PROTOCOL

Pre-eclampsia in Hospital: Early Induction or Expectant Management

ISRCTN01879376

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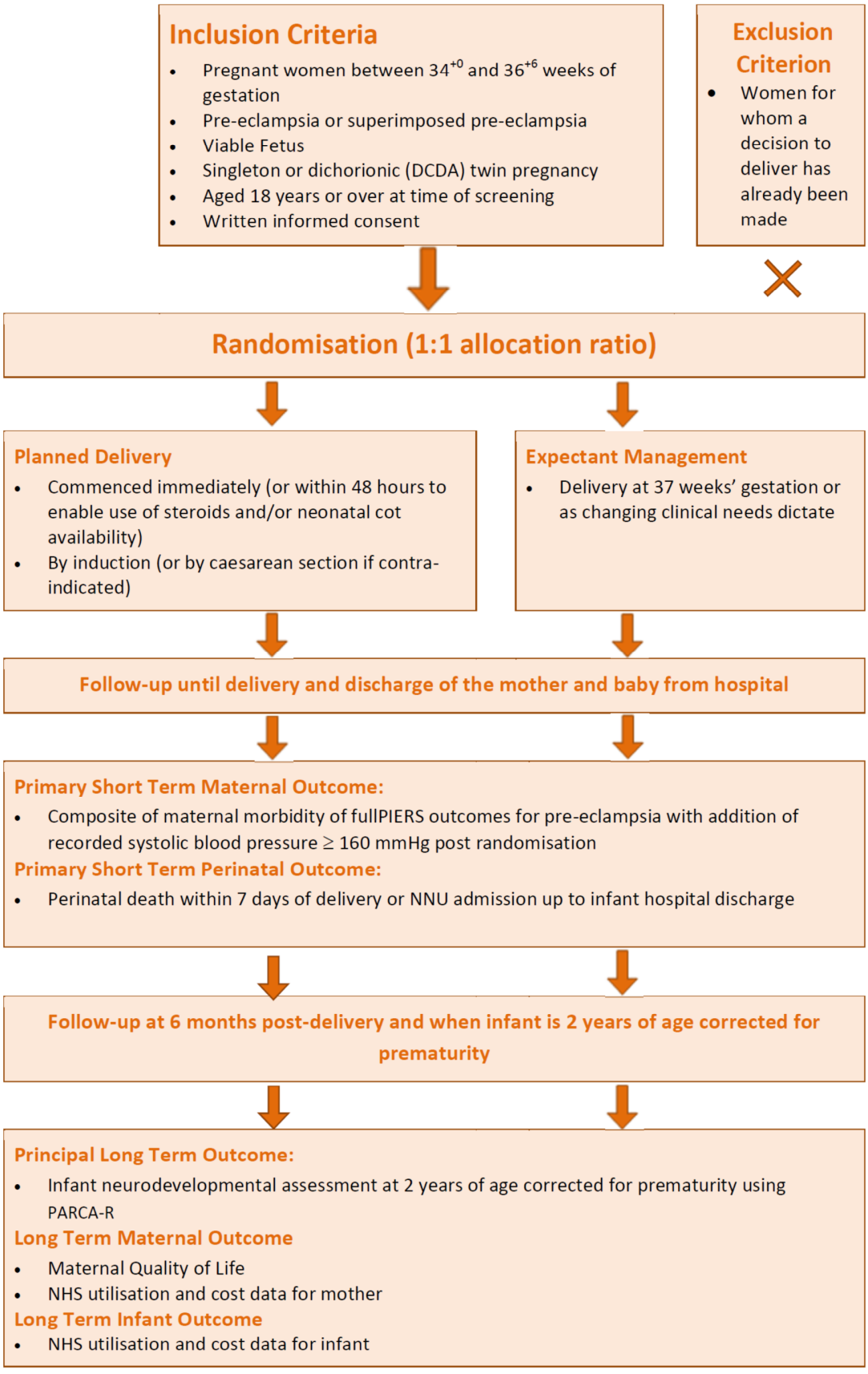
Inclusion Criteria
Pregnant women between 34+0 and 36+6 weeks of gestation
Pre-eclampsia or superimposed pre-eclampsia
Viable Fetus
Singleton or dichorionic (DCDA) twin pregnancy
Aged 18 years or over at time of screening
Written informed consent
Exclusion Criterion
Women for whom a decision to deliver has already been made
Randomisation (1:1 allocation ratio)
Planned Delivery
Commenced immediately (or within 48 hours to enable use of steroids and/or neonatal cot availability)
By induction (or by caesarean section if contra-indicated)
Expectant Management
Delivery at 37 weeks' gestation or as changing clinical needs dictate
Follow-up until delivery and discharge of the mother and baby from hospital
Primary Short Term Maternal Outcome:
Composite of maternal morbidity of fullPIERS outcomes for pre-eclampsia with addition of recorded systolic blood pressure ≥ 160 mmHg post randomisation
Primary Short Term Perinatal Outcome:
Perinatal death within 7 days of delivery or NNU admission up to infant hospital discharge
Follow-up at 6 months post-delivery and when infant is 2 years of age corrected for prematurity
Principal Long Term Outcome:
Infant neurodevelopmental assessment at 2 years of age corrected for prematurity using PARCA-R
Long Term Maternal Outcome
Maternal Quality of Life
NHS utilisation and cost data for mother
Long Term Infant Outcome
NHS utilisation and cost data for infant

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Title of Clinical Trial	Pre-eclampsia in Hospital: Early Induction or Expectant Management
Protocol Acronym	PHOENIX
Study Phase	Phase III
Sponsor Name	King's College London
Chief Investigators	Professor Andrew Shennan/Dr Lucy Chappell
REC number	13/SC/0645
Medical Condition or Disease Under Investigation	Women 34^{+0} to 36^{+6} weeks of gestation with pre-eclampsia
Purpose of Clinical trial	To determine whether delivery in women with pre-eclampsia between 34^{+0} and 36^{+6} weeks of gestation reduces maternal complications without short and long term detriment to the infant compared to expectant management and delivery at 37 weeks of gestation.
Primary Objective	The primary short term objective of the study is both: • To determine if delivery in women with pre-eclampsia between 34^{+0} and 36^{+6} weeks of gestation reduces adverse maternal outcomes up to post-natal discharge of the mother from hospital And: • To determine the impact of early delivery on the incidence of perinatal deaths within 7 days of delivery (excluding deaths due to congenital anomaly) or neonatal unit (NNU) admissions up to time of infant hospital discharge The primary long term objective is; • To determine the impact of both management strategies on infant neurodevelopmental status at 2 years of age corrected for prematurity
Secondary Objective(s)	The secondary objectives of the study are: • To investigate the effect of early delivery on other short term outcomes for both mother and infant • To assess the impact of both management strategies on maternal and infant health economic outcomes. • To evaluate maternal quality of life prior to delivery then at 6 months and 2 years
Trial Design	This will be a randomised controlled trial of planned immediate delivery (up to 48 hours) after randomisation of women between 34^{+0} and 36^{+6} weeks of gestation versus expectant management and delivery at 37 weeks of gestation in women with pre-eclampsia. The main study will be preceded by a pilot study to determine whether the study design and procedures will enable the objectives and recruitment targets to be met. The study will be conducted at 25 centres across England; 6 centres will be involved in the pilot study.
Outcomes	**Primary outcomes:** Primary short-term maternal outcome: Composite of maternal morbidity of fullPIERS outcomes with the addition of recorded systolic blood pressure ≥160 mmHg (with or without medication) post randomisation.

