST/ALT	600/70/70	Pulmonary oedema	1.4(0.74,2.6)	0.64(0.2,2.1)
	Martin Jr 1999	AST	150	Adverse outcome	1.4(1.2,1.5)	0.62(0.48,0.8)
	Martin Jr 1999	LDH	1400	Adverse outcome	1.4(1.2,1.6)	0.57(0.44,0.74)
	Martin Jr 1999	ALT	100	Adverse outcome	1.2(1.1,1.4)	0.72(0.57,0.91)
	Girling 1997	AST/ALT/Bil/GGT	30/32/14/41	Adverse outcome	2.2 (1.4,3.5)	0.12 (0.01,1.7)
	Odendaal 2000	LDH	350	Abruption	1.7(0.41,6.7)	0.97(0.89,1.1)
	Audibert 1996	LDH/AST/ALT	600/70/70	Abruption	1.5(0.78,2.9)	0.82(0.54,1.2)
	Haddad 2005	LDH/AST/ALT	600/70/70	Abruption	0.79(0.26,2.4)	1.2(0.57,2.6)
	Audibert 1996	LDH/AST/ALT	600/70/70	Maternal death	2.5(0.78,7.8)	0.46(0.05,4.4)
	Abramovici 1999	AST	70	Maternal death	4.8(2.1.11.1)	0.24(0.02,2.8)
	Yucesoy 2005	AST/ALT/LDH	Increased	Maternal death	5.6(3.19,9.7)	0.17(0.01,2.2)
	Audibert 1996	LDH/AST/ALT	600/70/70	DIC	3.9(3.0,5.1)	0.06(0.00,0.94)
	Haddad 2000	LDH/AST/ALT	600/70/70	DIC	2.3(1.44,3.7)	0.18(0.01,2.5)
Uric acid	Yassaee 2003	Uric acid	350 µmol/l	Eclampsia	2 (0.85,4.8)	0.14 (0.02,1.1)
	Fadel 1969	Uric acid	350 µmol/l	Eclampsia	7.3 (1.4,37.3)	0.67 (0.3,1.5)
	Lancet 1956	Uric acid	350 µmol/l	Eclampsia	1.9 (1.2,3)	0.29(0.13,0.62)
Proteinuria	Newman 2002	Proteinuria	5g/24h	Eclampsia	1.7(0.94,3.1)	0.55(0.18,1.7)
	Newman 2002	Proteinuria	10g/24h	Eclampsia	2.7(1.1,6.2)	0.62(0.28,1.4)
	Hall 2002	Proteinuria	Inc by 2g/24h	Eclampsia	2(0.83,4.6)	0.41(0.04,4.5)
	Buchbinder 2002	Proteinuria	5g/24h	Abruption	1.5(0.69,3.1)	0.68(0.23,2)
	Schiff 1996	Proteinuria	Inc by 2g/24h	Abruption	1.1(0.36,3.4)	0.94(0.45,2)
	Hall 2002	Proteinuria	Inc by 2g/24h	Abruption	0.74(0.27,2)	1.2(0.75,1.9)
	Newman 2002	Proteinuria	5g/24h	HELLP syndrome	1.2(0.82,1.8)	0.86(0.62,1.2)
	Newman 2002	Proteinuria	10g/24h	HELLP syndrome	1.2(0.59,2.3)	0.96(0.8,1.2)
	Schiff 1996	Proteinuria	Inc by 2g/24h	HELLP syndrome	0.9(0.38,2.2)	1.1(0.68,1.7)
	Hall 2002	'roteinuria	Inc by 2g/24h	HELLP syndrome	0.63(0.06,7)	1.2(0.55,2.8)
Symptoms	Witlin 1999	Headache		Abruption	1.3(0.97,1.7)	0.74(0.48,1.1)
	Ben Salem 2003	Headache		Eclampsia	1.3(1.2,1.5)	0.09(0.01,0.66)
	Witlin 1999	Headache		Eclampsia	1.4(1.1,1.9)	0.67(0.44,1.0)
	Harms 1991	Headache		HELLP	1.3(0.41,3.8)	0.96(0.79,1.2)
	Martin Jr 1999	Headache		HELLP	0.86(0.76,0.96)	1.3(1,1.6)
	Ben Salem 2003	Visual disturbances		Eclampsia	2.5(1.8,3.5)	0.22(0.1,0.47)
	Witlin 1999	Visual disturbances		Eclampsia	1.7(1.1,2.7)	0.82(0.65,1)
	Witlin 1999	Visual disturbances		Abruption	1.3(0.7,2.3)	0.93(0.75,1.2)
	Harms 1991	Visual disturbances		HELLP	0.87(0.12,6.4)	1(0.9,1.1)
	Martin Jr 1999	Vomiting		HELLP	1.6(1.1,2.3)	0.9(0.84,0.96)
	Harms 1991	Vomiting		HELLP	6.1(3.1,12.3)	0.57(0.37,0.88)
	Witlin 1999	Vomiting		Eclampsia	1.4(0.72,2.7)	0.93(0.8,1.1)
	Martin Jr 1999	Epigastric pain		HELLP	2.4(1.7,3.6)	0.79(0.73,0.85)
	Witlin 1999	Epigastric pain		Eclampsia	0.71(0.35,1.4)	1.1(0.94,1.3)
	Witlin 1999	Epigastric pain		Abruption	1.4(0.84,2.3)	0.87(0.68,1.1)
	Harms 1991	Epigastric pain		HELLP	8.3(4.7,14.7)	0.34(0.18,0.67)

1.3.3 Delphi survey to prioritise tests in the prediction of complications in women with pre-eclampsia

We asked 25 international experts on pre-eclampsia to prioritise tests that are considered to be clinically important in women with pre-eclampsia through a two round Delphi survey.[16;39] This has added to the face validity of the choice of tests for the development of PREP prediction rule in our project.

