Accuracy of clinical characteristics, biochemical and ultrasound markers in the prediction of pre-eclampsia: an Individual Participant Data (IPD) Meta-analysis

1. Background and rationale:

Pre-eclampsia remains a leading cause of maternal deaths worldwide (1) and is the main cause of maternal admissions to intensive care in developed countries. (2) It is also associated with increased perinatal mortality and fetal growth restriction, and contributes to approximately 10% of stillbirths and 15% of preterm births. (3, 4)

Pre-eclampsia is a heterogeneous disorder with a wide spectrum of multi-organ involvement, which reflects the various pathophysiological pathways. Two separate entities of the disease are well recognised: early onset pre-eclampsia occurring before 34 weeks' gestation and the late onset type occurring after 34 weeks' gestation. (5-7) Early onset pre eclampsia is considered to be a pathophysiologically different disease than late onset pre-eclampsia. It is associated with a considerably increased risk of maternal complications than the late onset type, such as a 20-fold higher maternal mortality, and early delivery is the only treatment. (8-10) In addition to the prematurity related complications, the risk of stillbirth and adverse perinatal outcomes are much higher in those with early than late onset disease. (11)

Although the proportion of women with early onset pre-eclampsia is less than 1% of all pregnancies, the complexity of the treatment gives rise to large health care costs. (12, 13) Mothers are often admitted in a tertiary care facility and 30% experience complications, which may necessitate an intensive care management. (14) Infants usually need prolonged care for management of complications including lifelong disabilities, arising as a result of premature delivery of the babies. The additional NHS costs incurred to care for a preterm baby born before 28 weeks, and between 28 and 33 weeks, are £94,190 and £61,509, respectively. (15) A total of £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)

Late onset pre-eclampsia, including pre-eclampsia at term also poses significant health burden. It accounts for the majority of the cases diagnosed with pre-eclampsia. One fifth of all women with late onset disease have maternal complications such as HELLP (Haemolysis, Elevated liver enzymes and Low Platelets) syndrome and over half have eclamptic seizures. (13, 16, 17)

Pregnant women at risk of pre-eclampsia are monitored closely in pregnancy, and commenced on preventative interventions such as aspirin to reduce adverse outcomes. Early commencement of these interventions has the potential for maximal benefit.(18) There is a need for an accurate screening strategy to predict pre-eclampsia. Currently, our clinical assessment in pregnancy for preeclampsia is mainly based on maternal history. (19) However, clinical history based risk factor approach has shown limited predictive accuracy. Additional tests for biochemical and ultrasound markers may improve performance. (20, 21) Impaired placentation with abnormal blood-flow velocity and resistance in placental vessels is associated with pre-eclampsia and fetal growth restriction. Angiogenic biomarkers, considered to be the markers of placental function, have the potential to identify early in pregnancy, the subsequent risk of pre-eclampsia. Doppler of the uterine artery, a non-invasive method, and a measure of uteroplacental resistance, provides an indirect estimate of abnormal placentation.

A robust prediction model should incorporate the clinical characteristics with biomarkers and uterine artery Doppler to increase the accuracy of risk assessment. (22) However risk factors based on clinical characteristics have been shown to have quantitatively different associations with the early and late onset pre-eclampsia. (11) Similarly biochemical markers and uterine artery Doppler have shown variation in their performance in predicting the two types of pre-eclampsia. (23, 24) It is likely that a single model will not be appropriate to accurately detect early and late onset pre-eclampsia. The National Institute for Clinical and Care Excellence (NICE) has prioritised screening for early onset pre-eclampsia in its research recommendations on antenatal care of women. (25)

Systematic reviews on the performance of tests in pre-eclampsia will need to take into account the variation in population and test characteristics, treatment provided and the timing of onset of pre-eclampsia. An IPD meta-analysis framework with

access to the predictor-outcome data of individual patients, will allow us to develop and validate a multivariable prediction model for early, late, and any onset pre-eclampsia.

3.1. Existing guidelines

Existing practice guidelines on predicting the risk of pre-eclampsia are based on clinical characteristics. The NICE guideline stratifies women at increased risk of pre-eclampsia based on the following clinical characteristics: history of hypertensive disease during a previous pregnancy, chronic kidney disease, autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome, type 1 or type 2 diabetes, chronic hypertension; or women with more than one moderate risk factor, defined as nulliparity, age 40 years or older, pregnancy interval of more than 10 years, body mass index (BMI) of 35 kg/m² or more at booking, family history of pre-eclampsia, or multiple pregnancy. The Society of Obstetricians and Gynecologists of Canada have endorsed a similar history-based screening policy (SOGC 2014). (26) The American College of Obstetricians and Gynecologists (ACOG) does not recommend routine screening to predict pre-eclampsia beyond taking an appropriate medical history to evaluate for risk factors (ACOG 2013). (27) None of the existing guidelines take into account biomarkers or uterine Doppler for screening women or focus on the prediction of early onset pre-eclampsia to stratify women at risk. (28, 29)

1.2. Current evidence on predicting risk of pre-eclampsia

A systematic review of controlled cohort studies identified the following clinical characteristics to be associated with high risk of pre-eclampsia: previous history of pre-eclampsia (RR 7.2, 95% CI 5.9 to 8.8), nulliparity (2.9, 1.3 to 6.6), anti-phospholipid antibodies (9.7, 4.3 to 21.8), multiple (twin) pregnancy (2.9, 2.0 to 4.2), family history (2.9, 1.7 to 4.9), raised blood pressure (diastolic ≥ 80 mm Hg) at booking (1.4, 1.0 to 1.9), pre-existing diabetes (3.6, 2.5 to 5.0), raised body mass index before pregnancy (2.5, 1.7 to 3.7) or at booking (1.6, 1.3 to 1.9), or maternal age ≥ 40 (2.0, 1.3 to 2.9, for multiparous women). The risk was also increased in women with an interval of 10 years or more since a previous pregnancy, autoimmune disease, renal disease, and chronic hypertension. The review did not quantify the association between clinical features and early onset pre-eclampsia. (30)

Individual biochemical markers currently used in clinical practice for Down's syndrome screening such as PAPP-A, hCG and serum AFP have low predictive accuracy for pre-eclampsia. (31) The magnitude of association between first trimester markers and early onset pre-eclampsia is higher than late onset pre-eclampsia. (23) First trimester uterine artery Doppler appears to have high specificity (0.92; 95% CI 0.88–0.94), but low sensitivity (0.48; 95% CI 0.39–0.57) in predicting early onset pre-eclampsia. The sensitivity was lower for predicting any pre-eclampsia. (24) Most Doppler indices have poor predictive characteristics, but this varies with the patient characteristic and outcome severity. An increased pulsatility index with notching was the best predictor of pre-eclampsia (LR+ 21.0 in high-risk patients and 7.5 in low-risk patients). (32)

1.3. Management of women at risk of pre-eclampsia

Currently, women at high risk of pre-eclampsia (based on their clinical characteristics) are recommended prophylactic treatment with aspirin from 12 weeks of pregnancy. (25) The IPD meta-analysis on the effectiveness of aspirin in preventing pre-eclampsia showed that the risk was reduced by 10% for any pre-eclampsia (RR 0·90; 95% CI 0·84–0·97), for delivery before 34 weeks (RR 0·90; 95% CI 0·83–0·98), and for pregnancy with a serious adverse outcome (RR 0.10; 95% CI 0·85–0·96). (33) Subgroup analysis based on individual risk factors did not show significant differences in the effectiveness of aspirin between the groups. However the differential effectiveness of aspirin for women deemed to be at high risk based on multiple risk factors in a prediction model compared to those at low risk is not known.