	Primary short term perinatal outcome: Composite of perinatal deaths (antenatal/intrapartum stillbirths and deaths within 7 days of delivery but not deaths due to congenital anomalies) or NNU admissions to infant hospital discharge. Primary long term infant outcome: Neurodevelopmental assessment at 2 years of age corrected for prematurity using PARCA-R Parent Report Composite. **Secondary outcomes:** Secondary short term maternal outcomes Individual components of the composite primary outcome plus; • Use of anti-hypertensive drugs • Progression to severe pre-eclampsia post-randomisation (defined as systolic blood pressure ≥160 mmHg, platelet count <100 x 10^9/litre, abnormal liver enzymes (ALT or AST >70 iu/litre)) • Estimated fetal weight (on ultrasound scan) <10^{th} centile post-enrolment • Absent or reversed end diastolic flow (on umbilical artery Doppler) • Time and mode of onset (spontaneous, induced or pre-labour caesarean section) and mode of delivery (spontaneous vaginal delivery, assisted vaginal delivery, caesarean section) • Confirmed thromboembolic disease requiring anticoagulation up to post-natal discharge • Confirmed sepsis (positive blood or urine cultures) up to post-natal discharge • Primary and additional indications for delivery in expectant management arm (maternal hypertension not controlled by maximal therapy, biochemical abnormality, haematological abnormality, fetal compromise on ultrasound scan, fetal compromise on cardiotocography, severe maternal symptoms, 37 weeks' gestation or specified other) • Placental Abruption Secondary short term perinatal outcomes • Stillbirth post randomisation • Neonatal death prior to hospital discharge • Admissions to NNU • Number of nights in each category of care (intensive, high dependency, special, transitional and normal) • Total number of nights in hospital • Birth weight (g) • Customised/population birth weight centile (GROW) • Birth weight <10^{th} and <3^{rd} customised/population centile • Gestational age at delivery • APGAR score at 5 minutes post birth • Umbilical arterial and venous pH (and base excess) at birth • Need for supplementary oxygen prior to discharge • Number of days when supplemental oxygen is required • Need for ventilation support (CPAP/high flow/endotracheal ventilation) • Pneumothorax (confirmed on chest X-ray) • Abnormal cerebral ultrasound scan

	• Confirmed sepsis (positive blood or cerebrospinal fluid cultures) • Necrotising enterocolitis (Bell's stage 2 and 3) • Seizures (confirmed by EEG or requiring anticonvulsant therapy) • Encephalopathy grade (worst at any time: mild, moderate, severe) • Hypoglycaemia (blood glucose <2.6 mmol/l on two or more occasions) • Other indications and main diagnoses resulting in NNU admission. • Exclusively breast-fed at discharge from the neonatal unit. Secondary long term maternal outcomes (assessed at 6 months and 2 years of age corrected for prematurity) • Maternal physical and mental health using the validated SF-12 questionnaire. Health economic/ quality of life outcomes • Quality of life using the validated quality of life questionnaire EQ-5D immediately after randomisation, at 6 months and when the infant is 2 years of age corrected age for prematurity. • Hospital attendances, nights and diagnostic tests from randomisation until delivery • Cost of delivery • Cost of neonatal care (hospital admissions, surgery and diagnostic tests) • Retrospective 6 month health/social care use by mother and infant at 6 months and 2 years. • EQ-5D for the calculation of maternal quality adjusted life years (QALYs).
Sample Size	900 women with pre-eclampsia between 34^{+0} and 36^{+6} weeks of gestation.
Summary of eligibility criteria	Inclusion criteria: • Pregnant women between 34^{+0} and 36^{+6} weeks of gestation inclusive • Pre-eclampsia (as defined by International Society for the Study of Hypertension in Pregnancy {ISSHP} 2014 statement) • Singleton or dichorionic diamniotic (DCDA) twin pregnancy • Viable fetus • Aged 18 years or over at time of screening • Able to give written informed consent Exclusion criterion: • Women for whom a decision has already made to deliver within the next 48 hours
Interventions	Planned immediate delivery (typically by induction with prostaglandins, or by Caesarean section if induction contra-indicated) undertaken as soon as feasible (up to 48 hours) after randomisation. Use of steroids will be at the discretion of the clinician. If induction fails, subsequent management options including re-induction and caesarean section should be considered. Treatment and care should take into account a woman's needs and preferences.
Version and date of final protocol	Version 2, dated 16 September 2014
Version and date of protocol amendments	Version 1, dated 11 October 2013 – Original approved version Version 2, dated 16 September 2014

2. Abbreviations

ACOG	American College of Obstetricians and Gynaecologists
AE	Adverse Event
APEC	Action on Pre-eclampsia
ARR	Absolute Risk Reduction
BP	Blood Pressure
CI	Chief Investigator
CIG	Co-Investigator Group
CSF	Cerebrospinal Fluid
CTRG	Clinical Trials and Research Governance, University of Oxford
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
FTE	Full Time Equivalent
GCP	Good Clinical Practice
GP	General Practitioner
HELLP	Hemolysis, Elevated Liver enzymes and Low Platelet count
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
ICF	Informed Consent Form
IRAS	Integrated Research Application System
ISF	Investigator Site File
ISSHP	International Society for the Study of Hypertension in Pregnancy
LRMN	Local Research Midwife or Nurse
NEC	Necrotising Enterocolitis
NHSIC MRIS	National Health Service Information Centre, Medical Research Information Service
NNU	Neonatal Unit
NICE`	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NPEU CTU	National Perinatal Epidemiology Unit Clinical Trials Unit
NRES	National Research Ethics Service
ONS	Office for National Statistics
PARCA-R	Parent Report of Cognitive Abilities-Revised
PI	Principal Investigator

PIL	Participant Information Leaflet
PMA	Post-menstrual Age
PMG	Project Management Group
PRC	Parent Report Composite
PROM	Patient Reported Outcome Measures (questionnaire)
PSS	Personal Social Services
QALY	Quality Adjusted Life Years
R&D	NHS Trust Research and Development Department
REC	Research Ethics Committee
RR	Response Rate
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SOP	Standard Operating Procedure
SVD	Spontaneous Vaginal Delivery
TRM	Trial Research Midwife
TMF	Trial Master File
TSC	Trial Steering Committee

3. Background & Rationale

In the UK, 10-15% of pregnant women develop hypertension in pregnancy, and 2-8% pre-eclampsia. Pre-eclampsia is a multisystem disorder, characterised by placental and maternal vascular dysfunction which is associated with significant morbidity and mortality for the mother and infant. Adverse outcomes of pre-eclampsia include severe hypertension, stroke, renal and hepatic injury, haemorrhage, fetal growth restriction and even death[1].

Early delivery may be indicated to prevent maternal and infant morbidity. Standard management of pre-eclampsia involves close monitoring whilst taking into consideration the gestational age of the fetus, fetal well-being and rate of progression of maternal disease to instigate timely delivery if needed. When a diagnosis of pre-eclampsia is made at or beyond 37 weeks of gestation, it is currently recommended that delivery be induced, since maternal and fetal risks can be significantly reduced without any apparent added risk associated with the intervention.

