Elsevier Editorial System(tm) for The Lancet
Manuscript Draft

Manuscript Number: THELANCET-D-19-04782R1

Title: Planned early delivery or expectant management for late preterm pre-eclampsia: a randomised controlled trial (PHOENIX trial).

Article Type: Fast Track (Randomised Controlled Trial)

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Abstract: Background
In women with late preterm pre-eclampsia the optimal time to initiate delivery is unclear, as limitation of maternal disease progression needs to be balanced against infant complications .

Methods
In this UK parallel-group, non-masked, multi-centre, randomised controlled trial, we compared planned delivery against expectant management (usual care) with individual randomisation in women with late preterm pre-eclampsia from 34 to 37 weeks' gestation and a singleton or dichorionic diamniotic twin pregnancy. The co-primary maternal outcome was a composite of maternal morbidity or recorded systolic blood pressure ≥160mmHg with a superiority hypothesis. The co-primary perinatal outcome was a composite of perinatal deaths or neonatal unit admission up to infant hospital discharge with a non-inferiority hypothesis. Analyses were by intention to treat, together with a per protocol analysis for the perinatal outcome. The trial was prospectively registered (ISRCTN Registry, number 01879376).

Findings
Between 29 September 2014 and 10 December 2018, 901 women were recruited across 46 maternity units. 450 women (448 women and 471 infants analysed) were allocated to planned delivery, and 451 women (451 women and 475 infants analysed) to expectant management. The incidence of the co-primary maternal outcome was significantly lower in the planned delivery group (64·7%) compared to the expectant management group (75·3%); adjusted risk ratio 0·86 (95% CI 0·79 to 0·94); p=0.0005. The incidence of the co-primary perinatal outcome was significantly higher in the planned delivery group (41·8%) compared to the expectant management group (33·5%); adjusted risk ratio 1·26 (95% CI 1·08 to 1·47); p=0.0034. The results from the per protocol analysis were similar. There were nine serious adverse events in the planned delivery group and twelve in the expectant management group.

Interpretation

There is strong evidence to suggest that planned delivery reduces maternal morbidity and severe hypertension, with more neonatal unit admissions related to prematurity, but no indicators of greater neonatal morbidity, compared to expectant management. This trade-off should be discussed with women with late preterm pre-eclampsia to allow shared decision making on timing of delivery.

Planned early delivery or expectant management for late preterm pre-eclampsia: a randomised controlled trial (PHOENIX trial).

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Summary

Background

In women with late preterm pre-eclampsia the optimal time to initiate delivery is unclear, as limitation of maternal disease progression needs to be balanced against infant complications .

Methods

In this UK parallel-group, non-masked, multi-centre, randomised controlled trial, we compared planned delivery against expectant management (usual care) with individual randomisation in women with late preterm pre-eclampsia from 34 to 37 weeks' gestation and a singleton or dichorionic diamniotic twin pregnancy. The co-primary maternal outcome was a composite of maternal morbidity or recorded systolic blood pressure ≥160mmHg with a superiority hypothesis. The co-primary perinatal outcome was a composite of perinatal deaths or neonatal unit admission up to infant hospital discharge with a non-inferiority hypothesis. Analyses were by intention to treat, together with a per protocol analysis for the perinatal outcome. The trial was prospectively registered (ISRCTN Registry, number 01879376).

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Introduction

Pre-eclampsia is a multisystem disorder of pregnancy, characterised by placental and maternal vascular dysfunction and associated with substantial morbidity and mortality for the mother and infant. Adverse outcomes of pre-eclampsia include maternal stroke, renal and hepatic injury, and fetal growth restriction, and maternal and perinatal death.[1] Around 10% of pregnant women develop hypertension, and 2-3% pre-eclampsia, characterised by hypertension and manifestations of multi-organ disease.[2]