1.4. Why is an IPD meta-analysis needed now, rather than an aggregate data meta-analysis?

Numerous systematic reviews with aggregate data meta-analysis have evaluated various risk factors separately or in combination for prediction of pre-eclampsia (Table 1). These aggregate data reviews are affected by the following limitations.

Firstly, the aggregate meta-analyses are restricted by the heterogeneity in the characteristics of the population, timing of tests and cut offs, and the type of outcome in published studies. This is especially problematic for the relatively rare but clinically

significant outcome of early onset pre-eclampsia, which is often not reported in individual studies. Heterogeneity in the patient selection can be reduced by IPD through strict inclusion and exclusion criteria (i.e. removal and addition of particular patients in the dataset). The relevant outcomes, particularly gestational age at onset of pre-eclampsia could be accessed in individual patients by IPD meta-analysis, and this is not possible when only aggregate data are available.

Secondly, primary studies often report on only one test, despite available information on more than one test. Furthermore, any information on the performance of multiple predictors in individual studies is provided as mean values for the population. Hence it is difficult to undertake sensible evidence synthesis by aggregate data meta-analyses, for evaluation of multiple predictors. Furthermore, aggregate data meta-analyses of multiple predictors have limited capabilities to develop prediction models, yielding accurate estimates of *absolute* risk for individual patients, certainly in the presence of between-study heterogeneity. By accessing the individual data, our IPD meta-analysis will have sufficient sample size to evaluate several candidate prognostic factors in combination and subsequently develop clinically relevant robust models. Access to IPD will also allow to recalibrate meta-analysis models in the presence of between-study heterogeneity, and hence to improve the quality of individual risk predictions.

Thirdly, there is a need for appropriate methods of meta-analysis to summarise the factor-outcome associations. Due to numerous problems of published primary studies investigating factor-outcome associations, especially publication bias and selective reporting, aggregate meta-analyses based on published results are notoriously prone to bias, and show inconsistent and even contradictory factor-outcome associations. The PROGRESS group have shown multiple examples, across a broad range of diseases, where aggregate data meta-analysis has failed to identify clear conclusions about prognostic factors (34) due to poor reporting. In IPD meta-analysis, the association between future outcome and patient-level characteristics and study level characteristics (setting, timing, study design) can be assessed more reliably; for example using a more consistent set of adjustment factors and modelling biomarkers on their continuous scale (rather than categorisation). (35)

Fourthly, prior to application of a model in clinical practice, there is a need to evaluate its performance in the population(s) in which it is intended for use. This requires external validation of the model in a dataset different to which it is developed, requiring additional sample size beyond model development, and only possible with IPD (as aggregate data does not allow predictions from a new model to be checked at the patient-level). Lack of external validation is one of the key reasons for the models not being adopted in clinical practice. IPD meta-analysis offers an accepted way to overcome this current lack of validation. (36) Further, we will maximise the data for model development and external validation by using an 'internal-external cross validation' approach, that accounts for multiple studies by rotating them toward model development and validation. External validation performance (e.g. in terms of calibration and discrimination) can then be checked in each study, and summarised itself in a meta-analysis. (37,57,67)

Fifthly, problems with aggregate data arise with differential treatment effects such as use of aspirin, by patient characteristics. Obtaining individual participant data (IPD) from these studies will facilitate a more reliable meta-analysis, as treatment with aspirin will be available at the individual-level. This will allow, for example, the external validation performance of a model to be evaluated across different groups of individuals defined by their treatment, and considering the inclusion of treatment as a predictor in the models. In Table 1 below, we have outlined the reasons for our IPD meta-analysis approach compared to standard aggregate meta-analysis.

Table 1. Comparison of aggregate data and IPD meta-analysis approach for evidence synthesis on prediction of pre-eclampsia

HTA call remit	Design and objectives	Objectives met	
		Aggregate meta-analysis	IPD meta-analysis
Population			
Pregnant women in the first or second trimester of pregnancy	Takes into account the different baseline risks across various groups of women in the included studies	No	Yes
	The association across between outcome risk and patient-level characteristics or between patient and study level characteristics (setting, study design) can	No	Yes

Identification of any subgroups in which markers appear to perform best	be assessed in this group of women, without the ecological fallacy problem		
	Evaluates the differential performance of the prediction model according the subgroups based on population (unselected vs. selected), timing of test (first vs. any trimester)	No	Yes
Tests			
New and existing biochemical markers, ultrasound markers and combinations of markers and risk models	Adjusts for multiple predictors such as clinical history, biochemical and ultrasound markers	Limited	Yes
	The cut offs of the test results can be maintained as continuous values instead of dichotomous measures, thereby maximising the prognostic information of the tests	No	Yes
	Takes into account the effect of management (e.g. aspirin) that influences the outcome	No	Yes
Outcome			
Risk of early pre-eclampsia and any pre-eclampsia	Predictive performance of the tests assessed for pre-eclampsia for various gestational ages	Limited	Yes
Clinical applicability			
If findings suggest it is appropriate model should be developed to explore the potential for use in screening	Produces a single, integrated prediction model that can be implemented in practice after validation	No	Yes
	Involves key global researchers in pre-eclampsia prediction and databases, with potential to improve implementation of the model	Limited	Yes

1.5. Identifying a good performing risk prediction tool

A good prediction model is one that yields accurate and consistent performance; 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 the following ways: use rigorous statistical methods to develop the model and assess accuracy; undertake a formal external validation within the IPD datasets; use unambiguous definitions of predictors and reproducible measurements using methods available in clinical practice; adjust and/or evaluate performance according to current clinical management; involve patient groups in model development and implementation; and produce personalised risk scores that enable mothers and clinicians to make more informed decisions on management aspects like commencement of aspirin early in pregnancy and frequent monitoring in secondary and tertiary care. The performance of the model will naturally be limited by the strength of the predictive relationships between the measured variables and the outcome.