Nearly half (40%) of all pre-eclampsia occurs preterm (before 37 weeks'), and these cases will have the most serious outcomes. Using data from previous pre-eclampsia trials[2, 3], we have estimated that 33% of women with pre-eclampsia will present between 34^{+0} and 36^{+6} weeks of gestation and not require immediate delivery.

Delivery before 34 weeks' (meta-analysis of two randomised controlled trials, n=133)[4] demonstrates worse neonatal risk (Hyaline Membrane Disease risk ratio (RR) 2.3 (95% CI 1.39 to 3.81) and necrotising enterocolitis (NEC) RR 5.54 (95% CI 1.04 to 29.56)) without sufficient benefit in maternal outcomes.

The optimal time to instigate delivery to prevent morbidity when pre-eclampsia occurs between 34 and 37 weeks of gestation, without increasing problems related to infant immaturity or complications, remains unclear. Current management involves close surveillance and action only when evidence of impending serious morbidity becomes apparent (e.g. deteriorating maternal or fetal conditions). As this may be rapid or unexpected, routine delivery beyond 34 weeks' may be valuable. Neonatal and infant mortality and morbidity may, nonetheless, be significant following delivery between 34 and 37 weeks of gestation. Respiratory function may be adversely affected, leading to hypoxic insult and as a result possible brain damage and chronic lung disease; however, this may be related to the underlying pathology that precipitated delivery i.e. placental insufficiency and hypoxia. However, neurodevelopmental morbidity and risk of growth restriction and death may be reduced by early delivery, lowering the risk of behavioural problems and intellectual

impairment in later life, and adverse events related to expectant management (including stillbirth and worsening growth restriction) may be decreased.

It is highly likely that routine delivery will reduce the maternal risk, as delivery cures pre-eclampsia. There is therefore a need to compare a policy of planned delivery between 34^{+0} and 36^{+6} weeks of gestation with that of expectant management, with particular regard to the benefit to the mother, whilst ensuring no increased risk to the baby, particularly in relation to longer neurodevelopmental outcomes.

This aim of this study is to remove the uncertainty about the timing of delivery in pregnancies affected by pre-eclampsia between 34 and 37 weeks of gestation. The study will be conducted according to the principles of the Declaration of Helsinki (dated 2008) and all applicable regulatory requirements. This protocol will be submitted to a NHS Research Ethics Committee (REC) and NHS Trust Research and Development Departments for approval.

4. Trial Objectives, Design and Statistics

4.1. Trial Objectives

The aim of this study is to determine whether planned delivery in women with pre-eclampsia between 34^{+0} and 36^{+6} weeks of gestation reduces maternal adverse outcomes without substantial worsening of neonatal/infant outcomes, compared with the current practice of expectant management and delivery at 37 weeks of gestation.

The primary objectives of the study are;

- To determine if planned early delivery for women with pre-eclampsia between 34^{+0} and 36^{+6} weeks of gestation reduces adverse maternal outcomes based on a composite listed in the fullPIERS[5] paper with addition of recorded systolic hypertension (systolic blood pressure (SBP) of ≥160 mmHg), as highlighted in the triennial Confidential Enquiry into Maternal Deaths (2006-8)[9].
- To evaluate the impact of the intervention on short and long term neonatal outcomes. Short term outcomes will be as assessed by a composite of perinatal deaths (antenatal/intrapartum stillbirths plus neonatal deaths within 7 days, but not deaths due to congenital anomaly) or neonatal unit (NNU) admissions up to time of infant hospital discharge.
- To determine the impact of both management strategies on infant neurodevelopmental status at 2 years

of age corrected for prematurity using PARCA-R[6] Parent Report Composite.

The secondary objectives of the study are;

- To investigate the effect of intervention on other secondary maternal and neonatal short-term outcomes.
- To assess the impact of both management strategies on health care resource use and quality adjusted life years (QALYs): in terms of the total number of nights for mother and neonate, including intensive care use from baseline until delivery; health care resource use for mother and infant retrospectively at 6 months and 2 years post-delivery covering the previous 6 months; EQ-5D[7] for the mother at baseline, 6 months and 2 years corrected age.
- To assess the impact of both management strategies on health economic outcomes: for mother and infant in terms of number of nights in each hospital setting; cost data to post-natal hospital discharge; health/social care use (using client Socio-Demographic and Service Receipt Inventory) at 6 months and 2 years corrected age post-delivery.
- To evaluate quality of life using questionnaires immediately after randomisation and at 6 months and 2 years corrected age

4.2. Trial Design

This will be a pragmatic, multicentre, randomised controlled trial of planned delivery versus expectant management in 900 women with pre-eclampsia between 34^{+0} and 36^{+6} weeks of gestation inclusive.

The trial will be conducted in approximately 25 consultant-led maternity units across England. A pilot phase will initially be run, involving 6 centres over a period of 6 months to establish whether the procedures and assessments are conducive to achieving the recruitment and other objectives of the study.

Recruitment is anticipated to take 36 months based on an assumption that each centre will on average recruit 1.5 women per month, with some allowance for unforeseen events and centres recruiting slower than expected. The study, including set-up, pilot phase, completion of mother and infant follow-up and reporting, is anticipated to take 72 months to complete.

Both the maternal and neonatal short term outcomes will be determined quickly as the time period from randomisation to outcome collection will not exceed 8 weeks (delivery + 28 days post-birth) and in many cases will be less. If the processes are shown to work in the pilot phase, recruitment to the main trial will

proceed with no break and data from the pilot phase will be analysed together with the main trial data collected.

An economic evaluation from the perspective of the National Health Service (NHS) and Personal Social Services (PSS) will be conducted alongside the main trial. Data on health and social care resource utilisation will be collected using patient administration systems, maternity and neonatal databases and logs of tests and procedures, together with data from questionnaires administered at 6 months and 2 years, capturing health and social care resource use for mother and child in the previous 6 months. No information on health or social care resource use will be collected from 6 to 18 months to reduce responder burden. Health and social care services will be costed using national published sources (NHS reference costs, Unit Costs of Health and Social Care (Personal Social Services Research Unit, British National Formulary). Quality adjusted life years (QALYs) for the mother will be calculated from EQ-5D[7] utility scores collected at baseline, 6 months and two years and the SF-12[8] questionnaire also at 6 months and two years These will be calculated as the area under the curve, adjusting for baseline differences using regression analysis. Differences in infant mortality between the two groups will be captured by assuming full health up to 2 years for surviving infants. A sensitivity analysis will be conducted where infant utility scores will be adjusted for any health or developmental problems observed over the 2 years. Where possible these values will be obtained from the literature. The final results of the economic evaluation analyses will be expressed as the mean incremental cost per mean QALY gained from baseline until 2 years follow up. Cost and QALYs in the second year will be discounted in line with NICE guidance[10]. Confidence intervals for costs and QALYs will be calculated using bootstrapping, the results of which will be used to construct cost-effectiveness planes and interpreted using cost-effectiveness curves. One, two and multi-way sensitivity analyses will be conducted for any assumptions made.

4.3. Sample Size

The sample size for the study is calculated on the ability to observe a clinically significant risk reduction in the primary short term maternal composite outcome of maternal morbidity and recorded systolic blood pressure of ≥160 mmHg, measured after randomisation.