Standard management of pre-eclampsia involves maternal and fetal assessment, and subsequent consideration of timely delivery to minimise maternal and perinatal morbidity, taking into consideration gestational age, progression of maternal disease and fetal well-being. After 37 weeks' gestation, most national guidelines recommend prompt delivery for a woman with pre-eclampsia,[3,4] since maternal and fetal risks can be significantly reduced without any additional risks from such an intervention.[5] In women with late preterm pre-eclampsia (between 34 and 37 weeks' gestation), the optimal time for delivery is less clear, as limitation of maternal disease progression needs to be balanced against complications for the infant either related to ongoing expectant management (including needing emergency delivery, worsening growth restriction and stillbirth) or those related to planned earlier delivery (infant immaturity and associated complications). Current usual practice in the UK for women with late preterm pre-eclampsia is for expectant management until 37 weeks' gestation, with delivery sooner if the clinical scenario changes and there is concern over impending severe pre-eclampsia and associated complications. In the absence of definitive new evidence, this advice has been maintained in the most recent management recommendations from the International Society for the Study of Hypertension in Pregnancy, published in 2018,[6] used to inform current practice in many countries worldwide.

This aim of this trial was to compare planned earlier initiation of delivery with expectant management (usual care) in women with pre-eclampsia between 34 and 37 weeks' gestation in the UK healthcare setting, in order to determine whether planned delivery reduces maternal adverse outcomes without substantial worsening of neonatal or infant outcomes.

Methods

Trial design

In this parallel-group, non-masked, multi-centre, randomised controlled trial, we compared planned delivery against expectant management (usual care) with individual randomisation using a 1:1 allocation ratio. There were no substantial changes to the published study design or methods or outcomes[7] after commencement of the trial.

Participants

A pregnant woman was eligible if she was between 34^{+0} and 36^{+6} weeks of gestation, had a diagnosis of pre-eclampsia or superimposed pre-eclampsia (as defined by International Society for the Study of Hypertension in Pregnancy),[8] with a singleton or dichorionic diamniotic twin pregnancy and at least one viable fetus, was aged 18 years or over, and able to give written informed consent. Women with any other co-morbidity (including pre-existing hypertension, diabetes) or with a previous caesarean section or any fetal position were eligible. The only exclusion criterion to participation in the study was a prior decision to deliver within the subsequent 48 hours. Current practice by national guidelines in use during the trial was for immediate delivery of a woman with persistent severe features of pre-eclampsia (including Haemolysis, Elevated Liver enzymes, Low Platelets syndrome), who would thus not be eligible for the trial.

The trial was approved by the South Central - Hampshire B Research Ethics Committee (no. 13/SC/0645).

Interventions

We allocated women to planned initiation of delivery within 48 hours of randomisation (to allow for corticosteroid administration to accelerate fetal lung maturation, and neonatal cot availability if necessary), usually by induction of labour (unless there was an additional specific indication for pre-labour Caesarean section) or to expectant management (usual care), with delivery at 37 weeks' gestation or sooner as clinical needs dictated in accordance with the UK national guidelines[4] (as assessed by the clinician responsible for her care) for maternal indications (e.g. uncontrolled hypertension, abnormal blood results), or fetal compromise, or eclampsia or other clinical crisis. Individual decisions around mode of induction and delivery and use of corticosteroids for fetal lung maturity was left to the discretion of the individual clinician, with the trial protocol advising that all options should be discussed with the pregnant woman and her needs and preferences taken into account.