2. Work leading to the proposal:

2.1. Review of reviews on prediction of pre-eclampsia (ST, AK)

We undertook a review of reviews that evaluated the performance of single or combined tests for predicting pre-eclampsia. Our Medline search (1990-to date) identified 73 citations, and after evaluation of the abstracts, we included 56 published reviews evaluating one or more than one test (Table 2). Of these, 38 reviews (67.8 %) have been published since our HTA review (2008) on accuracy of tests in predicting pre-eclampsia. (38) Clinical characteristics were studied in 23.2 % (13/56) of reviews, biochemical markers in 73.2 % (41/56), ultrasound markers in 8.9 % (5/56), and a combination of clinical, biochemical and ultrasound markers in 3.6 % (2/56) of the published reviews.

Table 2. Review of reviews on prediction of pre-eclampsia

Systematic review	No. of primary studies	No. of databases	No. of women	Risk factors evaluated	Early onset pre-eclampsia reported as outcome
Maternal characteristics					
Cnossen 2007	36	4	1699073	BMI	No
O'Brien 2003	13	2	1400000		No
Wang 2013*	29	N/A	1980761		No
Duckitt 2005	2	6	64789	multiple clinical features	No
Alpoim 2013*	2	4	1875	ABO blood group status	Yes
England 2007	48	1	N/A	smoking	Yes
Rebelo 2013*	23	3	4265	CRP, BMI	No
Duckitt 2005	2	3	37988	Parity	No
Luo 2007	26	1	N/A		No
Duckitt 2005	2	3	65314	Age	No
Duckitt 2005	2	1	907	Blood pressure	No
Cnossen 2008	34	4	60599		No
Sgolastra 2013*	15	8	5023	Periodontal disease	No
Kunnen 2010*	15	3	n/s		Yes
Morris 2012*	20	10	2978	Proteinuria	No
Sanchez-Ramos 2013*	24	N/A	3186		Yes
Wolf 2014*	11	2	5411	Leisure time physical activity	No
Uterine artery Doppler ultrasound					
Velauthar 2014*	18	3	55974	First trimester Doppler	Yes
Chien 2000	27	1	12994	Any trimester Doppler	No
Cnossen 2008	74	4	79547		No
Kleinrouweler 2013*	8	2	6708	Second trimester Doppler IPD	Yes
Pedrosa 2011*	N/A	1	N/A	Doppler combined with other markers	Yes
Biomarkers					
Kosmas 2003	19	2	5145	Factor V Leiden	No
Dudding 2008	6	2	6755		No
Rodger 2010*	10	2	21833		No
Xia 2012*	36	2	9203	MTHFR gene C677T polymorphism	No
Kosmas 2004	23	2	6213		No
Zusterzeel 2000	4	2	579		No
Li 2014*	49	4	18009		No
Wang 2013*	51	3	17749		No
Widmer 2007	10	5	1173	sFLT1	Yes
Jacobs 2011*	11	3	N/A		Yes
Kleinrouweler 2013*	19	3	6708		Yes
Widmer 2007	14	5	2045	PIGF	Yes
Kleinrouweler 2012*	27	3			No
Huppertz 2013*	19	N/A	16153	PP13	Yes
Schneuer 2012*	7	N/A	2989		Yes
Lau 2013*	41	4	1940	TNF alpha, IL6 and IL10	No
Tabesh 2013*	8	6	2485	Serum vitamin D	No
Morgan 2013*	12	2	5003	PAI1 promoter polymorphism	No
Dai 2013*	29	5	3228	eNOS polymorphisms	No
Chen 2012*	18	3	N/A		No

Qi 2013*	33	3	10671		No
Zhao 2013*	11	3	3088	PAI1 promoter polymorphism	No
Zhao 2012*	8	4	1995	AGTR1 +1166A>C polymorphism	No
Zhong 2012*	11	N/A	1749	ACE I/D polymorphism	No
Chen 2012*	30	4	8340		No
Ni 2012*	22	4	7534	AGT M235T polymorphism	No
Kleinrouweler 2012*	3	3		VEGF	No
Hui 2012*	37	3	115290	Wide range of serum markers	No
Giguere 2011*	37	2		71 different markers	Yes
Abou Nassar 2011*	28	3	5991	Anti phospholipid antibodies	No
do Prado 2010*	12	4	7950		No
Gupta 2009*	17	4	745	Lipid peroxidation	No
Bombell 2008	16	3	2374	TNF (-308A) polymorphism	No
Zafarmand 2008	17	3	5275	Angiotensin M235T polymorphism	No
Morris 2008	44	4	169637	Inhibin A, AFP and 3 others	No
Wiwanitkit 2006	6	N/A	1690	Plasminogen activator inhibitor-1	No
Other markers					
Leeflang 2007	5	4	573	FFN	No
Palmer 2013*	11	2	N/A	Occupational exposures	No
Bonzini 2007	9	2	N/A		No
Cnossen 2006	5	4	572	uric acid	No

*published after the HTA review (No. 01/64/04) on prediction of pre-eclampsia

2.2. Systematic review of predictors of pre-eclampsia (HTA No. 01/64/04): Clinical, biochemical and ultrasound tests (KSK, BWM)

Our comprehensive review (to January 2005) assessed the accuracy of various tests in the prediction of pre-eclampsia. (38) We included 144 studies that evaluated 27 tests. The tests with high specificity had low sensitivity. Most of these studies were limited by their poor quality, such as poor reporting, potential threats to validity, lack of blinding, incomplete test description and inadequate reference standard. These have reduced our confidence in the reported predictive ability of tests. Many studies did not provide separate spectrum-specific results, but included patients across the clinical risk spectrum. Diagnostic tests are often dichotomized and sensitivity/specificity are then presented for one or more specific thresholds. In an IPD-MA one often has access to the "raw" test results and hence these "raw" data can directly be used in prediction models, avoiding loss of information by dichotomization. The main recommendation from this work was to not offer testing in view of the poor predictive accuracy, but to first perform robust evaluation of new tests or those with reported high levels of both sensitivity and specificity, in the clinical setting where they will be applied. Future studies should investigate combinations of markers, and evaluate the added value of new tests to the risk profile based on the clinical history. More importantly, the report recommended that predictive models developed in the future should be validated using IPD diagnostic meta-analysis.

2.3. Systematic review of prediction models for pre-eclampsia (ST, KSK, BWM)

We recently undertook a systematic review to assess the variation in the development and reporting of prediction models in obstetrics (Medline until 2012). (39) Of the 263 models in obstetrics, 69 were developed for pre-eclampsia, the most widely studied outcome. More than 80% of the published models were on women at low risk of pre-eclampsia (58/69, 84%). Twenty -five (36%) models had 3-4 predictor variables, 22 (32%) included 5-6 predictors, seven evaluated 7-8 predictors (10%), three (4.3%) had 9-10 variables and 7 (10%) had more than 10 predictors in the model. Twenty models provided estimates for the prediction of early onset pre-eclampsia. A fifth of the models (14/69) were internally validated and only 7% (5/69) were externally validated. Details of model calibration were presented for 6 models (8.6%, 6/69). A prediction formula, rule or score that could be used by others was reported for 45 models and guidance for clinical use was discussed for 9 models (13%). We will assess the performance of the identified models by external validation in our IPD data.