1.3.4 Standardisation of adverse maternal and fetal outcomes

A composite maternal outcome measure has been developed through Delphic consensus and has 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 has been developed in the same way.

1.3.5 Agreement to share data with other ongoing studies for external validation of PREP model

The PIERS project led by Dr von Dadelszen has developed models to predict adverse maternal outcomes in women with pre-eclampsia of any gestation admitted to tertiary perinatal units in Canada, New Zealand, UK, and Australia. The data collection form for PREP has been adapted for use in the NHS from the validated standardised care protocol used in the PIERS project. The PETRA study is a randomised controlled trial evaluating the effectiveness of plasma expansion in expectant management of early-onset Hypertensive Disease in Pregnancy (HDP) including pre-eclampsia.[40] Datasets in the PIERS and PETRA studies have information on variables and outcomes useful for external validation of the PREP model.

1.4 Rationale and Risks/Benefits

A good performing prediction model is one that is accurate, validated in populations and datasets external to those used to develop the model, widely applicable in practice, acceptable to patients and ultimately improves clinical outcomes by helping clinicians and patients make more informed decisions. Our prediction model will attempt to achieve this by: using rigorous statistical methods to develop the model and assess accuracy; undertaking a formal validation in external datasets (PIERS and PETRA); using unambiguous definitions of predictors and reproducible measurements using methods available in clinical practice; adjust for current clinical management; obtain input from patient focus groups and produce personalised risk scores that enable patients and clinicians to make more informed decisions on management aspects like continuing the pregnancy or delivery of a pre term baby. The performance of the model will naturally be limited by the strength of the predictive relationships between the measured variables and the outcome.

The predictors that are evaluated for inclusion in the PREP prediction model are routinely performed as part of standard clinical practice in women admitted with early onset pre-eclampsia. The PREP study does not influence the management of these patients. There is no added risk due to the study as there is no interference with the investigation or clinical management of these patients. The performance and reporting of the laboratory investigations will be standardised during the PREP study. Introduction of a similar standardised form has been shown to reduce the risk of maternal complications in women with pre-eclampsia.[52]

2 Study Objectives and Design

2.1 Study Objectives

The study has been developed according to existing recommendations on prognostic research, model development and validation, and prediction rule development.[41-43]

Primary Objectives

- To develop and internally validate a prediction model in women with early onset pre-eclampsia between 20 and 34 weeks of gestation for timely assessment of the risk of adverse maternal outcome at 48 hours and by discharge

- To externally validate and update the model through two external datasets of patients with a diagnosis of early onset pre-eclampsia in
  a) PIERS (Pre-eclampsia Integrated Estimate of RiSk for mothers) study in Canada
  b) PETRA (The Pre-eclampsia Eclampsia TRial Amsterdam) study in Netherlands.

We will develop two separate prediction models, one for the 48 hour endpoint and one for the discharge endpoint.

Secondary Objectives

- To assess the risk of adverse fetal and neonatal outcomes at birth and by discharge

2.2 Outcome measures

The primary outcome will be adverse maternal outcome at 48 hours after admission and at discharge (Table 2). The 48 hours time interval is chosen because (i) that period would improve perinatal outcomes by giving time for steroid administration remote from term and (ii) that period informs decisions about the place of delivery/in utero transfer to tertiary units. Maternal wellbeing is the key clinical factor during decision making. This is because the risk of maternal mortality and morbidity far outweighs the risks to fetus of early delivery. Adverse maternal outcome correlates to poor fetal outcome.[3;7] The law also favours maternal over fetal wellbeing when both mother and baby are at risk. Early identification of women at high risk of complications in secondary care through the PREP rule will enable appropriate early transfer to a tertiary unit. Adverse fetal outcome will be the secondary outcome. It will provide the opportunity to maximise fetal outcome by early administration of steroids and plan delivery in a unit with appropriate neonatal care facilities where delivery is contemplated due to increased maternal risks.

There is no obvious single outcome measurement that determines clinical management in early onset pre-eclampsia. As the risk of more than one outcome needs evaluation simultaneously, we have chosen a composite measure consisting of several complications (Table 2).[51] The composite outcomes are constructed by including those components whose underlying biology is similar.[52] The outcome components have been selected by Delphic survey of experts ensuring face validity of the components.[9;39] Through our systematic reviews we have shown that there is an association between the predictor variables included in the PREP study and the individual component outcomes thereby ensuring content validity of the chosen composite outcome measure.[26;28;29]

Table 2. Structured question of population, predictor variables and outcomes in the development of PREP prediction model

Question Components	
Population	Women with early onset pre-eclampsia
Candidate prognostic factors (predictor variables)	History: 1)symptoms of headache, epigastric pain , nausea, chest pain, dyspnoea or visual disturbance, 2) pre existing hypertension, renal disease, diabetes mellitus, autoimmune disease and other past relevant history of pre-eclampsia obtained at antenatal booking Examination: 3) blood pressure; 4) exaggerated tendon reflexes or clonus; 5)papilloedema

Investigations: 6) Serum uric acid, 7) urine dipstick,24 hour urine protein, Protein Creatinine Ratio (PCR), 8) renal and liver function tests; 9) pulse oximetry; 10) ultrasound (fetal growth, liquor volume, umbilical artery doppler, uetrine artery doppler at 20-24 weeks of gestation)

Outcome

Primary outcome

Adverse maternal outcome at 48 hours and at discharge that includes maternal death or one or more of the following; involvement of *Central Nervous System* - eclamptic seizures, Glasgow coma score of less than 13, stroke or RIND (Reversible Ischaemic Neurological Deficit), cortical blindness, retinal detachment, posterior reversible encephalopathy, Bell's palsy; *Hepatic*- hepatic dysfunction, hematoma, or rupture, *Cardio respiratory* - need for positive ionotrope support, myocardial ischaemia or infarction, infusion of any third parenteral antihypertensive, at least 50% FIO2 for greater than 1 hour, intubation, pulmonary oedema; *Renal*- acute renal insufficiency (creatinine >200uM), dialysis; *Haematological*-transfusion of any blood product