Outcomes

Outcomes were recorded on the web-based trial database through case-note review by trained researchers after maternal and infant primary hospital discharge. The co-primary maternal outcome was a composite of maternal morbidity of fullPIERS[9] outcomes: maternal death; central nervous system (eclampsia, Glasgow coma score <13, stroke or reversible ischaemic neurological deficit, transient ischaemic attack, cortical blindness or retinal detachment, posterior reversible encephalopathy); cardiorespiratory (positive inotropic support, infusion of a third parenteral antihypertensive drug, myocardial ischaemia or infarction, SpO2 <90%, ≥50% FiO2 for >1 hr, intubation (other than for caesarean section), pulmonary oedema); haematological (transfusion of any blood product, platelet count $<50\times10^9$ per L, with no transfusion); hepatic (hepatic dysfunction, hepatic haematoma or rupture); renal (acute renal insufficiency (creatinine >150 µmol/L; no pre-existing renal disease) or acute renal failure (creatinine >200 µmol/L; pre-existing renal disease, dialysis); placental abruption), with the addition of recorded systolic blood pressure ≥160mmHg post-randomisation (on any occasion), and its presence or absence was independently countersigned by the site principal investigator or delegate. The co-primary perinatal outcome was a composite of perinatal deaths (antenatal/ intrapartum stillbirths or deaths within seven days of delivery) or neonatal unit admissions (physical separation of baby from the mother) prior to infant hospital discharge. Secondary outcomes are as listed in the published protocol:[7] maternal: individual components of the composite primary outcome, use of anti-hypertensive drugs, progression to severe pre-eclampsia, defined as systolic blood pressure ≥160mmHg, platelet count $<100 \times 10^9$/L and abnormal liver function enzymes (ALT or AST >70 IU/L), 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 and mode of delivery, confirmed thromboembolic disease, confirmed sepsis, primary and additional indications for delivery, placental abruption and perinatal: stillbirth, neonatal death, admissions to neonatal unit, number of nights in each category of care, total number of nights, birth weight, birth weight centile, birth weight <10th and <3rd centile, gestational age at delivery, Apgar score at 5 min post-birth, umbilical arterial and venous pH at birth, need for supplementary oxygen prior to discharge, number of days when supplemental oxygen is required, need for ventilation support, abnormal cerebral ultrasound scan, confirmed sepsis, necrotising enterocolitis, seizures, encephalopathy, hypoglycaemia, other indications and main diagnoses resulting in neonatal unit admission, exclusively breastfed at discharge from the neonatal unit and health resource use outcomes. The primary indication for neonatal unit admission was allocated as part of usual clinical care practice by a clinical neonatologist (not involved in the trial), from a pre-specified list of exclusive admission reasons, on an electronic clinical database used nationwide in England and Wales. The category of neonatal care (intensive care, high dependency

care, special care) followed nationally defined guidance, with days in each category of care individually recorded on the national electronic clinical patient database.[10]

Sample Size

Superiority hypothesis in maternal outcome

Assuming an expected adverse maternal outcome incidence of 43% in the expectant management (usual care) group, based on data from the PELICAN study[11] a sample size of 850 women would demonstrate a relative risk reduction of 25% to 32·25% (deemed clinically important) in the planned delivery group with a 2-sided 5% significance level and 90% power. With 5% loss of women in follow-up, the overall target for recruitment was 900 women (450 per group).

Non-inferiority hypothesis in neonatal outcome

Assuming a composite adverse neonatal outcome incidence of 24% in the expectant management group,[11] and assuming a sample size of 850 women would result in approximately 860 infants (430 per group, allowing for twin births). 93% power would be achieved to detect a non-inferiority margin of no less than 10% (judged as clinically relevant) and 78% power to detect a margin of no less than 8%.

Randomisation

Randomisation was performed using a probabilistic minimisation algorithm to ensure approximate balance within the following groups: study centre, singleton/ twin pregnancies, severity of hypertension in 48 hours prior to enrolment (highest systolic blood pressure with or without medication: <150mmHg, 150-159mmHg, ≥160mmHg), parity (previous delivery of a baby past 24 weeks), previous caesarean section, and gestational age at randomisation (34, 35, 36 weeks). Randomisation was managed via a secure web-based randomisation program provided by MedSciNet.

Allocation concealment and masking

The minimisation algorithm was implemented by a MedSciNet database programmer, with balance and predictability monitored by the independent National Perinatal Epidemiology Unit Clinical Trials Unit statistician during the trial. The intervention was not masked from women or clinicians, due to the nature of the intervention.

Implementation

Site research teams approached women to confirm eligibility and provided verbal and written information. A trained clinician (obstetrician or obstetric physician) obtained written informed consent. A research team member entered baseline data on a web-based database and then performed randomisation, communicating the results directly to the woman. All other aspects of pregnancy management were expected to be in accordance with the UK national guidelines[4] at the discretion of the responsible clinician. Research teams undertook standard assessment of safety, with reporting of serious adverse events following usual governance procedures.

Statistical Analysis

The primary analysis for all maternal outcomes was by intention to treat with participants analysed in the groups to which they were assigned regardless of protocol non-compliances. The primary analysis for all perinatal and infant outcomes was by both an intention to treat and a per protocol analysis, since the hypothesis under examination for these outcomes was a non-inferiority hypothesis.