2.4. Accuracy of uterine artery Doppler in predicting pre-eclampsia: Aggregate and IPD meta-analyses

Aggregate meta-analysis:
First uterine artery Doppler (ST, BT, KSK): Our systematic review (1951-2012) identified 18 studies (55 974 women) evaluating the accuracy of first trimester Doppler in predicting pre-eclampsia. (24) The sensitivity and specificity of abnormal flow velocity waveform (FVW) for early-onset pre-eclampsia were 47.8% (95% CI: 39.0–56.8) and 92.1% (95% CI: 88.6–94.6) respectively. The sensitivity and specificity for predicting any pre-eclampsia were 26.4% (95% CI: 22.5–30.8) and 15.4% (95% CI: 12.4–18.9), respectively. The findings of our review have highlighted the need for development of prediction models, incorporating the clinical characteristics with uterine artery Doppler to increase the accuracy of risk assessment. An IPD meta-analysis was recommended to allow development of optimal testing strategies for prediction of pre-eclampsia across different study populations.

Uterine artery Doppler in any trimester (KSK, BWM): In our systematic review (until 2006) of 74 studies on pre-eclampsia (79497 women) we showed that the performance of uterine artery Doppler varied with patient risk and outcome severity. (32) An increased pulsatility index with notching was the best predictor of pre-eclampsia (positive likelihood ratio 21.0 among high-risk patients and 7.5 among low-risk patients).

IPD meta-analysis:
Second trimester uterine artery Doppler (BWM): This IPD meta-analysis involved eight studies (1995-2009) with 6708 nulliparous women, of whom 302 (4.5%) developed pre-eclampsia. (40) Doppler findings included higher, lower and mean (PI) and any or bilateral notching. The best predictors of pre-eclampsia by Doppler were combinations of mean pulsatility index (PI) or resistance index (RI) and bilateral notching, with areas under the receiver-operating characteristics curve (AUC) of 0.75 (95% CI 0.56-0.95) and 0.70 (95% CI 0.66-0.74), respectively. Addition of Doppler findings to the patient characteristics blood pressure or body mass index (BMI) significantly improved discrimination. A model with blood pressure, PI and bilateral notching had an AUC of 0.85 (95% CI 0.67-1.00).

Prediction of hypertensive disorders using Previous pregnancy data, Anthropometric parameters and maternal Risk factors (PREPARE) (BWM): The PREPARE IPD meta-analysis aims to assess the risk of recurrence of a hypertensive disorder after delivery before 37 weeks of gestation due to a hypertensive disorder. The database currently includes 21 studies involving 60,000 women. The current proposal is strengthened by the support of the PREPARE members who are co-applicants (BWM) and collaborators (WG).

Access to the above IPDs will allow us to build on the existing work in this area, including standardisation of definitions of population, tests and outcomes. Furthermore, the performance of the model in subgroups based on previous clinical history can be assessed robustly.

2.5. Biomarkers and onset of pre-eclampsia: Systematic review

We undertook two meta-analyses in this area. The first review by BWM (1951- 2010; 34 studies) assessed the accuracy of the biomarkers circulating placental growth factor (PlGF), vascular endothelial growth factor (VEGF), soluble fms-like tyrosinekinase-1 (sFLT1) and soluble endoglin (sENG) in any trimester for predicting pre-eclampsia. (41) PlGF, sFLT1 and sENG showed modest but significantly different concentrations before 30 weeks of gestation in women who developed pre-eclampsia. Test accuracies of all four markers were too poor for accurate prediction of pre-eclampsia in clinical practice.

In the second review by ST (1951- 2013; 30 studies; 65,538 women), we evaluated the association between all first trimester biomarkers and early, and any onset pre-eclampsia. (23) The biomarkers, PAPP-A (OR 2.1, 95% CI 1.6, 2.6), PP13 (OR 4.4, 95% CI 2.9, 6.8), sflt-1 (OR 1.3, 95% CI 2.9, 6.8), pentraxin (OR 5.3, 95% CI 1.9, 15.0) and inhibin-A (OR 3.6, 95% CI 1.7, 7.6) were significantly associated with any pre-eclampsia. The odds of early onset pre-eclampsia were significantly increased when the five biomarkers, PlGF (OR 3.4, 95% CI 1.6, 7.2), PAPP-A (OR 4.8, 95% CI 2.5, 22.5), PP13 (OR 7.5, 95% CI 2.5, 22.5), soluble endoglin (OR 18.5, 95% CI 8.4, 41.0) and inhibin-A (OR 4.1, 95% CI 1.9, 8.8) were abnormal. Two biomarkers, soluble endoglin (OR 2.1, 95% CI 1.9, 2.4) and inhibin-A (OR 1.9, 95% CI 1.4, 2.8) were significantly associated with late onset pre-eclampsia.

2.6. IPPIC (International Prediction of Pre-eclampsia IPD Collaborative) Network

We have established a collaborative network of investigators (IPPIC) involved in the primary studies and have contacted the relevant primary study researchers and Networks and have received positive reply to share 61 datasets, thereby demonstrating an overwhelming interest for a joint endeavour in this field. Currently over 60 investigators have offered provisional support to access data of over 400,000 women. We anticipate this number to increase in the future.

The IPPIC Network is strengthened by support from the Global Obstetrics Research Network (GONet), comprised of a group of international investigators involved in clinical trials and observational studies in maternal fetal medicine and obstetrics (www.globalobstetricsnetwork.org). Our collaborative group has brought together other international pre-eclampsia research networks such as PRE-EMPT (https://pre-empt.cfri.ca), Co-Lab (https://pre-empt.cfri.ca/colaboratory), PREPARE (http://www.studies-obsgyn.nl/IPD-PREPARE/), SCOPE (http://www.scopestudy.net/) and South West Thames Obstetric Research Collaborative (STORK) that focus on the prediction of pre-eclampsia. This provides us with access to large databases on biochemical and ultrasound markers in addition to the clinical characteristics for the clinically relevant outcomes.

3. Objectives:

We will develop, externally validate and update separate prediction models for (i) early (<34 weeks' gestation), (ii) late (≥ 34 weeks) and (iii) any onset pre-eclampsia.

Primary

1. To estimate the prognostic value of individual clinical, biochemical and ultrasound markers for predicting pre-eclampsia in individual subjects by IPD meta-analysis
2. To validate, and improve or tailor the performance of existing models in relevant population groups, for predicting early, late and any pre-eclampsia in individual subjects of our IPD dataset based on
   - Clinical characteristics only
   - Clinical and biochemical markers
   - Clinical and ultrasound markers
   - Clinical, ultrasound and biochemical markers
3. Using IPD meta-analysis, to develop and externally validate (using internal-external cross-validation) multivariable prediction models for early, late and any pre-eclampsia in the following circumstances: existing predictive strategies cannot be adjusted for the target population, no such models exist, or the relevant pre-eclampsia outcomes are not studied. We will also externally validate the performance of the developed models on other available independent datasets.