Outcome	Definition
Maternal	
Mortality	Maternal death occurring by 48 hours or discharge, 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 hematoma or rupture	Blood collection under the hepatic capsule as confirmed by ultrasound or laparotomy
Glasgow coma score < 13	Based on GCS scoring system[61]
Stroke	Acute neurological event with deficits lasting longer than 48 hours
Cortical Blindness	Loss of visual acuity in the presence of intact papillary response to light
Reversible Ischaemic Neurologic Deficit (RIND)	Cerebral ischaemia lasting longer than 24 hrs but less than 48 hours revealed through clinical examination
Retinal detatchment	Separation of the inner layers of the retina from the underlying retinal pigment epithelium (RPE, choroid) and is diagnosed by opthamological exam
Acute renal insufficiency	For women with an underlying history of renal disease: defined as creatinine >200 uM; for patients with no underlying renal disease: defined as creatinine >150 uM
Dialysis	Including haemodialysis and peritoneal dialysis
Platelet count < 50,000 without blood transfusion	Measurement of platelet count recorded as less than 50,000 without patient being given a blood transfusion
Transfusion of blood products	Includes transfusion of any units of blood products: fresh frozen plasma (FFP), platelets, red blood cells (RBCs), cryoprecipitate (cryo) or whole blood
Positive ionotropic support	The use of vasopressors to maintain a sBP > 90 mmHg or Mean Arterial pressure > 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 pathologic Q waves on serial ECGs. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time that has passed since the infarct developed. 2) Pathological findings of an acute, healed or healing MI 3) Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following: a) ischaemic symptoms; b) development of pathologic Q waves on the ECG; c) ECG changes indicative of ischaemia (ST segment elevation or depression); or d) coronary artery intervention (e.g., coronary angioplasty)
	Require >50% oxygen for greater than one hour	Oxygen given at greater than 50% concentration based on local criteria for longer than 1 hour
	Intubation other than for Caesarean section	Intubation may be by ventilation, EIT or CPAP
	Pulmonary Oedema	Clinical diagnosis with x-ray confirmation or requirement of diuretic treatment and SaO_2 <95%

Secondary outcome

Adverse perinatal outcome at birth and by discharge that includes one or more of the following:

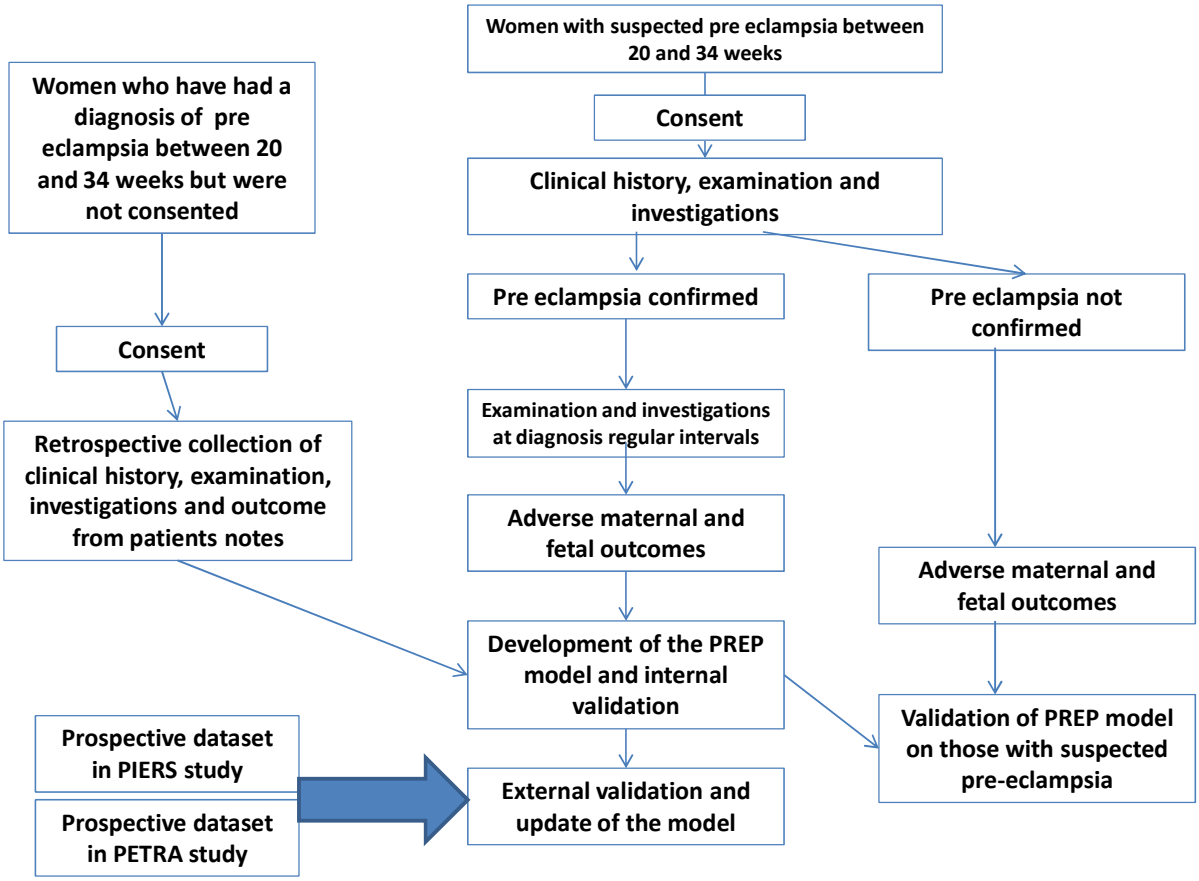
- perinatal or infant mortality
- bronchopulmonary dysplasia (defined as oxygen requirement at 36 weeks corrected gestation unrelated to an acute respiratory episode),
- necrotising enterocolitis (include only Bell's stage 2 or 3. Definition - evidence of pneumotosis intestinalis on abdominal x-ray and/or surgical intervention),
- grade III/IV intraventricular haemorrhage,
- cystic periventricular leukomalacia,
- stage 3-5 retinopathy of prematurity,
- hypoxic ischaemic encephalopathy (Apgar score </= 5 at 10 mins and/or pH 7.00 in first 60 minutes of life and/or Base deficit >/= -16 in first 60 minutes associated with abnormal conscious level (lethargy, stupor or coma) and seizures and/or poor/weak suck and/or hypotonia and/or abnormal reflexes).