Superiority hypothesis in maternal outcome

Based on data from the PELICAN study[2], 49 of 115 women with suspected pre-eclampsia (42.6%, 95% CI 33.4% to 52.2%) enrolled between 34^{+0} and 36^{+6} weeks of gestation developed maternal morbidity and hypertension of ≥160 mmHg. Therefore, assuming an expected adverse maternal outcome incidence of 43% in the control group (expectant management), a sample size of 850 women will be needed to demonstrate a relative risk reduction of 25% to 32.25% (deemed clinically significant) with a 2-sided 5% significance level in the planned delivery group. Taking into account a 5% loss of women in follow-up, the overall target sample size for the study is 900 women (450 per group).

Non-inferiority hypothesis in neonatal outcome

A sample size of 850 women will result in approximately 860 live births (assuming 1 in 80 pregnancies are twin pregnancies). The PELICAN study[2] reported that a composite of perinatal death or any neonatal admission occurred in 27 of 115 infants (23.5%; 95% CI 16.1% to 32.3%). Assuming a composite adverse neonatal outcome incidence of 24% in the control group (expectant management), a sample size of 860 (430 per group) will achieve 93% power to detect a non-inferiority margin of difference in incidence of no less than 10% and 78% power to detect a margin of no less than 8%.

In order to examine the component of perinatal death specifically, using Office for National Statistics (ONS) data for all babies born in England and Wales in 2010[11], of all pre-term births, 3.1% (212/6872) were perinatal deaths (stillbirth, early neonatal, late neonatal). A similar incidence is expected in women with pre-eclampsia as those deaths prevented by increased surveillance would be offset by pre-eclampsia associated co-morbidities of fetal growth restriction and placenta abruption. Thus, for the component of perinatal death, assuming a control group incidence of 3%, a sample size of 430 in each group would achieve 90% power to detect a non-inferiority margin of difference in incidence of no less than 6%. A non-inferiority margin of difference in incidence of no less than 5% would be detected with 80% power. If the control group incidence was 2%, then a margin of no less than 5.7% could be detected.

For the component of neonatal unit admission, assuming a control group incidence of 21%, a sample size of 430 in each group will achieve 90% power to detect a non-inferiority margin of difference in incidence of no less than 11%. A non-inferiority margin of difference in incidence of no less than 9% would be detected with 80% power.

Assuming a loss to follow-up at two years of 20% we should obtain long term outcomes for approximately 690 infants (345 per group assuming no difference in the loss to follow-up between the groups). The PARCA-R[6] questionnaire provides a composite score for neurodevelopment with a standardised mean of 100 and standard deviation of 15. With a one-sided significance level of 2.5%, under a non-inferiority hypothesis, a sample size of 345 in each group achieves a 94% power to detect a non-inferiority margin of difference in the mean PARCA-R score of no less than 4 points (1/4 of a standard deviation). A margin of no less than 3 points can be detected with 75% power.

4.3.1. Randomisation

The allocation ratio of intervention (planned delivery) to control (expectant management) will be 1:1.

Randomisation will be managed via a secure web-based randomisation facility hosted by MedSciNet with telephone back-up available at all times. A minimisation algorithm will be used to ensure balance between the groups with respect to the collaborating hospital, singleton/twin pregnancies, severity of hypertension in 48 hours prior to enrolment (highest systolic blood pressure with or without medication: <=149 mmHg, 150-159 mmHg, ≥160 mmHg) parity, previous caesarean section and gestational age at randomisation (34/35/36 weeks). MedSciNet will write the randomisation program and hold the allocation code.

Following randomisation, the consultant obstetrician will then arrange for delivery or ongoing expectant management as the randomisation indicates.

4.3.2. Analysis

The primary analysis will be by intention to treat for all outcomes, with participants analysed in the groups to which they are assigned regardless of deviation from the protocol or intervention received. If women in the expectant management arm are delivered prior to 37 weeks of gestation due to clinical need (i.e. with new indications for delivery by NICE guidelines[12,13]) this will not be considered a protocol deviation.

All outcomes will be analysed adjusting for minimisation factors at randomisation[14]. Binary outcomes will be analysed using log binomial regression models. Results will be presented as adjusted risk ratios with associated confidence intervals. If the model does not converge, log Poisson regression models with robust variance estimation will be used[15]. Continuous outcomes will be analysed using linear regression models. Results will be presented as differences in means and associated confidence intervals. 95% confidence intervals will be presented for all primary outcomes and 99% for all secondary outcomes.

For the analysis of perinatal outcomes the adjusted analysis will also account for the correlation of outcomes in twins included in the trial by adjusting standard errors for clustering by mother. Pre-specified sub-group analysis will be undertaken for parity, mild versus all other degrees of hypertension and gestation at the time of randomisation and for singleton vs. twin pregnancy. The consistency of the effect of planned delivery vs. expected management across subgroups will be assessed using the standard statistical test of interaction (or test for trend where appropriate). Results will be presented as risk ratios with confidence intervals. A sensitivity analysis will be conducted on both co-primary outcomes excluding women who do not receive the allocated intervention as per protocol.

Lost to short term follow-up is expected to be about 5%. A sensitivity analysis will be conducted on the short term primary outcomes using multiple imputation methods to impute missing data, assuming that the outcome is not linked to the reason for being lost to follow-up (i.e. missing at random).

Loss to long term follow-up is expected to be around 20%. Babies for whom no 2 year follow-up data are received will be compared to babies with 2 year data on demographic and clinical characteristics as well as short term outcomes. Severity of disability is expected to be linked to loss to long term follow-up and so imputation techniques will not provide meaningful information. For partially complete data collection forms received, a sensitivity analysis will be performed using multiple imputation methods to impute missing data under the assumption that the data are missing at random.

Each centre will be asked to maintain a screening log of all women presenting with pre-eclampsia, that will collect their basic demographic data together with their eligibility to allow an assessment of generalizability. Women deciding not to take part in the trial will be asked for permission to collect minimal information about their baby's birth, this would be limited to mode of delivery, infant sex, survival status, weight and gestational age.

5. Selection and Withdrawal of Participants

5.1. Inclusion Criteria

Women who meet the following criteria will be eligible for enrolment into the study;

- Pregnancy of between 34^{+0} and 36^{+6} weeks of gestation inclusive (see note below on determination of gestational age)
- Pre-eclampsia

  For the purposes of this study; pre-eclampsia is defined by the ISSHP 2014[16] statement as meeting the following criteria after 20 weeks' gestation;

Diastolic blood pressure (BP) ≥90 mmHg (twice, ≥4 hours apart) (or diastolic BP >=110 mmHg on one occasion (ACOG[17] criterion))

- o and one or more of the following:
  - Proteinuria (≥0.3 g/day by 24-hour urine collection, or ≥30 mg/mmol by spot urinary protein creatinine ratio)
  - Thrombocytopenia (platelet count <150 x 109/L)
  - Renal insufficiency (creatinine ≥90 µmol/L)
  - Impaired liver function (ALT or AST >70 IU/L)
  - Fetal growth restriction (EFW <10th centile confirmed by ultrasound)

- Superimposed pre-eclampsia
- Singleton or dichorionic diamniotic twin pregnancy
- Viable fetus
- Aged 18 years or over at the time of screening
- Able to give written informed consent

Women with any other co-morbidity (including pre-existing hypertension, diabetes etc.) or having had a previous caesarean section or with the fetus in any position will be eligible.