Secondary

4. To assess the differential performance of the models in various predefined subgroups based on population characteristics (unselected; selected) and timing of model use (first trimester; second trimester)
5. To study the added role of novel biomarkers on the accuracy of the developed models

4. Research Methods

Our IPD meta-analytical approach will follow existing guidelines and our output will comply with the PRISMA statement, (42) and adhere to recent reporting guidelines for IPD meta-analysis. (43) We will collect the raw individual data from each study identified from our systematic reviews and from the IPPIC collaborative Network. This will be followed by standardisation of predictors and outcome variables, data cleaning and formatting, and summarisation of the evidence by data synthesis, whilst preserving the clustering of patients within the studies. We will address the following structured question in our project (Table 3).

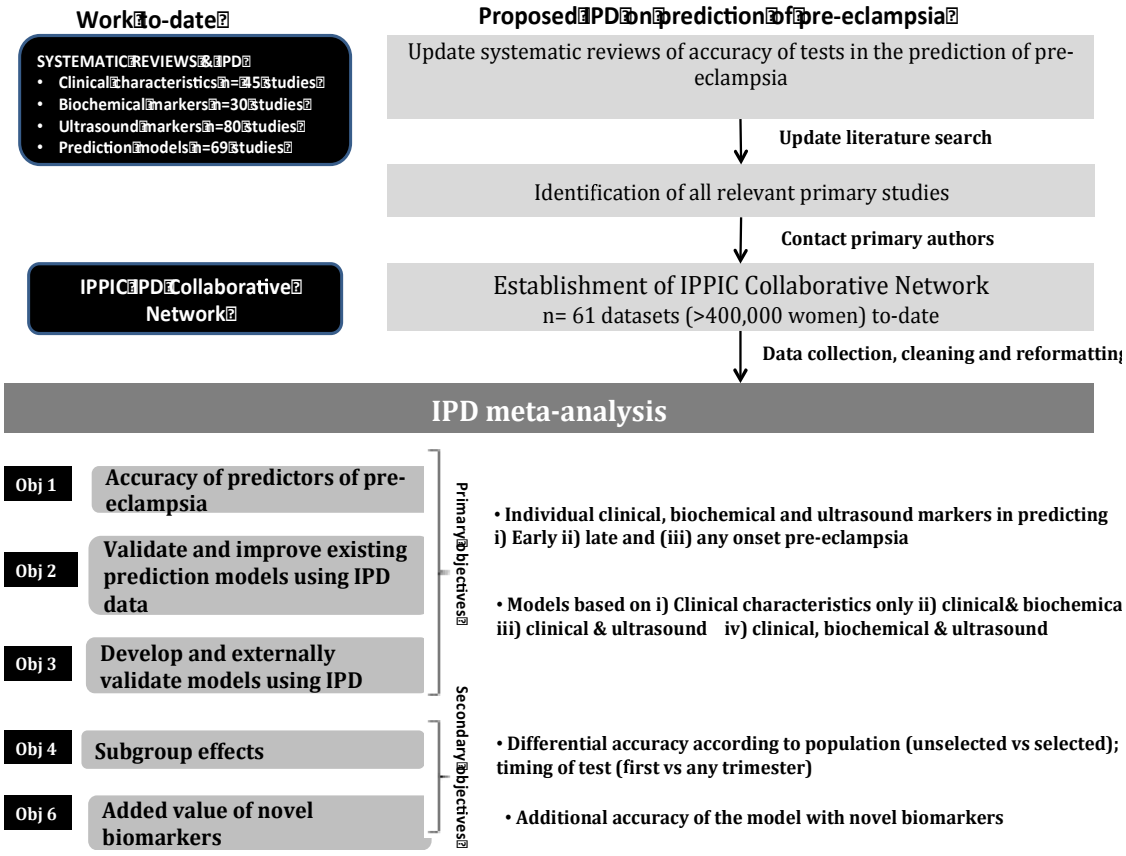
Table 3: Structured questions for IPD meta-analysis of accuracy of tests and markers in the prediction of pre-eclampsia

Question Components		
Population		Pregnant women
Article I.	**Predictors**	Maternal clinical characteristics at booking – Maternal characteristics: Age, BMI, ethnicity, smoking,; Medical history: pre-existing chronic kidney disease, autoimmune disease such as systemic lupus erythematosus (SLE) and anti-phospholipid syndrome, type 1 and 2 diabetes and hypertensive diseases, Previous obstetric history: parity, previous hypertensive disease, pregnancy interval more than 10 years, family history of pre-eclampsia, , previous miscarriages, stillbirth or small for gestational age fetus; Current pregnancy: Multiple pregnancy, early pregnancy bleeding, systolic and diastolic blood pressure Biochemical markers (first or second trimester)– PAPP-A , PP13, sflt-1, inhibin-A, activin A, PlGF, AFP, HCG, VEGF and soluble endoglin Ultrasound markers (first or second trimester)– Uterine artery Doppler (resistance index, pulsatility index, unilateral or bilateral notching) Other markers- pentraxin, ADAM 12, IL-8, matrix metal-loproteinase-9, human leukocyte antigen-G (HLA-G) and chemokine (CXC motif) ligand 10, metabolic and micro RNA based biomarkers
Outcomes		**Primary outcomes:** Early onset (<34 weeks), late onset (≥ 34 weeks) and any onset pre-eclampsia **Secondary outcomes:** Maternal complications: Eclampsia, HELLP syndrome, abruption, hepatic and renal failure, cortical blindness, pulmonary oedema, antepartum and postpartum haemorrhage, DIC, preterm delivery, admission to HDU, maternal death, caesarean section, maternal infection Fetal and neonatal complications: Birth weight in Kg and centile, small for gestational age fetus, stillbirth, neonatal death, abnormal pH at birth, hypoxic ischemic encephalopathy, respiratory distress syndrome, septicaemia, admission to neonatal unit, Apgar score <7 at 1' and 5'
Study design		IPD meta-analysis of observational studies and cohorts nested within randomised trials

4.1 Primary outcome

Our primary outcomes are early (< 34 weeks), late (≥ 34 weeks) and any pre-eclampsia. Pre-eclampsia is defined as new onset hypertension after 20 weeks gestation (BP greater than or equal to 140/90 mmHg) and new onset proteinuria of 1+ or more on standard urinary dipstick tests and proteinuria on spot urine PCR (protein creatinine ratio) test greater than 30mg/mmol or 24 hour urine >300mg/24 hours. (25)

Fig 1. Flow chart of the plan of investigation in the IPD meta-analysis on prediction of pre-eclampsia



Our methods will be as follows:

4.2 Updating literature searches

The existing reviews are summarised in Table 1. Our collaborative team has undertaken the relevant systematic reviews on clinical characteristics, biochemical and ultrasound markers for prediction of pre-eclampsia. (24, 31, 32, 38, 41, 44-53) As a first step in the IPD meta-analysis, we will update the relevant reviews as new research evidence may have appeared since completion of our work. The following databases will be searched: MEDLINE, EMBASE, BIOSIS, LILACS, Pascal, Science Citation Index, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment Database (HTA). Research reported in the grey literature will be sought by searching a range of relevant databases including the Inside Conferences, Systems for Information in Grey Literature (SIGLE), Dissertation Abstracts and Clinical Trials.gov. Internet searches will also be carried out using specialist search gateways (such as OMNI: http://www.omni.ac.uk/), general search engines (such as Google: http://www.google.co.uk/) and meta-search engines (such as Copernic: http://www.copernic.com/). Language restrictions will not be applied to the electronic searches. Identification of prognostic studies has been hindered by the lack of standard descriptors and indexing terms. We will overcome this by using search strategies with high sensitivity in identifying prognostic studies in Medline, such as exp epidemiologic studies OR incidence.sh OR prognos:.tw OR predict:.tw OR course:.tw along with terms specific to pre-eclampsia. (54) Authors of the included studies from the IPPIC Collaborative Network will also be asked to examine the included study list to identify any studies or data that might have been missed. In addition to information on studies in progress, we will seek input from collaborative groups such as PRE-EMPT and GONET for unpublished research.

4.3 Contact with authors and establishment of the collaborative group

A major challenge in an IPD meta-analysis is to persuade the primary study authors to provide their raw data. (35) We have already established the IPPIC-IPD collaborative group that includes representatives from research groups that have published

studies on clinical characteristics, biochemical and ultrasound markers in the prediction of early and any pre-eclampsia. We have provisional support from over 60 study investigators for access to individual patient data for over 400,000 women. From our current HTA IPD project (No. 12/01/50), it is clear that development of mutual trust is a key issue. A related website will be developed to improve visibility and communication. A memorandum of understanding will cover the provision of data by the principal investigators of the individual trials, and any publication of the IPD meta-analysis section of this project will be in the name of the collaborative group, with all contributors listed. A team building exercise will be undertaken by bringing members of the collaborative group together in a workshop. In the first workshop we will explicitly define the aims of the project, the target population, endpoints to be assessed, potential predictors and assess whether there is a hierarchy in these variables. We will standardise the definitions, coding and measurement techniques for the predictors and outcomes as much as possible between datasets. We will agree on a timetable and publication policy (policy of collaborative/group authorship will be confirmed). Our group has experience in undertaking such global collaborative exercise for IPD meta-analysis projects.

4.4 Data collection, entry and checking, and study quality assessment

The minimum data to be collected for IPD meta-analysis will be agreed at the first collaborators' workshop. All variables recorded, even those not reported in the published studies, will be considered for collection and for planning subgroup analyses with sufficient statistical power. We will build on the existing efforts undertaken in standardising the variables in the IPD meta-analysis projects on prediction of pre-eclampsia, in specific subgroups of women, such as those with previous history of pre-eclampsia and for particular tests such as uterine artery Doppler ultrasound in the second trimester.

Access to the existing IPD datasets will allow us to rapidly set-up the database for the proposed project. Researchers will be allowed to supply data in whatever way convenient to them. This project will take responsibility for converting the data to the required format. There will be flexibility in the format and method of transfer of primary data. All data supplied will be subjected to range and consistency checks. Any missing data, obvious errors, inconsistencies between variables or outlying values will be queried and rectified through input from the original authors. The predictors of the original dataset will be matched with the variables in our IPD, and where a direct match is not available in our data, the original variable will be replaced with a proxy variable to avoid having to drop the model.

The quality of each study will also be assessed at this stage, for example to evaluate the integrity of the data collection and ascertainment of the outcome. The risk of bias in individual studies will be assessed by tools such as PROBAST (which is currently being developed by co-investigators RR and KGM), and QUIPS. (55) Criteria considered will include population (adequate description, details on recruitment), test (adequately described, timing of tests, missing tests results), attrition (length of follow-up time, amount and timing of censoring, reasons for loss to follow-up), outcome measurement (adequately described, evaluated blind to the test) and analysis issues (data provided as categorised variables, inappropriate methods of measurement). Sensitivity of external validation performance of the developed models will be checked in relation to the risk of bias.

4.5 Data synthesis

i. Summarising the overall predictive accuracy of individual predictors of pre-eclampsia

Meta-analyses of the predictive accuracy of tests in pregnancy will be performed for early (<34 weeks), late (≥34 weeks), and any pre-eclampsia. The predictors will be identified from our systematic reviews in this area.

Initially, all studies will be reanalysed separately and the original authors asked to confirm accuracy of the individual study results, with any discrepancies resolved. Then, for each test and outcome separately, we will perform either a one-step or a two-step IPD meta-analysis to obtain the pooled accuracy effect. The one-step approach analyses the IPD from all studies simultaneously, whilst accounting for the clustering of patients within studies. In contrast, the two-step approach first estimates the accuracy of the test from the IPD in each study separately, and then pools them using a conventional meta-analysis of the predictive accuracy estimates obtained. Given the heterogeneity identified in our previous reviews, we also expect to observe significant heterogeneity in the IPD meta-analysis. Hence, we will use a random effects meta-analysis approach, which allows for between-study heterogeneity. If no between-study heterogeneity is found to exist, this model

suitably reverts to a fixed effect model. Heterogeneity will be summarised using the I^2 statistic (which provides the proportion of total variability that is due to between-study heterogeneity) and 95% prediction intervals

We will synthesise relative risks or odds ratios, with the binomial nature suitably modelled using, for example, a one-step logistic regression adjusting for clustering. For any time-to-event outcome, we will aim to fit a Cox regression model (after checking for proportional hazards) in each study and then synthesise the estimated hazard ratios obtained.

ii. Assessing the performance of existing predictive models

We will evaluate the performance of the identified (and relevant) published models based on our systematic review. (39)

External validation: The validation cohort will be from our large IPD database of the IPPIC Collaborative Network (details in Section 8.6 iii). For each external validation, we will quantify the predictive performance of the existing models, and assess the extent to which they need to be improved or tailored for the target population to assess the risk of early, late and any pre-eclampsia. For example, two recalibration techniques will be considered. This includes intercept or baseline hazard (depending on type of prediction model) and adjustment of individual predictor weights (regression coefficients). Using these data, the probability of early, late and any pre-eclampsia for each individual patient in our validation cohort will be calculated. We expect the sample sizes to be adequate; as for such validation often only one parameter (the linear predictor of the original model) is fitted, (56) with 100 events needed for validating dichotomous outcomes. Missing data will be analyzed using multiple imputation that accounts for potential between-study heterogeneity, conform to current guidelines. (57, 58)