Design	Prospective cohort study

2.3 Study Design

Prospective cohort study to develop and internally and externally validate clinical prediction models in women with early onset pre-eclampsia (Fig 1). 500 women will be recruited and tested on diagnosis, at 24 hours and twice weekly thereafter. The primary outcome will be maternal outcome by 48 hours (model 1) and maternal outcome by discharge (model 2); in secondary analyses fetal outcomes at birth and by discharge will also be considered. Maternal and fetal outcomes will be determined using validated composite outcome measures. Information on maternal interventions will be collected. The dataset assembled will be used to develop the prediction models, and they will be validated further using external data.

Fig 1. Development and validation of a Prediction Model for Risk of complications in Early onset Pre-eclampsia (PREP)



*PIERS (Pre-eclampsia Integrated Estimate of RiSk) * PETRA (The Pre-eclampsia Eclam

3 Subject Selection

3.1 Number of Subjects and Subject Selection

This will be a multicentre study in obstetric units in the UK.

This multicentre study involves participation of trusts within several of the Comprehensive Local Research Networks (CLRNs) throughout England. The CLRNs include representatives from the Trusts and are composed of academics, R&D managers, professionals and consumers. The network has well established infrastructure that has recently delivered several large HTA funded studies in recent years. They have, following discussion, already adopted/approved the study for support and have provided a detailed feasibility of recruitment. As PREP is a portfolio study, it is eligible for CLRN support for Trust R&D approvals; research ethics applications; service user involvement; honorary NHS contracts for researchers; project publicity; recruitment; assessment of patients; and dissemination of results.

The following strategy will be followed to ensure recruitment to target.

- Provision of research midwife support as appropriate for the various participating units in addition to the CLRN support. The research midwives will have responsibility for overseeing consent, testing and data

collection in the antenatal ward, day assessment unit, delivery suite and post-natal ward. The research midwives will liaise with the local midwives at each centre and trouble-shoot recruitment and other problems.

- Provision of simple written study information supported by face to face discussion with midwifery staff in antenatal clinics and the community
- Provision of the information leaflet in minority languages and as audio recordings, supported by interpretation facilities
- Identification of those who have received information, and who have declined participation, through coloured stickers on the hand-held maternity notes
- Close and regular communication with midwifery staff in the community, antenatal clinic and the post-natal ward
- Provision of regular feedback on progress in study recruitment, including individual hospital teams' performance and progress against targets
- Regular newsletters to all relevant staff involved in the study

3.2 Sample size

From our systematic reviews, 20% of women (100 of 500) with early onset pre-eclampsia are known to have adverse maternal outcome at any time point. Given the source population with 50,000 deliveries (with 500 early onset pre-eclampsia) per year we expect a recruitment of 500 women with early onset pre-eclampsia in 30 months. Thus, given the 20% event-rate, we expect there to be 100 adverse maternal events. Rules of thumb for fitting multivariate models suggest that 10 events for every variable are required to avoid overfitting[53] , and we will work within this limitation. Ten candidate predictor variables will thus be chosen a priori from the set of possible variables shown in Table 1. The 10 chosen will be the most promising predictor variables as identified with our previous systematic review in this field. Women with suspected pre-eclampsia (urine dipstick 1+) who are not confirmed as having pre-eclampsia will not be counted towards the 500 target number.

3.3 Inclusion criteria:

The following women will be considered for inclusion in the study

1. Aged 16 or over
2. Gestational age between 20+0 weeks' and 33+6 weeks
3. Pre-eclampsia defined as new onset hypertension (systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg on 2 occasions 4 -6 hours apart in women) after 20 weeks of pregnancy and new onset proteinuria (≥ 2+ in urine dipstick or PCR ratio of greater than 30mg/mmol or 300 mg of protein excretion in 24 hours)[51]

   OR

   Women with suspected pre-eclampsia defined as new onset hypertension (systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg on 2 occasions 4 -6 hours apart in women) after 20 weeks of pregnancy and 1+ proteinuria on urine dipstick

   OR

   Women with a diagnosis of 'superimposed pre-eclampsia'.