All outcomes were analysed adjusting for minimisation factors (as listed above) at randomisation.[12] Binary outcomes were analysed using mixed effect Poisson regression with a robust variance estimator and presented as adjusted risk ratios with associated confidence intervals. Site was treated as a random effect, and all other minimisation factors as fixed effects. For perinatal outcomes, mother's identification was nested within site to take account of clustering within twins. For continuous outcomes, differences in medians and associated confidence intervals were estimated using quantile regression. In these models, site was treated as a fixed effect, and robust standard errors were used. 95% confidence intervals are presented for all primary and secondary outcomes. No adjustment of co-primary outcomes was made for multiplicity.[13]

Ancillary analyses

Pre-specified subgroup analyses were performed for co-primary outcomes, using the statistical test of interaction, based on criteria selected for minimisation: parity (0 and ≥1 previous pregnancy), highest systolic blood pressure in the 48 hours prior to enrolment (<150 and ≥150mmHg), gestation at the time of randomisation (34/ 35/ 36 weeks) and singleton/ twin pregnancy. To allow for clinical and logistical delays, a pre-specified sensitivity analysis was carried out on the co-primary outcomes excluding women (and infants) randomised to the planned delivery arm where initiation of delivery was more than 96 hours post-randomisation.

Economic Analysis

Data on mother and infant inpatient care and mode of delivery were costed using the National Schedule of Reference costs.[14] Descriptive statistics are reported including mean cost per participant and 95% confidence intervals constructed using bootstrapping. The time-horizon of the analysis is from recruitment until hospital discharge following labour. Comparative difference in costs was calculated using linear regressions and adjusted for centre, singleton/ twin pregnancies, severity of hypertension in 48 hours prior to enrolment, parity, previous caesarean section and gestational age at randomisation.

The trial is registered with the ISRCTN registry, number 01879376.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Participant flow, recruitment and numbers analysed

Between 29 September 2014 and 10 December 2018, of 1,606 women found to be eligible, 901 women (56%) were recruited, across 46 maternity units in England and Wales (Supplementary Table 1). 450 women were allocated to planned delivery, and 451 women to expectant management (usual care). For the intention to treat analysis, data from 448 women and 471 infants (two women withdrew, with consent to use all data withdrawn) in the planned delivery group, and 451 women and 475 infants in the expectant management group were included. Follow-up to maternal and infant discharge continued until January 2019. One woman was lost to follow-up in the planned delivery group, and two women in the expectant management group. Recruitment ended after 901 women had been enrolled.

Baseline data

Baseline characteristics were similar between the two groups, with groups well balanced on minimisation factors (Table 1, Supplementary Table 2).

Outcomes

The proportion with the primary maternal outcome was statistically significantly lower in the planned delivery group (64·7%) compared to the expectant management group (75·3%); adjusted risk ratio 0·86 (95% CI 0·79 to 0·94); p=0.0005. The proportion with the primary perinatal outcome was significantly higher in the planned delivery group (41·8%) compared to the expectant management group (33·5%); adjusted risk ratio 1·26 (95% CI 1·08 to 1·47); p=0.0034 (Table 2).

In women allocated to planned delivery, a significant reduction in both components of the primary adverse maternal outcome was found, as was progression to severe pre-eclampsia (Table 3). Other than two women who had spontaneous onset of labour, all other women in the planned delivery group received the trial intervention, although this was not always achieved within 48 hours as intended. Of women allocated to planned delivery, 73% (327 of 448) had delivery initiated within 48 hours (Figure 1). In women allocated to expectant management, 53·9% had medically indicated delivery prior to 37 weeks' gestation and only two women were delivered prior to 37 weeks' gestation without an additional medical indication. Additional maternal secondary outcomes are shown in Supplementary Table 3. Intervals between randomisation and initiation of delivery are shown in Supplementary Table 4.