The performance of the models will be assessed using discrimination and calibration statistics.(59) Discrimination describes the ability of the model to correctly distinguish those who will have an adverse outcome from those who will not. Calibration indicates the ability of the model to correctly estimate the absolute risks and will be examined using calibration plots. In a calibration plot the predictive risk will be 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-degree line. The calibration plot will be extended to a validation plot as a summary tool. (60, 61) Discrimination and calibration of the models for prediction of the risk in the validation cohort will be quantified, using C and D statistics (with 95% CI) for discrimination, and calibration slopes and intercepts (with 95% CI) for calibration. If needed, the existing models will be updated i.e. recalibrated (both in baseline risks or hazards and in predictor weights) to individual studies or populations.

iii. Improving the performance of prediction models using IPPIC-IPD

We will identify the relevant population from the IPPIC- IPD studies recruited, develop (or improve) and validate the models using the internal-external cross-validation (IECV) approach (as detailed below). A set of candidate predictors will be identified *a priori*, based on prior evidence and clinical judgement. A suitable multivariable modelling framework will be chosen, for example logistic regression for binary outcomes or a survival model for time-to-event outcomes, such as Cox regression or preferably a (flexible) parametric model. Intricate modelling decisions will be pre-defined, such as the handling of continuous predictors (i.e. fractional polynomial modelling), identification of non-linear trends, methods for dealing with partially and systematically missing data (i.e. multiple imputation), (62, 63) specification of the baseline hazard function in survival models, and dealing with heterogeneity and clustering in an IPD meta-analysis model. Shrinkage techniques to adjust for optimism in regression coefficients may also be incorporated to produce the final model. If data on determinants and outcome are derived from case-control studies, we will apply a weighting of the cases and controls for the inverse sampling fractions. We will explicitly study whether the various subtypes of pre-eclampsia (early and late pre-eclampsia; pre-eclampsia with and without complications) require different predictors and models. We will develop and externally validate, and if needed update new prediction strategies for outcomes for which there are no existing models, or for populations that require newly developed models if the existing ones do not suffice.

Validation and updating (if required) of the prediction models
Our developed models will be examined externally in each of the IPD studies by IECV approach as follows. Let there be IPD available from K studies. First, study 1 is excluded and the risk prediction model is developed using the remaining data (studies 2 to K). Study 1 can then be used to externally validate the model. This is then repeated, excluding study 2 rather than study 1 and fitting the model using studies 1 and 3 to K. Study 2 is then used to externally validate the model. This

process is continually repeated, each time omitting a different study, until the model has been fitted excluding each study once. This process therefore provides K values for each validation statistic of interest, one for each excluded study. If required, these validated prediction models will be updated (or recalibrated) to different subgroups of women.

We will ensure that each cycle of the IECV approach retains sufficient sample size for model development; in this manner, each cycle will retain the majority of the available IPD for model development, and so the final models produced in each cycle are likely to be very similar to each other. A consistent model development strategy will be used in each cycle of the IECV approach.

A wide range of validation statistics will be considered, focusing primarily on discrimination and calibration. Performance measures will include the C statistic, D statistic, calibration slope, calibration in the large, and the Brier score. Calibration plots will also be given to aid clinical interpretation.

iv. Examining heterogeneity and potential subgroup effects

The external validation performance will be investigated not just on average (i.e. the average across all IPD studies), but also in terms of the heterogeneity in performance across studies, settings, and clinically relevant subgroups (e.g. defined by treatment and populations). We will produce forest plots and meta-analyses for each validation statistic, (37) to summarise average performance and heterogeneity, with latter reported in terms of I-squared, tau-squared, and a 95% CI and PI (prediction interval) for the expected performance in a single population. (64, 65)

An ideal model will have little heterogeneity and consistently good performance. The further away from this ideal, the model is less reliable. For example, if the model performs well on average but there is large heterogeneity, this would mean that in some settings the model performs poorly. Calibration will also be examined across the range of clinically relevant values (e.g. across the entire age range), to check whether performance deteriorates for any subgroups. We will assess whether there is a differential accuracy in the performance of the models for early pre-eclampsia, late with and without complications.

v. Added value of novel biomarkers

Novel metabolic and micro-RNA based biomarkers are on the horizon supported by new mechanisms. (66) Models with and without such novel biomarkers will be compared in terms of their average external validation performance, and also the heterogeneity in their performance across studies, settings and subgroups.

vi. External validation of the IPPIC models

The fetal-medicine foundation group (FMF) led by Prof Kypros Nicolaides have established a cohort of studies on prediction of pre-eclampsia in the UK. We will externally validate the performance of the developed IPPIC models in this dataset of patients.

4.6 Sample size considerations

Early onset pre-eclampsia (0.5% of all pregnancies) is uncommon. In order to develop a sound prediction model, as a rule of thumb, we will need 10 events for each candidate predictor variable. Our IPD dataset is the largest of its kind world-wide, and most likely the only study that allows development of extensive, detailed and precise prediction models in women, both for early and late pre-eclampsia.

From our collaborators IPD datasets, we expect to have a sample size of at least 400,000 women, with at least 1000 women with early pre-eclampsia. This will enable us to develop and robustly validate the models with ± 20 determinants by IPD meta-analysis for the rare but clinically important outcome of early pre-eclampsia, and also for late and any pre-eclampsia. Data on clinical characteristics are available in over 400,000 women (≅ 1000 early; ≅4000 any pre-eclampsia), clinical and biochemical data in 300,000 women (≅750 early; ≅3000 any), both clinical and ultrasound data in 150,000 women (≅375 early; ≅1500 any) and in 80,000 women, data are available for clinical, biochemical and ultrasound markers ((≅200 early; ≅800 any). We have used conservative estimates of 0.25% for early pre-eclampsia.

5. Potential difficulties and solutions

The co-applicants are aware of the potential hurdles to be faced in the project. The IPPIC Collaborative Network has brought together a wide variety of international experts with varied research interests in translational medicine, basic science research and methodological expertise. While this is undoubtedly a great strength of the proposal, there is a risk that it could lead to a lack of consensus on the optimal way to handle and present data. We have taken this into account and ensured that frequent team building activities are undertaken, with the common goal of identifying a strategy to predict pre-eclampsia. Based on our experience in the current HTA i-WIP IPD that involves 37 teams, involvement of the collaborators in all aspects of the project such as the development of the proposal, standardisation of the data, and analysis plan are crucial to the success of the project. The support of GONET, the Global Obstetric Network and collaborators from other consortia such as SCOPE, Co-Lab and PRE-EMPT will be valuable in promoting consensus, and in aligning various national and international initiatives on the prediction of pre-eclampsia.

Our project involves multiple datasets acquired from studies with varied study design. The IPD meta-analysis will take this into account with adequate steps to standardise the data, and ensure that the findings are applicable to the relevant population(s). The team is experienced in collecting, cleaning and formatting large data needed for the IPD meta-analysis. The final limitation is the cost of the proposal, which is higher than what is usually incurred in a standard aggregate meta-analysis. We strongly believe that a standard aggregate meta-analysis will be very limited in its ability to change clinical practice (as has been demonstrated by the current lack of predictive model in use) whilst IPD meta-analysis provides valuable information, based on large number of individual data, and the findings can be applied very soon into clinical practice. Given the large number of data and models in this area, a further large primary study is likely to be more expensive and less feasible than the current project; and the aggregate meta-analysis is unlikely to minimise the current uncertainty faced regarding the performance of tests in predicting pre-eclampsia.