5.1.1. Determination of gestational age

For all calculations relating to gestational age (eligibility for enrolment, gestational age at delivery), gestational age will be calculated based on the following hierarchical model, as set out in the NICE guidelines for antenatal care:

i) From crown-rump length measurement on early ultrasound scan between 10+0 weeks and 13+6 weeks

ii) From head circumference on ultrasound scan if crown–rump length is above 84 mm

5.2. Exclusion Criterion

Women will be excluded from participation in the study if;

- A decision has already been made to deliver within the next 48 hours

5.3. Study Periods

A woman's participation in the study may be from 34 weeks of gestation until their child reaches 2 years of age corrected for prematurity; thus a maximum duration of 28 months. For regulatory purposes the end of the study is defined as the last child's assessment at 2 years of age corrected for prematurity. An End of Trial Declaration will be made to the approving Research Ethics Committee (REC) within 3 months of this date.

5.4. Withdrawal of Participants

Women will be able to withdraw their consent at any time without giving a reason. Withdrawal from the study will not affect their (or their baby's) on-going care and there will be no requirement for any study related follow-up safety assessments. Women may also be withdrawn from the study if their clinician feels it is in their baby's best interests. If consent is withdrawn, permission will be sought to compete and use data up to the point of withdrawal from the study.

There is no requirement to replace women who do not complete the study or need to be delivered prior to their planned delivery date.

6. Assessment of Outcomes

6.1. Primary Outcomes

Outcomes of early delivery (prior to 37 weeks of gestation) will be assessed by computing;

- A composite of maternal morbidity using the fullPIERS list of outcomes (see the PHOENIX trial handbook) at randomisation and incidence of systolic blood pressure (with or without medication) of ≥160 mmHg post randomisation
- A composite of perinatal deaths (antenatal/intrapartum stillbirths and deaths within 7 days of delivery but excluding deaths due to congenital anomalies) or NNU admissions to infant hospital discharge.
- Infant neurodevelopment at 2 years of age corrected for prematurity.

All primary outcomes will be evaluated by an adjudication panel masked to treatment allocation arm.

6.2. Secondary Outcomes

Secondary maternal outcomes will include assessment of;

- Severe hypertension post randomisation (systolic BP ≥160 mmHg with or without medication on at least one occasion)
- Use of anti-hypertensive drugs
- Progression to severe pre-eclampsia (defined as systolic blood pressure ≥160 mmHg, platelet count <100 x 10^9/litre, abnormal liver function enzymes (ALT or AST >70 iu/litre))
- Estimated fetal weight (on ultrasound scan) <10^{th} centile post-enrolment
- Absent or reversed end diastolic flow (on umbilical artery Doppler)
- Time and mode of onset (spontaneous, induced or pre-labour caesarean section) and mode of delivery (spontaneous vaginal delivery, assisted vaginal delivery, caesarean section)
- Confirmed thromboembolic disease requiring anticoagulation up to post-natal discharge

- Confirmed sepsis (positive blood or urine cultures) up to post-natal discharge
- Primary and additional indications for delivery in the expectant management arm (maternal hypertension not controlled by maximal therapy, biochemical abnormality, haematological abnormality, fetal compromise on ultrasound scan, fetal compromise on cardiotocography, severe maternal symptoms, 37 weeks of gestation or specified other)
- Placental Abruption

Secondary perinatal outcomes will include assessment of;

- Stillbirth post randomisation
- Neonatal death prior to hospital discharge
- admissions to NNU
- Number of nights in each category of care (intensive, high dependency, special, transitional and normal)
- Total number of nights in hospital
- Birth weight (g)
- Customised/ population birth weight centile (GROW)
- Birth weight <10th and <3rd customised/ population centile
- Gestational age at delivery
- APGAR score at 5 minutes post birth
- Umbilical arterial and venous pH (and base excess) at birth
- Need for supplementary oxygen prior to discharge
- Number of days when supplemental oxygen is required
- Need for ventilation support (CPAP/high flow/endotracheal ventilation)
- Pneumothorax (confirmed on chest X-ray)
- Abnormal cerebral ultrasound scan
- Confirmed sepsis (positive blood or CSF cultures)
- Necrotising enterocolitis (Bell's stage 2 and 3)
- Seizures (confirmed by EEG or requiring anticonvulsant therapy)
- Encephalopathy grade (worst at any time: mild, moderate, severe)
- Hypoglycaemia (blood glucose <2.6 mmol/l on two or more occasions)
- Other indications and main diagnoses resulting in NNU admission.

- Exclusively breast-fed at discharge from the neonatal unit.

Secondary long term maternal outcomes will include assessment of;

- Quality of maternal physical and mental health using the validated questionnaire SF-12 at 6 months and when the infant is 2 years of age corrected for prematurity.

Secondary health economic and quality of life outcomes will include assessment of:

- Quality of life using the validated quality of life questionnaire EQ-5D[7] immediately after randomisation, at 6 months and when the infant is 2 years of age corrected for prematurity.
- Hospital attendances, nights and diagnostic tests from randomisation until delivery
- Cost of delivery
- Cost of neonatal care (hospital admissions, surgery and diagnostic tests)
- Retrospective 6 month health/social care use by mother and infant at 6 months and 2 years.
- EQ-5D[7] for the calculation of maternal quality adjusted life years (QALYs).

6.3. Study Procedures (for Assessing Outcomes)

Procedure	Screening[1]	Randomisation	Delivery[2]	Post-natal Hospital Discharge	6 Months Following Birth	Infant 2 Years of Age Corrected for Prematurity
Obstetric Medical History	✓					
Consent	✓					
Demography	✓					
Blood Pressure	✓[3]	✓[4]	✓[5]	✓[6]		
Haematology and Biochemistry	✓[7]	✓[8]		✓[9]		
Reason for Delivery			✓			
Mode of Delivery			✓			
Birth weight			✓			
Umbilical Venous and Arterial pH			✓			
APGAR Assessment			✓			
SAEs[10]	✓	✓	✓	✓		
Concomitant Medication[11]	✓	✓	✓	✓		
PARCA-R[6] Assessment						✓
EQ-5D Questionnaire		✓			✓	✓
SF-12 Questionnaire					✓	✓

[1] Screening to be conducted of all women suspected of being eligible for the study.
[2] Delivery to be commenced within 48 hours of randomisation for women randomised to the planned delivery group.
[3] Eligibility for study to be assessed from blood pressure recorded at the time the diagnosis of pre-eclampsia
[4] Blood systolic pressure reading within the 48 hours prior to randomisation to be recorded.
[5] Highest systolic blood pressure recorded between randomisation and delivery to be recorded.
[6] Highest systolic blood pressure recorded between delivery and discharge to be recorded.
[7] Haematology and/or Biochemistry results that contributed to diagnosis of pre-eclampsia to be recorded.
[8] The most recent Haematology and/or Biochemistry results prior to randomisation to be recorded.
[9] Abnormal Haematology and/or Biochemistry results from randomisation to discharge to be recorded at discharge
[10] Serious Adverse Events (SAEs) to be recorded from randomisation to post-natal discharge. Only unexpected SAEs to be reported.
[11] Brief details of anti-hypertensive and medication for induction will be recorded; all other concomitant medication will only be recorded in the event that an unexpected SAE is reported.
[12] EQ-5D[7] to be given to the participant to complete immediately after randomisation.