Median gestational age at enrolment was identical, but women allocated to planned delivery delivered at 252 days of gestation compared to 257 days in the expectant management group (adjusted median difference -3 (95% CI -3·5 to -2·5) days) and were significantly more likely to achieve a spontaneous vaginal delivery (36·0% vs. 29·3%; adjusted risk ratio 1·21 (95% CI 1·04, 1·41). There were no stillbirths or neonatal deaths in either group. There were more infants admitted to the neonatal unit in the planned delivery group (41·8%) compared to the expectant management group (33·5%); adjusted risk ratio 1·26 (95% CI 1·08 to 1·47); the principal recorded indication for admission was 'prematurity'. There was no evidence of differences in the proportions requiring supplementary oxygen or additional respiratory support, and no evidence of differences in the intensity of neonatal care or length of stay for the infant (Table 4). Additional perinatal secondary outcomes are shown in Supplementary Table 5. A planned per protocol analysis gave similar results for the perinatal outcomes (Supplementary Tables 6, 7).

Health economic analysis showed that total maternal and infant costs were lower in the planned delivery arm (mean £11,574, standard error £302) compared to the expectant management arm (mean £13,090, standard error £389), with an adjusted cost saving of £1478 (95% CI £2354 to £605; p=0·001) (Table 5).

There were similar numbers of serious adverse events in both groups: nine in the planned delivery group compared to 12 in the expectant management group (Supplementary Table 8). Two serious adverse events in each group were judged possibly related to the intervention in each group; one serious adverse event was judged probably related to the intervention in the expectant management group. All other serious adverse events were deemed unrelated to the intervention. There was one maternal death (in the expectant management group), considered unrelated to the trial allocation.

In planned sub-group analyses, there was no statistically significant interaction of gestational age at randomisation, singleton/ twin pregnancy, highest systolic blood pressure prior to enrolment and parity and the incidence of the primary maternal or perinatal outcome (Figure 2, Supplementary Figure 1). A planned sensitivity analysis including women or infants randomised to the planned delivery arm with initiation of delivery before 96 hours had little impact on the results (Supplementary Table 9).

Discussion

In this randomised controlled trial in women with late preterm pre-eclampsia, planned delivery reduced maternal morbidity (including severe systolic hypertension), but led to more neonatal unit admissions for the baby, principally for a listed indication of prematurity and without an excess of respiratory or other morbidity, intensity of care or length of stay. Women in the expectant management group at this gestation had a median additional prolongation of pregnancy (from enrolment to delivery) of five days, and over half of these women had indicated delivery before 37 weeks' gestation, with three quarters subsequently meeting the criteria for progression to severe pre-eclampsia. Women in the planned delivery group had significantly more vaginal deliveries. In this healthcare setting, there were no stillbirths or neonatal deaths. Planned delivery has lower costs than expectant management in the UK healthcare setting.

Strengths of the trial include a sufficiently large sample of women specifically with late preterm pre-eclampsia, in whom the benefits and risks of planned delivery may be different from those with gestational or chronic hypertension in pregnancy, related to the likelihood of progression to severe features of the disease and need for medically indicated emergency delivery. The trial was conducted to rigorous standards, with a pre-specified protocol without changes. Findings are likely

to be generalisable to similar healthcare settings, as it was undertaken in a large number of maternity units across England and Wales, with diverse representation of women both in demographic terms and disease spectrum and with recommendations for expectant management and indications for delivery in clinical practice similar in our trial (which followed UK national guidelines[4]) and current international guidelines.[6] Over half of eligible women approached agreed to participate in the trial, indicating agreement of equipoise in this scenario.

Limitations of the trial include the challenge of finding a perinatal outcome that adequately represented the potential risks of both groups, (related to intervention in the planned delivery group and to ongoing pre-eclampsia in the expectant management group), as there are potential harms from continuing pregnancy as well as initiating earlier delivery. As adjudication of multi-organ neonatal morbidity is complex and subjective, and no widely accepted validated measure of neonatal morbidity is currently available, we chose neonatal unit admission (involving separation of the baby from the mother), supported by our lay representatives, and intending that this would capture underlying neonatal morbidity. Although UK clinical practice guidelines do not recommend routine admission of an infant based solely on gestational age after 34 weeks of pregnancy, admission solely for prematurity in this trial suggests different real-world clinician behaviour, despite no differences in objective measures of direct neonatal morbidity being demonstrated. Choice of a maternal outcome that reflects the multi-organ manifestations of pre-eclampsia is also challenging, particularly as no intermediate complication exists between severe systolic hypertension (relatively common) and stroke (very rare in high-income healthcare settings), and treatment paradox may mean that women are (appropriately) delivered on the basis of moderate deterioration in biochemical parameters before severe complications occur. The incidences of maternal and perinatal primary outcomes were higher than anticipated based on previous studies, but this did not limit the interpretation of the analysis. Although it is acknowledged that for women enrolled after 36 weeks' gestation, expectant management would only be for a maximum of seven days, immediate planned delivery would still represent a change in clinical care from usual practice and the research uncertainty remained at trial conception. The proportion of women enrolled at 36 weeks' gestation was similar (and even slightly lower) than that enrolled in a similar trial,[15] and maternal benefit shown even at this gestation.