6. Dissemination

Dissemination of research findings is a key responsibility of the researcher. Apart from it being an ethical obligation, dissemination of the results to the following groups is necessary to facilitate rapid translation of relevant findings into clinical care where appropriate.
Funder: The findings will be provided as a detailed report to NIHR and other relevant agencies that fund the work. Any outputs as scientific publications, presentations and websites will highlight the support provided by the NIHR.
Scientific papers and presentations: Every effort will be made to ensure that the studies are conducted and reported with the highest standard necessary for publication in high impact journals. This is one of the principal factors that determine incorporation of findings into clinical guidelines. The findings will be disseminated to peers and experts through presentations in relevant specialty conferences and Network meetings.
Patient and Public: A regular newsletter will be sent to the collaborators updating and highlighting the work. We will provide the details of the findings in the APEC website.
Websites: The details of the project and findings will be provided through the institutional websites of the collaborators. Additionally, websites dedicated to collaborative endeavours such as GONET, SCOPE, PRE-EMPT will be vehicles for dissemination.
Mainstream and Social media: QMUL has an active press department to facilitate the research findings to the public by staging press releases that are relevant, factual and informative. The increasing integration of social media in our day today lives will be exploited to effectively disseminate the findings through applications such as Twitter and LinkedIn.
Professional Societies: Through existing links, the findings will be disseminated to the Association of Medical Royal Colleges (AoMRC), Royal College of Obstetricians and Gynaecologists (RCOG), Royal College of Midwifery and Nursing (RCM), Royal College of General Practitioners (RCGP) and British Maternal Fetal Medicine Society (BMFMS).

7. Contribution to Collective Research Effort

Pre-eclampsia continues to be a research priority area. In recent years there have been considerable advances in the evaluation of individual tests, including novel biomarkers and ultrasound techniques to identify those women at risk of pre-eclampsia. Despite these advances, early identification of mothers at risk in clinical practice, especially for the early onset disease, still poses considerable challenges. It is well recognised that under the umbrella of pre-eclampsia, there are various subtypes, with variation in their presentation, their association with predictive factors and outcomes. Many networks such as

the Co-Lab, SCOPE, STORK and PRE-EMPT have already joined forces in the standardisation of the definitions, collection of relevant datasets and outcomes. Our proposal is collaborative and complementary to the above efforts and involves the leading researchers active in the above endeavours. In addition to the access to the robust, large databases, the project provides a platform for leading global researchers in the field of pre-eclampsia, to develop and adopt a unified prediction model. Furthermore, development of the central repository will enable future work to be seamlesslessly continued, by incorporating emerging data on new biomarkers, and updating the developed models beyond the lifetime of the project.

The recent NIHR EME call has commissioned a primary study on the prediction of pre-eclampsia. We will work closely with the successful applicants to ensure that the research output benefits from incorporation of the study findings within our IPD framework. If this is not feasible within the lifetime project, we will ensure that steps are taken to enable such a plan in the future, by standardising the relevant databases.

The NICE guidelines and ACOG have called for predictive tests or strategies to identify women at risk of various subtypes of pre-eclampsia, particularly the early onset type. Our proposal, will focus in this area, and develop and assess the performance of a prediction model for the early onset disease, which has not been assessed to-date due to lack of sample size.

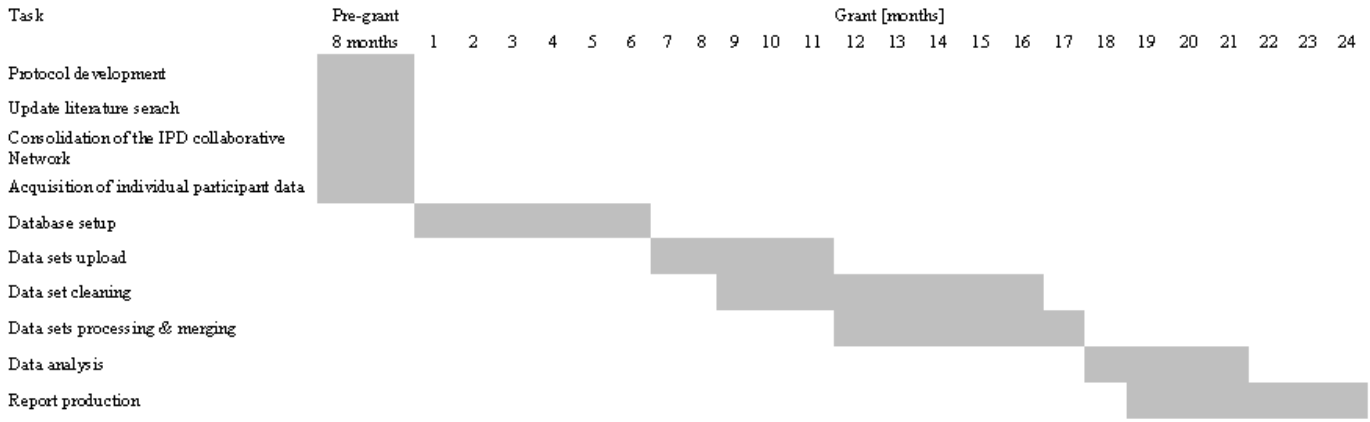
Identification of subsets of women who are at high risk of pre-eclampsia, will allow us to evaluate whether targeted treatment of these high groups with aspirin will improve the outcome. We will liaise with the PARIS Collaborative group, that has access to the IPD on aspirin treatment to prevent to identify those groups of women who will benefit the most.

Expected impact: Once completed the findings will be disseminated to healthcare policy makers through the HTA report, national guidelines, publications in peer reviewed journals and presentations in national and international conferences. We anticipate the findings of this project to provide specific national and international recommendations on early identification of women at risk of pre-eclampsia. The Chief Investigator will work closely with the collaborative partners and co-ordinate dissemination of data from this trial. All publications using data from this trial to undertake original analyses will be submitted to the Project Steering Committee (PSC) for review before release. To safeguard the scientific integrity of the trial, data will not be presented in public before the main results are published without the prior consent of the PSC.

8. Project time table

Fig 2 shows the project timetable and milestones for IPD meta-analysis. Based on our current experience on IPD meta-analysis (HTA No. 12/01/50), we expect a large proportion of time to be spent in obtaining the data from the individual collaborators and collaborative groups. This phase of the project requires minimal monetary support. We have therefore allocated the first eight months of the pre-grant phase for data acquisition. We have carefully evaluated the on-going work and the level of staffing within our departments and feel that with some readjustments we would be able to commence the work in Jan 2015, with the grant phase starting in Oct 2015.

Fig 2. Project timetable



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