- This was defined as new-onset proteinuria (as defined previously) in women with chronic hypertension and no proteinuria at base line.
- In women who had proteinuria at base line, the diagnosis of preeclampsia required an elevated serum alanine aminotransferase concentration (>70 U per litre) or worsening hypertension (either two diastolic BP of at least 110 mm Hg four hours apart or one diastolic measurement of at least 110 mm Hg if the woman had been treated with an antihypertensive drug), plus one of the following: increasing proteinuria, persistent severe headaches, or epigastric pain.[44]

OR

Women with diagnosis of HELLP syndrome with no proteinuria or hypertension[45;46]

OR

Women with one episode of eclamptic seizures with no hypertension or proteinuria[47]

4. Be capable of understanding the information provided, with use of an interpreter if required

5. Give written informed consent

* Note that recruitment will continue until we are confident we have reached the required number of women with confirmed early onset pre-eclampsia. However, we have included women with 1+ dipstick for additional inclusion for the following reasons: Firstly, the definition of pre-eclampsia varies across countries and 1+ proteinuria with raised blood pressure is also defined as pre-eclampsia in obstetric practice; The accuracy of urine dipstick in comparison to spot proteinuria or 24 hr collection is still not clear and NIHR has recently commissioned a primary study to answer the question. Secondly, by consenting these women, we avoid the potential long wait the patients may need to endure, until confirmation of proteinuria status is available by PCR for which the results take between 4 and 6 hours. We anticipate a significant proportion of women with 1+ proteinuria to have abnormal 24 hr proteinuria or PCR that confirms research definition of pre-eclampsia. Thirdly, by checking the calibration and discrimination of our models (which will be developed in women with confirmed early onset pre-eclampsia) in women with 1+dipstick who are not subsequently confirmed to have pre-eclampsia, we can examine the potential generalisability of our models to a broader set of women.

3.4 Exclusion criteria:

Women will be excluded if:

1. There is occurrence of the outcome (including recurrent eclamptic seizures) prior to testing
2. There is insufficient time for gaining informed consent before discharge.
3. The mother does not comprehend spoken and written English adequately and a translator is not available.

4 Study Procedures

4.1 Informed Consent Procedures

A study leaflet will be given to all women at the time of booking for antenatal care by the community and clinic midwives. The leaflet will provide brief details of the study and advise women that they may be invited to take part if they are diagnosed with, or suspected of having developed, pre-eclampsia before 34 weeks of gestation. A recruitment poster will also be prominently displayed in various areas within the participating hospitals and their community antenatal clinics. The leaflets and posters will be translated into the most frequently occurring minority languages across the study hospitals and made available on the internet.

Women who become eligible for the study, as defined in section 3.3 and 3.4 above, will be given a Participant Information Sheet. It will inform them that the tests being evaluated are mostly currently done as routine care. Participation in the study will not influence the frequency of testing or clinical management. Women will be entitled to choose whether or not they would like to provide access to the data on tests and outcomes. In addition to women at booking, any eligible women not previously approached for inclusion in the PREP study and seen in the antenatal clinic, antenatal ward, day assessment unit, postnatal ward or delivery suite will be consented by the midwife or clinician. If women were seen after the diagnosis of early onset pre-eclampsia or after delivery with early onset pre-eclampsia, consent will be obtained to collect data since diagnosis.When necessary, trained professional interpreters will be arranged to discuss study participation.

Informed consent will be obtained from women when they present with suspected early onset pre-eclampsia. The principal or local investigator, clinicians or research midwives will be responsible for obtaining written informed consent from each subject prior to any participation in the study. This will involve adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. If the research midwife undertakes consent and the participant wishes to speak to a clinician, the clinician or sub-investigator will be present or contactable via telephone, and further information can be given to the participant and any questions can be answered immediately. If for some reason, a clinician is not accessible in person or by phone and the participant wishes to speak with them, a second consent visit should be arranged. The investigator or research midwife will explain to the potential participant that they are free to refuse any involvement within the study or alternatively withdraw their consent at any point during the study and for any reason.

4.2 Screening Procedures

Pregnant women who present with raised BP >=140/90 before 34 weeks of gestation will be screened for eligibility in the study. The research midwife will contact the antenatal clinic, antenatal ward, day assessment unit, postnatal ward and delivery suite to identify these potential patients. Their details will be logged into the screening log and their eligibility will be checked against the inclusion and exclusion criteria. Consent from eligible women will be requested in secondary care preferably at the first visit and if not possible at any time until discharge. . Women consented into the study will be assigned unique identifiers, including site number and study reference number, to generate a study specific patient identifier.

4.3 Schedule of assessment

For antenatal assessment of women with suspected pre-eclampsia before 34 weeks

The investigations listed in Table 3 below are the minimum to be requested in women participating in the study. Depending on the severity and the progress of the disease, some of these tests may be requested at frequent intervals by the doctor.

Table 3. Schedule of assessments

Tests	Presentation	Presentation + 24 hours (if clinically indicated for 24 hr review)	Presentation + 48 hours	Twice weekly until delivery	Delivery	Discharge
Clinical history	x	x	x	x	x	
Clinical examination	x	x	x	x	x	
Urine tests	x	x	x	x	x	
Blood tests	x	x	x	x	x	
Ultrasound (if done as clinical	x	x	x	x		

practice)							
Clinician's management score	x	x	x	x			
Maternal outcome assessment			x		x	x	
Fetal outcome assessment						x	

4.4 Follow up Procedures

Participants diagnosed to have pre-eclampsia will be followed up by collection of data twice a week until discharge of the mother and baby by the research midwives. Clinicians managing the women will be requested to complete the Clinicians Management Plan score at each encounter with the mother from admission to delivery. This will provide details of the management plan for the woman.

Women who have a urine dipstick test result of 1+ on presentation but a normal 24 hour urine test will be advised that they do not have pre-eclampsia according to NICE definition and followed up according to usual clinical practice at the site. Follow up data will be collected including maternal and fetal outcome data. If any of these women subsequently develop pre-eclampsia, they will be followed up in accordance with the schedule of assessments in Table 3.

4.5 End of Study Definition

When the last enrolled participant is discharged from hospital, the REC will be notified of the study completion. The final study report will be completed 8 months after enrollment of the last participant.
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4.6 Subject Withdrawal

The PREP study collects data of tests that are done as routine practice and therefore we do not anticipate subjects withdrawing consent.