Sources of bias

We considered sources of possible bias for the trial. Selection bias was unlikely due to the randomisation process including robust allocation sequence concealment, such that probability of

371 determining next allocation was unlikely. Performance and detection bias were possible, as it was
372 not possible to mask the intervention to clinicians or women and data collectors (as timing of
373 delivery was contained within maternity records where morbidity was recorded). Every primary
374 maternal outcome was additionally signed off by each site principal investigator, and we used a
375 primary neonatal outcome (independently recorded by the attending clinical team) to minimise bias
376 where possible. There was minimal attrition in both groups. We have reported all pre-specified
377 secondary outcomes, interpreting them cautiously.
378
379 *Comparison with other studies*
380 This trial has similar findings of a reduction in maternal adverse outcomes to a previous smaller
381 study,[15] but that trial included only 352 women with late preterm pre-eclampsia, and the reduction
382 was not statistically significant. However, our trial found no difference in respiratory morbidity (as a
383 secondary outcome) and much higher antenatal corticosteroid use (60%), in contrast to the previous
384 trial which reported increased respiratory distress syndrome in those with planned delivery, with
385 lower corticosteroid use (8%) and a longer interval to delivery in the expectant management group
386 likely related to inclusion of women with chronic or gestational hypertension.[15] Systematic reviews
387 of planned early delivery in women with pregnancy hypertension to date have been constrained by
388 insufficient numbers to draw definitive conclusions for specific groups of women where the benefit
389 and risk balance may differ (i.e. those with late preterm pre-eclampsia),[16,17] but a recent individual
390 patient data meta-analysis suggested that some women in these groups may benefit from earlier
391 delivery.[18] Developing accurate validated prognostic tools to best identify those at highest risk
392 remains challenging and infant follow-up is useful to further evaluate the longer term outcomes[19]
393 with such strategies.
394
395 *Interpretation*
396 In women with late preterm pre-eclampsia, planned delivery is associated with improved maternal
397 outcomes, but more neonatal unit admissions for prematurity (though not respiratory or other
398 morbidity, higher intensity of neonatal care or duration of stay), compared to expectant
399 management. Whilst UK guidance does not recommend routine admission for prematurity alone,
400 individual clinicians may vary in their thresholds for neonatal unit admission. Additional prolongation
401 of pregnancy by five days (in the expectant management group) may move an infant out of a
402 notional group where admission is dictated by a guideline (for example based on a gestational age
403 threshold), rather than by clinical need. Increased use of transitional care arrangements (where a
404 baby stays with its mother but with enhanced surveillance and care in a postnatal setting) may be

particularly beneficial in these babies and avoid unnecessary separation of the baby from its mother. For women with pre-eclampsia at this gestational age, prolongation of pregnancy may only be for a few days; over half of these women require indicated delivery, potentially necessitating emergency management. Rates of vaginal delivery are similar to those reported from a large US study of women with early preterm pre-eclampsia,[20] suggesting that these results can be extrapolated across similar settings. The increase in spontaneous vaginal births with planned delivery may be judged an important advantage by women and clinicians, particularly for future pregnancies. It is notable that there were no stillbirths or neonatal deaths in this setting, and one maternal death was likely related to comorbidities in association with pre-eclampsia, rather than trial allocation. The benefits and risks of planned delivery in women with late preterm pre-eclampsia may vary in low resource healthcare settings and require further evaluation, although the potential disadvantages of increased prematurity would need to be balanced against a much high incidence of stillbirth in women with pre-eclampsia managed expectantly, such as that reported in a South African setting.[21] The trial findings relate to women with late preterm pre-eclampsia and should not be extrapolated to women with chronic or gestational hypertension, in whom the likelihood of developing maternal morbidity is lower.