The management of pregnant women whilst in hospital should be in accordance with the NICE guidelines for the Management of Hypertension in Pregnancy[12,13]. Delivery will be in accordance with standard procedures but will most likely be through induction with prostaglandins, unless contraindicated. If induction fails, other management options including caesarean section should be considered. All options should be discussed with the pregnant woman and her needs and preferences taken into account.

Otherwise, women will be managed as follows;

Intervention (Planned Delivery) Group

Planned delivery with minimal delay (with initiation of delivery within 48 hours of randomisation to allow for steroid use and neonatal cot availability). Use of corticosteroids will be left to the discretion of the individual clinician as indicated in the NICE guidelines. Postnatal care should follow NICE guidelines[12,13].

Control (Expectant Management) Group

Expectant management of pregnancy, as indicated by the NICE guidelines and delivery at 37 weeks of gestation or sooner as clinical needs dictate.

The NICE guidelines cover care on admission to hospital, treatment, measurement of blood pressure, testing for proteinuria and other parameters depending whether the woman has mild or moderate hypertension.

If mild hypertension (blood pressure 140/90 to 149/99 mmHg) care would be as follows;

- Admission to hospital
- Measure BP at least 4x a day
- No treatment of blood pressure
- No repeat quantification of proteinuria
- Blood test monitoring twice a week to determine kidney function, electrolytes, full blood count, transaminases, bilirubin.

If moderate hypertension (blood pressure 150/100 to 159/109 mmHg) care would be as for mild hypertension with the addition of the following assessments

- Administration of oral labetalol to keep diastolic blood pressure between 80-100 mmHg/systolic blood pressure < 150 mmHg)
- Blood test monitoring thrice a week to determine kidney function, electrolytes, full blood count, transaminases, bilirubin.

6.4. Time of Delivery - Adherence to Protocol

Following randomisation to either the planned delivery group or expectant management group, the time of the onset of planned delivery (first method for induction of labour or time of planned caesarean section along with the indication) or onset of spontaneous labour will be recorded for all women. This will enable the monitoring of adherence to the protocol for both study groups to be reviewed and protocol deviations to be identified and investigated.

7. Assessment of Safety

A Data Monitoring Committee (DMC) will be established to ensure the wellbeing of study participants. The DMC will periodically review study progress and outcomes as well as reports of unexpected SAEs. The DMC will, if appropriate, make recommendations regarding continuance of the study or modification of the study protocol.

7.1. Adverse Event (AE)

An adverse event is any untoward medical occurrence in a participant, which does not necessarily have to have a causal relationship with this intervention. Due to the high incidence of adverse events routinely expected in this patient population (e.g. abnormal laboratory findings, new symptoms etc.), only those adverse events identified as serious will be recorded for the trial.

7.2. Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that:

- Results in death.

- Is life-threatening.
- Requires participant hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is an important medical event.

The term ‘severe’ is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance. This is not the same as ‘serious’, which is based on participant/event outcome or action criteria usually associated with events that pose a threat to a participant’s life or functioning.

The term ‘life-threatening’ in the definition of serious refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Medical and scientific judgement should be exercised in deciding whether an adverse event is serious in other situations.

7.3. Expected Serious Adverse Events

Expected SAEs are those events which are expected in the patient population or as a result of the routine care/treatment of a patient.

The following events are expected in women with pre-eclampsia and their infants and as such do not require reporting as SAEs;

Expected maternal SAEs;

- Hepatic dysfunction
- Hepatic haematoma or rupture
- Coma/impaired consciousness (Glasgow coma score <13)
- Cortical blindness
- Reversible ischaemic neurological deficit
- Retinal detachment

- Acute renal insufficiency or failure
- Postpartum haemorrhage requiring transfusion or hysterectomy
- Platelet count <50,000
- Severe uncontrolled hypertension
- Myocardial ischaemia/infarction
- Severe breathing difficulty
- Pulmonary oedema
- Sepsis

Although it is known that maternal death and strokes can occur in women with pre-eclampsia, they should still be reported as an SAE.

Expected infant SAEs

- Perinatal death (unless unexpected in this population)
- Congenital anomaly
- Low birth weight
- Reversed end diastolic flow
- Requirement for supplemental oxygen or ventilation support
- Intraventricular haemorrhage
- Sepsis confirmed by positive cerebrospinal fluid or blood cultures
- Necrotising enterocolitis
- Seizures
- Encephalopathy
- Hypoglycaemia

Although it is known that neonatal death and stillbirth can occur in infants born to women with pre-eclampsia, they should still be reported as an SAE.

7.4. Unexpected Serious Adverse Events

An unexpected SAE is any event that meets the definition of a SAE and is not detailed in the list above as expected. The following unexpected SAEs must be reported:

- Maternal death
- Maternal stroke

- Stillbirth
- Neonatal death

7.5. Safety Reporting Procedures

7.5.1. SAE Recording

All SAEs (described above) will be recorded from randomisation to post-natal discharge from hospital of mother and baby.

7.5.2 Unexpected SAE reporting

Only unexpected SAEs will be reported; these will be followed-up until post-natal discharge of mother and baby from acute hospital care.

Unexpected SAEs for both the mother and infant will be recorded and reported to the NPEU Clinical Trials Unit (CTU) within 24 hours of research staff at the site becoming aware of the event. Details of the SAE should be recorded on a SAE form (filed in the Investigator Site File) and the form faxed or emailed back to the NPEU CTU. If this is not possible at the time, the SAE may be reported by telephone and the SAE form completed by staff at the NPEU CTU. A SAE form should however be completed as soon as possible by the site and sent to the NPEU CTU. Follow-up SAE information should be reported on a new SAE form and this forwarded to the NPEU CTU by fax or email.

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form.

All reported SAEs will be reviewed by the DMC at regular intervals throughout the study. The Chief Investigators will inform all Investigators concerned of relevant information that could adversely affect the safety of participants.

8. Study Governance

8.1. NHS Trust Research and Development (R&D)

Individual sites will only start recruitment once they have received approval from their NHS Trust Research and Development (R&D) Office. Applications to R&D offices will be submitted through the NIHR Co-ordinated System for gaining NHS permission.

8.2. Study Sponsor

The study is co-sponsored by Kings College London and Guy's and St Thomas' NHS Foundation Trust.

8.3. Study Coordinating Centre

The trial co-ordinating centre will be at the NPEU CTU University of Oxford where the Trial Co-ordinator will be based. The NPEU CTU will be responsible for study data entry, statistical analyses, servicing both the DMC and Trial Steering Committee (TSC), and, in collaboration with the Chief Investigators and the Local Research Midwives/Nurse(s) for the general day-to-day running of the study including recruitment of sites and training of staff. An emergency helpline is available for out-of-hours queries relating to the trial.

8.4. Project Management Group (PMG)

The study will be supervised on a day-to-day basis by the Project Management Group (PMG). This group reports to the Trial Steering Committee (TSC) which has overall responsibility for the conduct of the study. At each participating site, a local Principal Investigator will report to the PMG via the staff based at the NPEU CTU.

The core PMG will ordinarily consist of the Chief Investigators and NPEU CTU staff including:

- Director – Clinical Trials Unit
- Senior Trials Manager
- Trial Coordinator
- Trial Statistician
- Administrator/Data Manager

The core PMG will meet regularly (at least monthly). The Co- Investigators' Group (CIG) will meet at regular intervals through the duration of the trial; this will comprise all co-applicants and the members of the core PMG.