4.7 Data Collection and Follow up for Withdrawn Subjects

If, for whatever reason the patient discontinues monitoring, the participant will not be withdrawn from the study and data collection will continue, unless consent to do this is withdrawn. Primary outcome data (adverse maternal outcome) should be available for all patients owing to the serious nature of the outcome.

5. Laboratories

5.1 Central/Local Laboratories

The tests will be performed as routine practice in the local units.

5.2 Sample Collection/Labelling/Logging

The samples will be taken as part of routine clinical care by the midwives / doctors. The sample will be labelled according to local clinical protocol.

5.3 Sample Receipt/Chain of Custody/Accountability

Handling of the samples upon arrival at the laboratory will be as per routine clinical practice and local policies.

5.4 Sample Analysis Procedures

Samples will be analysed as usual practice.

5.5 Data Recording/Reporting

Data will be entered in the NHS computer by the local laboratories as usual practice.

6. Statistical Considerations

The study will be divided into 2 distinct phases: 1. Model Development and Internal validation phase and 2. External validation and model update phase.

6.1 Model development and internal validation:

Consecutive women diagnosed with early onset pre-eclampsia will be included in the main analysis .

Candidate predictor variables will be obtained from patient demographic characteristics, and from clinical assessment including clinical history, examination and investigations (Table 1). They are routinely used in clinical practice. The predictors will be clearly defined and standardised through a prospective protocol to ensure reproducibility and enhance generalisability and application of study results to practice.[45] The test results will be prospectively entered in the data collection forms. Only those tests that will be available at the time of presentation will be used.[46] Data will also be collected on any interventions applied between and before outcome onset that may modify the outcome. Those predictors that are highly correlated with others contribute little information and will be excluded from the statistical analysis.[3;47] A trained research midwife will assess the occurrence of adverse maternal and fetal outcomes. A database will collate all this information. The predictors of adverse maternal outcomes will be identified to develop and externally validate and shrink for optimism a simple, interpretable prediction model with considerations of practicality and face validity for clinical applications using the techniques described below.

6.2 External validation and model update:

To show that the PREP prognostic model is valuable, it is not sufficient to show that it successfully predicts outcome in the initial development data even after having it internally validated. We need evidence that the model performs well for other (external) patients. We will thus externally validate the model in patients admitted with diagnosis of early onset pre-eclampsia in 2 prospective datasets; PETRA, Netherlands and PIERS, Canada. The resulting geographical and domain validation will enable us to assess the prognostic performance and the generalisability of the model. We would investigate whether the predicted accuracy and the correctly predicted versus observed proportions of events were similar in groups of patients from other settings and whether separation in outcome across those groups was maintained.

6.3 Sample Size

From our systematic reviews, 20% of women (100 of 500) with early onset pre-eclampsia(confirmed) are known to have adverse maternal outcome at any time point. Given the source population with 50,000 deliveries (with 500 early onset pre-eclampsia) per year we expect a recruitment of 500 women with early onset pre-eclampsia in 30 months. Thus, given the 20% event-rate, we expect there to be 100 adverse maternal events. Rules of thumb for

fitting multivariate models suggest that 10 events for every variable are required to avoid overfitting[53] , and we will work within this limitation. The 10 chosen will be the most promising predictor variables as identified with our previous systematic review in this field.

6.4 Statistical Analysis

We will develop two prediction models; one for adverse maternal outcome by 48 hours after admission, and one for adverse maternal outcome by discharge. These will both be developed using a general methodological and statistical framework as outlined below.

6.4.1 Multivariable model derivation and internal validation

a. Selecting candidate variables

We will chose a priori 10 candidate predictors to be considered in the prediction model, based on the most promising predictor variables as identified with our previous systematic review in this field. Ten variables is an appropriate number here to ensure adequate power based on our target sample size (see below), to avoid overfitting, and to encourage parsimony and applicability of the model in clinical practice.[53] After developing and validating the prognostic model based on these 10 variables, we will additionally investigate whether further variables significantly improve the accuracy of the model; however this will clearly be noted as secondary analyses and data-dredging requiring the need for internal validation (bootstrapping) and adjustment for overfitting.

b. Primary and secondary outcomes

The primary outcome is adverse maternal outcome at 48hours after diagnosis with pre-eclampsia and by discharge as defined in Table 2; we will consider this at 48 hours post diagnosis and also at discharge. The prediction model will thus seek to predict this outcome correctly. The secondary outcome is adverse neonatal outcome at birth; once the prediction model for adverse maternal outcome is completed, we will also assess its performance for predicting adverse neonatal outcome, and also its performance for predicting either adverse maternal outcome or neonatal outcome. Such analyses will again clearly be labelled as secondary.

c. Development of a multivariable prediction model

Though there is currently no consensus on the ideal way of developing a prediction model,[54] we will use a transparent process that implements appropriate statistical methods and adheres to current methodological recommendations. As the outcome is binary (adverse maternal outcome – yes/no), a logistic regression modelling framework will be undertaken with the logit-probability of an adverse outcome the response variable. A backwards selection procedure will be used to decide which of the candidate predictor variables should be included in the final prediction model (with $p < 0.15$ conservatively taken to warrant inclusion and prevent overfitting). Continuous variables will be kept as continuous in the model (rather than say dichotomising), to avoid a loss of power[55;56]. Non-linear trends will also be considered using fractional polynomials and the multivariable fractional polynomial procedure,[57;58] which is an extension to multivariable models including at least one continuous predictor and combines backward elimination of weaker predictors with transformation of continuous predictors. Large missing variable data is not expected, but some will inevitably occur, with not all patients providing all variables of interest. In this situation, multiple imputation will be used to impute, under a missing at random assumption, missing values so to avoid excluding patients from the analysis[55;56]. Once a final model is identified, methods will be applied to simplify and adapt the presentation of the model to a scoring system to facilitate its application in practice.