In conclusion, our trial supports offering initiation of delivery in women with late preterm pre-eclampsia. The trade-off of lower maternal morbidity and severe hypertension against higher neonatal unit admissions, albeit without additional respiratory or other morbidity, should be discussed with women with late preterm pre-eclampsia to allow shared decision making on timing of delivery.

Research in context

Evidence before this study

At conception of this study (in 2012), there were no published randomised controlled trials evaluating planned delivery against expectant management for women with late preterm pre-eclampsia between 34 and 37 weeks, although some women with mild pre-eclampsia may have been included in the HYPITAT-1 trial, in women with pregnancy hypertension from 36 weeks' gestation. A Cochrane systematic review on this topic, updated on 15 January 2017, concluded that 'For women suffering from hypertensive disorders of pregnancy after 34 weeks, planned early delivery is associated with less composite maternal morbidity and mortality. There is no clear difference in the composite outcome of infant mortality and severe morbidity; however, this is based on limited data (from two trials) assessing all hypertensive disorders as one group. Further studies are needed to look at the different types of hypertensive diseases and the optimal timing of delivery for these conditions.'

Added value of this study

The trial reported here is considerably larger (901 women) than the number of women with late preterm pre-eclampsia in previous trials (352 and 183 women). Previous trials have not impacted on clinical practice as there was continued uncertainty over the trade-off between maternal benefit and perinatal harms. The trial reported here is large, multicentre and represents contemporaneous management of women with late preterm pre-eclampsia. The neonatal endpoint chosen reflects potential harms from both the intervention (planned early delivery) and ongoing pre-eclampsia (in the expectant management arm).

Implications of all the available evidence

The results of this trial, taken together with smaller trials published since the trial started, support a lower threshold for considering planned delivery in women with late preterm pre-eclampsia. This benefit appears to be greater in women with pre-eclampsia (compared to women in other studies with gestational or chronic hypertension alone). Whilst planned delivery may result in more babies being admitted under current guidelines to a neonatal unit, the observed lack of associated morbidity and provision of alternative care strategies that avoid separation of the baby from the mother (such as transitional care) should enable management of these women to be optimised.

Other information

Registration

ISRCTN registry, ID: ISRCTN01879376. Prospectively registered on 25 November 2013.

Protocol

The full protocol is published.[7]

Funding and role of funding source

The trial was funded by the National Institute for Health Research Health Technology Assessment Programme. LCC is funded by the National Institute for Health Research Professorship, RP-2014-05-019. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care. The study sponsor and funders have had no input into study design; collection, management, analysis and interpretation of data; writing of the report; or the decision to submit the report for publication (beyond usual governance activities) and will not have any such input in the future.

Declaration of interests

The authors' institutions received funding from the National Institute for Health Research for this work. No conflicts of interests are reported.

Author contributions

LCC, PB, MEG, RH, PH, EJ, NM, JS, AS were involved in the study conception and in securing funding for the study. LCC and AS were co-chief investigators responsible for all aspects of the study. LL supervised the study analyses, with input from LCC. VC, MG, JT did statistical analyses. AP made a substantial contribution to the running of the trial. RMH did the health economic analysis. LCC wrote the article. All authors reviewed, contributed to and approved the final version of the manuscript.

Data sharing

The dataset will be available to appropriate academic parties on request from the Chief Investigator (Prof Lucy Chappell) in accordance with the data sharing policies of King's College London and the National Perinatal Epidemiology Unit Clinical Trials Unit, with input from the Co-investigator group where applicable.

Acknowledgements

We thank the independent Trial Steering Committee: Jane Norman (chair), Simon Gates, Alison Leaf, Katie Lean, Stavros Petrou, Jacqui Williams, and the independent Data Monitoring Committee: Diana Elbourne (chair), Phil Bennett, Jon Dorling.

We thank Ursula Bowler, Angela Garrett, Eleanor Hendy, Pauline Rushby, Laura Scholz, Jenie Sparkes, Sue Tohill, Zarko Alfirevic and Stephen Robson, all the participating women, site research midwives and doctors for their contribution to the trial.