8.5. Trial Steering Committee (TSC)

The role of the TSC is to provide the overall supervision of the study. The TSC should monitor the progress of the study and conduct and advise on its scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the DMC and ultimately carries the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy.
The TSC will consist of an independent chair and at least two other independent members. Committee members will be deemed to be independent if they are not involved in study recruitment and are not employed by any organisation directly involved in the study conduct.

Representatives from relevant Patient/Public Involvement groups, the Chief Investigators and other Investigators/Co-applicants will be joined by observers from the NPEU CTU. The HTA programme manager will be invited to attend all TSC meetings.

A TSC charter will be written after the first TSC meeting to document how the committee will operate.

8.6. Data Monitoring Committee (DMC)

A DMC independent of the applicants and the TSC will review the progress of the trial at least annually and provide advice on the conduct of the trial to the TSC who will report to the HTA programme manager. The committee will periodically review study progress and outcomes. The timings and content of the DMC reviews will be detailed in a DMC Charter, which will be agreed at its first meeting.

8.7. Adjudication Panel

A sub-group of the co-investigators and other senior clinicians will form a review panel to perform blinded outcome adjudication.

8.8. Competing Interests

All PHOENIX co-investigators will declare competing interests or affiliations. Members of the TSC and DMC Committees and any observers to their meetings will be required to declare any competing interests they may have prior to participating in the meeting as documented within the charters.

9. Direct Access to Source Data and Documents

Direct access to source data/documents (including hospital records/notes, clinical charts, laboratory reports, pharmacy records and test reports) will be granted to authorised representatives from the NPEU CTU, the Sponsor and host organisations to permit study related monitoring, audits and inspections.

10. Ethics and Regulatory Approvals

10.1. Declaration of Helsinki

Investigators will ensure that this study is conducted in accordance with the current principles of the Declaration of Helsinki (October 2008).

10.2. ICH Guidelines for Good Clinical Practice

The conduct of this study will be in full compliance with the relevant regulations and principles of Good Clinical Practice .

10.3. Approvals

The study will only start after gaining approval from a NHS registered REC. Additionally, approval of the appropriate Trust R&D Office will be sought for individual trial sites.

Applications will be submitted through the Integrated Research Application System (IRAS).

A copy of the protocol, Participant Information Leaflet, Informed Consent Form, and GP Letter will be submitted to the REC for approval. The CI or their delegate will submit and, where necessary, obtain approval from the REC for any substantial amendments. Substantial amendments are defined as those that affect:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any investigational medicinal product used in the trial.

11. Trial Procedures

11.1. Informed Consent

Written consent will be sought from the woman only after she has been given a full verbal explanation and written description (via the participant information leaflet [PIL]) of the trial. Women who do not speak English will only be approached if an adult interpreter is available. Relatives may not interpret.

Introductory verbal and written information will be offered to all potentially eligible women with pre-eclampsia.

Written informed consent will be given using an informed consent form (ICF) completed, signed and dated by the woman (with countersignature by an interpreter where required) and signed by the person who obtained informed consent; this will be the Principal Investigator (PI) or healthcare professional with delegated authority. A copy of the signed ICF will be given to the woman. A further copy will be retained in the woman's medical notes, a copy will be retained in the Investigator Site File (ISF), and the original will be sent to the PHOENIX Coordinating Centre.

At all stages it will be made clear to the woman that she is free to withdraw from the trial at any time without the need to provide any reason or explanation. Participants will be made aware that this decision will have no impact on any aspect of their continuing care.

11.2. Data Collection

11.2.1 Data Collection before Post-natal Discharge

Much of the outcome data for this trial are routinely recorded clinical items that can be obtained from the clinical notes or local hospital results system. No additional blood or tissue samples are required for this trial. Clinical information will be collected using the following eCRFs:

- Screening Log
- Eligibility
- Maternal Details
- Prior to Randomisation
- EQ-5D[7]
- Contact Details
- Abnormal Lab Parameters
- Delivery
- Maternal Discharge
- Maternal Adverse Outcomes
- Infant Delivery
- Infant Discharge

Women will be requested to complete the EQ-5D[7] questionnaire at the time of randomisation: this usually takes fewer than five minutes. The data will be entered onto the trial database by the local research team.

11.2.2 Data Collection after Discharge

Questionnaires will be sent to all participants at 6 months post-delivery and 24 months of age corrected for prematurity. Participants will be invited to complete the paper copy of the questionnaire and return this via FREEPOST to the coordinating centre, or to complete an on-line version that will be captured by the MedSciNet study database.

The six month questionnaire will collect the following data:

- EQ5D[7]
- SF-12[8]
- Maternal Health and social care use from hospital discharge
- Infant Health and social care use from hospital discharge

The 24 month questionnaire will collect:

- EQ5D[7]
- SF-12[8]

- Maternal Health and social care use (for the previous six months only)
- Infant Health and social care use (for the previous six months only)
- PARCA-R[6] (Parent Report of Children's Abilities – Revised)

11.3. Data Processing

All hospital trial data will be collected using bespoke eCRFs and entered directly into the study's electronic database by the centre's research staff. Data will be single entered only and at the point of entry the data will undergo a number of validation checks to verify the validity and completeness of the data captured.

Follow-up questionnaires completed by the mother on-line will also undergo a number of validation checks at the point of entry. Paper copies of the questionnaire completed and returned to the coordinating centre will be entered manually by a member of the coordinating team.

11.4. Masking

Due to the nature of this study masking of the clinicians, nursing staff, and participants is not possible.

11.5. Withdrawal from the Trial Intervention

If a participant chooses to withdraw from receiving the allocated intervention, they will be asked for permission for us to use the study data already collected and to complete data collection and/or follow-up.

For a woman allocated to the expectant management group, the attending clinician will make a decision for delivery based on the NICE guidelines, with delivery planned for 37 weeks of gestation. If clinical needs dictate delivery prior to 37 weeks' gestation, this will not constitute withdrawal from the trial allocation.

11.6. End of Trial

The PHOENIX trial has two phases: an intervention phase and a follow-up phase. The end of the intervention phase will be when the last participating mother and infant have been discharged from hospital or dies in hospital. NHS Trusts will be notified of the end of trial for their records.

The end of the follow-up phase will be the latest date any participating infant reaches 24 months of age corrected for prematurity. The REC and Sponsor will be notified at this point.

11.7. Early Cessation

In the light of interim data and other evidence from relevant studies, the DMC will inform the TSC if, in its view, there is proof beyond reasonable doubt that the data indicate that the trial should be terminated. A decision to inform the TSC of such a finding will in part be based on statistical considerations. Appropriate proof beyond reasonable doubt cannot be specified precisely. A difference of at least 3 standard errors in the interim analysis of a major outcome may be needed to justify halting or modifying the study prematurely, for the superiority hypothesis.