d. Accounting for clinical management

Ideally, to develop a prediction model we would like to observe outcomes in a cohort of women who receive no clinical management at all, to be able to predict the likelihood of an adverse outcome independent of clinical management. Clearly, this is unethical and all women who present with pre-eclampsia receive clinical management, but such clinical decisions also affect maternal outcome. Thus, in the development of our prediction model we must recognise the importance of accounting for current clinical management; however this is currently an under-researched methodological issue. We will tackle this problem in our project in the following manner:

(i) *including a covariate for clinical management in the prediction models*: We will identify those patients who receive the same or very similar treatment and clinical management decisions, and designate them the same 'clinical management' variable value. By adjusting for this clinical management variable in our prediction model, we can then predict the risk of adverse outcome for patients with specific predictor variable values if they were given a certain clinical management or treatment. Effectively, this process is identifying subgroups of patients with the same or similar clinical management / treatment decisions, and predicting outcome in each of these subgroups based on their predictor variables. This is particularly important for assessing outcome by discharge, as by this point a number of different clinical management decisions may have occurred; it is less of an issue of assessing outcome by 48 hours, as most clinical decisions (e.g. early delivery) are made after 48 hours following presentation, and treatment before 48 hours is standard including use of steroids to enhance fetal lung maturity, anti hypertensives and magnesium sulphate to reduce risk of seizures.

(ii) *accounting for current clinical management decisions*: Clinical management decisions may already be influenced informally (i.e. not through a validated prediction model) by some of our prognostic variables of interest, making it hard to disentangle some predictor variables at baseline from the choice of treatment / clinical management strategy actually used. This is a common problem for prediction modelling, and little advice exists on how to tackle it. We will conduct rigorous methodological work to help address this and apply it within the development of our prediction models. Clinicians will be asked to complete a clinician management plan to indicate their reason(s) for choosing a particular treatment plan We will use this data to ascertain what variables are influencing such clinical decisions. Methodological work will be required to work out how to allow for variables used currently in treatment decisions in the development of the prediction model. All expert methodological members of the research team will be involved in this process; such methodological work was permitted in the scope of the original remit of the grant call.

e. Assessing the performance of the prediction models

An important goal of a prediction model is to classify patients into risk groups. The developed logistic regression models will produce a risk score for each individual, based on their own predictor values. We will then use a cut-off value to decide when a risk score is high (such that we predict an adverse outcome) and when it is low (such that we predict a good outcome). The calibration of the model will be assessed by grouping women into deciles ordered by predicted risk and considering the agreement between the mean predicted risk and the observed events in each decile. The derived decision rule will be cross validated by comparing the classification of each patient with their actual primary outcome of maternal complications, allowing an estimate of the sensitivity and specificity of the prediction model. Then, by varying the chosen cut-off level, we can produce a receiver operating characteristic (ROC) curve summarising the sensitivity and specificity of the predictive rule across the range of cut-offs.[59] The overall discriminatory ability will be summarised as the Area Under Receiver Operating Characteristic curve (AUC ROC) with 95% confidence interval. The most suitable cut-off level can then also be detected. The internal validity of the final model will also be assessed by the bootstrap re-sampling technique to adjust for overoptimism in the estimation of model performance due to validation in the same dataset that was used to develop the model itself. By analysing the difference among the prognostic factors a shrinkage factor will be calculated and the model will be corrected by this shrinkage factor.

6.4.2 External Validation

In the external dataset not used for model development, we will compare the predicted number of events from our model with the observed events to assess calibration (as described above), and we will also calculate the area under the ROC curve to assess discriminatory ability. We will update the model if it shows poor performance to adjust to the new situation by recalibration or revision methods depending on discrimination performance.

The models we develop (which use data from women diagnosed with pre-eclampsia) will also be tested in women defined with suspected pre-eclampsia (urine dipstick 1+ on admission but normal 24 hour proteinuria, <300 mg/24h and normal pcr <30 mg/mmol). Such women will have been identified from our recruitment process, and by checking the calibration and discrimination of our models for such patients, we can examine the potential generalisability to a broader set of women.

7. Data Handling & Record Keeping

All participants in the study will be identified to the central organisers by their NHS and hospital number and will be given a unique study number. Following the MRC's guidance for retention of data, we will keep the data collected for 20 years following the close of the study to allow for verification and any further data sharing e.g. Individual patient data meta analysis. The PCTU (Pragmatic Clinical Trials Unit) has standard operating procedures for legacy archiving. The Queen Mary University of London will act as custodians of the data.

7.1 Confidentiality

The Investigator has a responsibility to ensure that patient anonymity is protected and maintained. They must also ensure that their identities are protected from any unauthorised parties. Information with regards to study patients will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldicott Guardian, The Research Governance Framework for Health and Social Care and Research Ethics Committee Approval.

The study will collect personal data and sensitive information about the participants either directly or from their clinical team. Participants will be informed about the transfer of this information to the study office and will be asked to consent to this. The data will be entered onto a secure computer database, either by trials unit staff or directly via a secure internet connection. Any data to be processed will be anonymised. All personal information obtained for the study will be held securely and treated as (strictly) confidential. All staff, at each hospital or the trials unit, share the same duty of care to prevent unauthorised disclosure of personal information. No data that could be used to identify an individual will be published

The Chief Investigator, Professor Khalid Khan is the 'Custodian' of the data.