12. Participant Confidentiality, Data Handling and Record Keeping

Overall responsibility for ensuring that each participant's information is kept confidential will lie with the study Sponsor. All paper documents will be stored securely and kept in strict confidence in compliance with the Data Protection Act (1998). Data entered onto the eCRFs will be automatically transferred for storage in an electronic database held by MedSciNet [AB] on behalf of the Sponsors in which the participant will be identified only by a study specific number and their initials. The participant's name and any other identifying details will be stored in a separate database also held by MedSciNet [AB] on behalf of the Sponsors which will be linked only to the database containing study data by the participant's study number. This information will be collected and retained when the participant's explicit consent to enable follow-up to be undertaken. After the study has been study has completed and the reports published, the data will be archived in a secure physical or electronic location with controlled access.

Electronic files will be stored on a file server that has restricted access. The server is in a secure location and access. Access is restricted to a few named individuals. Access to the building in which the NPEU CTU is situated is via an electronic tag and individual rooms are kept locked when unoccupied. Authorisation to access restricted areas of the NPEU CTU network is as described in the NPEU CTU security policy. Data will be processed on a workstation by authorised staff. The computer workstations access the network via a login name and password (changed regularly). No data are stored on individual workstations. Backing up is done automatically overnight to an offsite storage area. The location of the back-up computer is in a separate department which has electronic tag access. Access to the room in which the back-up machine is located is via a key-pad system.

12.1. Retention of Personal Data

Personal data will be needed to contact parents when their children are 2 years of age, to co-ordinate follow up, and to disseminate the results of the study to participants.

12.2. Data Security

An IT Security Risk assessment of MedsciNet AB will be undertaken by the sponsor and a data sharing agreements instigated to ensure all study data is captured and stored as per the sponsor's Security Policy and complies with all required UK data storage requirements prior to recruitment commencing.
A similar risk assessment and data sharing agreement will also be instigated to ensure EQ-5D data captured via the Euroqol website is also captured, stored and transferred to the MedSciNet database as per the sponsor's security policy.

12.3. Insurance

Kings College London/ Guy's and St Thomas' NHS Foundation Trust, as Co-Sponsors of the study, have a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research. NHS indemnity operates in respect of the clinical treatment which is provided.

13. Quality Control and Assurance

13.1. Site Initiation and Training

The site PI and Local Research Midwife or Nurse (LRMN), or their delegates, from each recruiting centre will be fully trained in the protocol and data collection procedures. They will then be responsible for delivering this training to all relevant site staff, to make sure that they are conversant with the trial's procedures prior to opening their centre for recruitment. The LRMN, with support from the Trial Research Midwife (TRM), will also promote the trial so that the necessary recruitment targets are reached within the timescale. The site PI and LRMN will have primary responsibility for educating any new centre clinicians and research staff about the trial, for maintaining enthusiasm, and encouraging recruitment in their centre. The LRMN will act as the point of contact for the PHOENIX Coordinating Centre and assisted by the TRM who will troubleshoot as the need arises.

13.2. Site Monitoring and Auditing

The LRMN with support from the TRM will be responsible for the day-to-day smooth running of the trial at a recruiting site. The CTU will monitor recruitment against targets, provide staff education and training, and monitor data collection completeness and quality. No other routine monitoring will be carried out unless the central monitoring exercises raise cause for concern. Likewise, sites will only be audited if central monitoring indicates a necessity.

13.3. Risk Assessment

A study risk assessment has been performed as part of the application to receive funding. This risk assessment will be reviewed at regular intervals during the course of the study to ensure there is no change in the risk statement.

13.4. National Registration Systems

The study will be registered on at least one global trial register.

14. Communication

After REC approval has been obtained, this protocol will be submitted for publication and will be available for download via the NPEU website.

14.1. Study Website

The PHOENIX study website will provide information regarding the study to recruiting centres, participants and their families. Copies of all eCRFs, the study protocol, participant information leaflet and training literature will be available along with information on centres participating in the study and contact details for the coordinating centre. The participant's page will also provide and links to other websites that may provide advice and support to people affected by pre-eclampsia.

14.2. Publication Policy

The CI and NPEU CTU will coordinate dissemination of the results from this trial. All publications using data from this trial to undertake original analyses will be submitted to the TSC for review before release. The research will be published in high impact, peer reviewed, scientific journals.

More general dissemination of the results will be achieved through publication of summary findings. There are no commercial or intellectual rights issues that would delay publication of results. A writing committee drawn from the co-investigators (trial grant holders), trial co-ordinators and others substantially involved in execution, analysis and interpretation will be named authors on the principal publications arising from the trial provided they meet the authorship criteria used by most high impact peer reviewed journals see http://www.icmje.org.

Local Principal Investigators will be named formally as collaborators on the publication; Principal Investigators in non-recruiting centres and other trial personnel with significant input to the running of the trial will be named in the Acknowledgements in publications. The Chief Investigators will nominate and agree appropriate authorship on all publications prior to commencement of writing.

15. Finance

15.1. Funding

The study is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme.

16. Signatures

16.1. Protocol Approval Signatures

The signatures below constitute approval of this protocol and provide assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to ethical and regulatory requirements, other applicable regulations and ICH guidelines.

Sponsor Representative Keith Brennan	Date
Co-Chief Investigator Professor Andrew Shennan	Date
Co-Chief Investigator Dr Lucy Chappell	Date
Statistician Pollyanna Hardy	Date

16.2. Site Principal Investigator Signatures

By signing this protocol signature page, I agree to;

- Conduct the study in accordance with the protocol and only make changes in order to protect the safety, rights or welfare of the participants.
- Personally conduct or supervise the study and ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations.
- Ensure requirements with regard to obtaining informed consent are adhered.
- Report unexpected SAEs that occur during the course of the study and maintain adequate and accurate records to enable representatives of the Sponsor or regulatory authority to confirm adherence with the protocol.

_____ _____

Principal Investigator's Signature Date

_____

Print name

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5 Von Dadelszen P, Payne B, Li J, Ansermino J. M, Broughton Pipkin F, Cote A. M, Douglas M. J, Gruslin A, Hutcheon J. A, Joseph K. S, Kyle P. M, Loghna P, Menzies J. M, Merialdi M, Millman A. L, Moore M. P, Moutquin J. M, Ouellet A. B, Smith G. N, Walker J. J, Walley K. R, Walters B. N, Widmer M, Lee S. K, Russel J. A, Magee L. A, PIERS Study Group. Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model. Lancet. 2011 Jan 15; 377 (9761): 219-27.

6 PARCA-R is a questionnaire for assessing cognitive and language development in preterm infants born at or after 32 weeks' gestation, validated against a gold standard developmental assessment.

7 EQ-5D™ is a standardised instrument for use as a measure of health outcome. It is applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. It is primarily designed for self-completion by respondents and is ideally suited for use in postal surveys, in clinics and face-to-face interviews. It is cognitively simple, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire. EQ-5D™ is a trade mark of the EuroQol Group.

8 QualityMetric's SF-12v2® Health Survey is a shorter version of the SF-36v2® Health Survey that uses just 12 questions to measure functional health and well-being from the patient's point of view. Taking only two to three minutes to complete, the SF-12v2 is a recognised as a practical, reliable, and valid measure of physical and mental health and is particularly useful in large population health surveys or for applications that combine a generic and disease-specific health survey.

9 Centre for Maternal and Child Enquiries (CMACE). Saving Mothers' Lives: reviewing maternal deaths to make motherhood safer: 2006–08. The Eighth Report on Confidential Enquiries into Maternal Deaths in the United Kingdom. BJOG 2011;118 (Suppl. 1):1–203.

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