7.2 Study Documents

- A signed protocol and any subsequent amendments
- Sponsor Self-Monitoring template for the study team to complete on a regular basis as detailed by the Monitoring section
- Current/Superseded Patient Information Sheets (as applicable)
- Current/Superseded Consent Forms (as applicable)
- Indemnity documentation from sponsor
- Conditions of Sponsorship from sponsor
- Conditional/Final R&D Approval
- Signed site agreement
- Ethics submissions/approvals/correspondence
- CVs of CI and site staff
- Laboratory accreditation letter, certification and normal ranges for all laboratories to be utilised in the study

- Delegation log
- Staff training log
- Site signature log
- Patient identification log
- Screening log
- Enrolment log
- Monitoring visit log
- Protocol training log
- Correspondence relating to the study
- Communication Plan between the CI/PI and members of the study team

7.3 Case Report Form

The PI or research nurse will be responsible for the completion of the CRF throughout the life cycle of the study. The CRF will be completed on presentation with suspected pre-eclampsia , at 24 and 48 hours after presentation and then twice every week until discharge of both mother and baby from hospital.

	Screening	Presentation	**Presentation + 24 hours (if clinically indicated for 24 hr review)**	Presentation + 48 hrs	Twice Weekly until delivery	Delivery	Discharge
Informed Consent		x					
Inclusion Criteria fulfilled	x	x	x	x	x	x	x
Demographics (including Date of Birth and Gender)		x					
Gravida & Parity		x					
Height & Weight		x					
Clinical History		x	x	x	x	x	
Fetal Measures (scan)		x	x	x	x		
Biochemical measures		x	x	x	x	x	
Current Treatment		x	x	x	x	x	x
Clinical Measures		x	x	x	x	x	
Haematological measures		x	x	x	x	x	
Maternal Morbidity		x		x			x
Delivery of baby							x
Birth details							x
Baby discharge details							x
Baby death							x
Mother discharge details							x
Mother death				x			x

7.4 Record Retention and Archiving

During the course of research, all records are the responsibility of the Chief Investigator and must be kept in secure conditions. When the research study is complete, it is a requirement of the Research Governance Framework and Trust Policy that the records are kept for a further 20 years. For studies involving BLT Trust patients, undertaken by Trust staff, or sponsored by BLT or QMUL, the approved repository for long-term storage of local records is the Trust Modern Records Centre which is based at 9 Prescot Street. Site files from other sites must be archived at that external site and cannot be stored at the Modern Records Centre.

7.5 Compliance

The CI will ensure that the study is conducted in compliance with the principles of the Declaration of Helsinki (1996), and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework, Trust and Research Office policies and procedures and any subsequent amendments.

7.6 Clinical Governance Issues

7.6.1 Ethical Considerations

This protocol and any subsequent amendments, along with any accompanying material provided to the patient in addition to any advertising material will be submitted by the Investigator to an Independent Research Ethics Committee. Written Approval from the Committee must be obtained and subsequently submitted to the JRO to obtain Final R&D approval.

7.7 Quality Control and Quality Assurance

7.7.1 Summary Monitoring Plan

Investigators and their host Trusts will be required to permit study-related monitoring and audits to take place by the PREP Study Coordinator, providing direct access to source data and documents as requested. Trusts may also be subject to inspection by the Research and Development Manager and should do everything requested by the Chief Investigator in order to prepare and contribute to any inspection or audit. Study participants will be made aware of the possibility of external audit of data they provide in the participant information sheet.

7.7.2 Audit and Inspection

Auditing: Definition "A systematic and independent examination of study related activities and documents to determine whether the evaluated study related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)."

A study may be identified for audit by any method listed below:
1. A project may be identified via the risk assessment process.
2. An individual investigator or department may request an audit.
3. A project may be identified via an allegation of research misconduct or fraud or a suspected breach of regulations.
4. Projects may be selected at random. The Department of Health states that Trusts should be auditing a minimum of 10% of all research projects.
5. Projects may be randomly selected for audit by an external organisation.

Internal audits will be conducted by a sponsor's representative

7.8 Non-Compliance

(A noted systematic lack of both the CI and the study staff adhering to SOPs/protocol/ICH-GCP, which leads to prolonged collection of deviations, breaches or suspected fraud.)

These non-compliances may be captured from a variety of different sources including monitoring visits, CRFs, communications and updates. The sponsor will maintain a log of the non-compliances to ascertain if there are any trends developing which to be escalated. The sponsor will assess the non-compliances and action a timeframe in which they need to be dealt with. Each action will be given a different timeframe dependant on the severity. If the actions are not dealt with accordingly, the JRO will agree an appropriate action, including an on-site audit.

8. Study Committees

8.1 Study Steering Committee

The Study Steering Committee (SSC) provides independent supervision for the study, providing advice to the Chief and Co- Investigators and the Sponsor on all aspects of the study and affording protection for patients by ensuring the study is conducted according to the principles of Good Clinical Practice in Clinical Trials.

If the Chief and Co-Investigators are unable to resolve any concern satisfactorily, Principal Investigators, and all others associated with the study, may write through the Study Office to the chairman of the SSC, drawing attention to any concerns they may have about the possibility of particular side-effects, or of particular categories of patient requiring special study, or about any other matters thought relevant.

8.2 Data Monitoring Committee

Interim analyses of outcomes will be supplied, in strict confidence, to an independent Data Monitoring Committee (DMC) along with updates on results of other related studies, and any other analyses that the DMC may request. The DMC will also be given reports of data quality at least yearly intervals.

9. Publication Policy

A meeting will be held after the end of the study to allow discussion of the main results among the collaborators prior to publication. The success of the study depends entirely on the wholehearted collaboration of a large number of doctors, nurses and others. A writing committee will be convened to produce publications on behalf of the PREP Collaborating Group. Centres will not be permitted to publish data obtained from participants in the PREP Study that use study outcome measures without discussion with the Chief Investigator and/or the SSC.

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a. Appendices

- Data Protection Act Research Form
- Consent Form
- Patient Information Sheet
- GP letters/ advertisements/any other letters and documents to be given to the patient
- Data collection baseline form
- Data collection investigations form
- Data collection outcome form