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Table

Table 1: Maternal demographic and pregnancy characteristics at trial entry

Characteristic	Planned delivery (n=448)	Expectant management (n=451)
Maternal age (years)	30·6 ± 6·39	30·8 ± 6·30
Ethnicity		
White	313 (70%)	311 (69%)
Mixed	10 (2%)	23 (5%)
Asian	60 (13%)	50 (11%)
Chinese	0 (0%)	1 (0%)
Black	58 (13%)	52 (12%)
Other	5 (1%)	13 (3%)
Unknown	2 (0%)	1 (0%)
Deprivation Index quintile 5 (most deprived)*	161/425 (38%)	160/428 (37%)
Parity†: nulliparous	254 (57%)	260 (58%)
Parity†: multiparous	194 (43%)	191 (42%)
Previous caesarean section†	77/194 (40%)	78/191 (41%)
History of pre-eclampsia	85/194 (44%)	92/191 (48%)
Body mass index at booking (kg/m^2)	29·8 ± 7·3	29·8 ± 7·2
Smoking at booking	53 (12%)	50 (11%)
Systolic BP at booking (mmHg)	118·7 ± 14·4	119·6 ± 13·7
Diastolic BP at booking (mmHg)	72·7 ± 10·2	73·4 ± 10·4
Pre-existing chronic hypertension	51 (11%)	53 (12%)
Pre-existing chronic renal disease	6 (1%)	4 (1%)
Pre-pregnancy diabetes	25 (6%)	28 (6%)
Gestational diabetes	62 (14%)	53 (12%)
Aspirin prescribed during pregnancy	170 (38%)	189 (42%)
LMWH prescribed during pregnancy	125 (28%)	117 (26%)
At randomisation		
Median (IQR) gestational age (weeks)	35·6 (34·7 to 36·3)	35·6 (34·7 to 36·3)
Gestational age category†		
34^{+0} to 34^{+6} weeks	131 (29%)	135 (30%)
35^{+0} to 35^{+6} weeks	137 (31%)	132 (29%)
36^{+0} to 36^{+6} weeks	180 (40%)	184 (41%)
Number of live fetuses‡		

Singleton	425 (95%)	427 (95%)
Dichorionic diamniotic twin	23 (5%)	24 (5%)
Highest systolic BP in previous 48 hours (mmHg)	154·5 ± 14·5	155·2 ± 15·4
Highest diastolic BP in previous 48 hours (mmHg)	95·7 ± 9·5	95·8 ± 10·1
Highest BP in previous 48 hours†		
<=149 mmHg	163 (36%)	163 (36%)
150-159 mmHg	121 (27%)	123 (27%)
>=160 mmHg	164 (37%)	165 (37%)
Urinary protein-creatinine ratio measured	434 (97%)	441 (98%)
Median (IQR) urinary protein-creatinine ratio (mg/mmol)	83 (42 to 186)	80 (42 to 172)
Fetal growth ultrasound in previous two weeks	366 (82%)	375 (83%)
Suspected fetal growth restriction on ultrasound	79/366 (22%)	85/375 (23%)
Cervical assessment (prior to randomisation)		
Bishop's score <2	2 (0%)	2 (0%)
Bishop's score 2-6	7 (2%)	4 (1%)
Not assessed	439 (98%)	445 (99%)
In-patient at time of randomisation	362 (81%)	371 (82%)

Data are n (%) or mean ± standard deviation unless shown otherwise· n/N (%) indicates that the denominator only includes participants with a relevant measurement for that variable. LMWH: low molecular weight heparin; BP: blood pressure; IQR: interquartile range.

*Deprivation quintiles calculated for participants in England only (not available for participants in Wales).

† Minimisation factors used to ensure balance at randomisation.

Table 2: Primary maternal and perinatal outcomes

	Planned delivery	Expectant management	Effect measure	Adjusted effect measure*
			Effect size (95% CI) p-value	**Effect size (95% CI) p-value**
Composite of maternal morbidity and/or recorded systolic BP >=160 mmHg post randomisation	289/448 (65%)	338/451 (75%)	Risk ratio 0·86 (0·79, 0·94) 0.0006	Risk ratio 0·86 (0·79, 0·94) 0.0005
Intention to treat analysis				
Composite of perinatal deaths, and NNU admissions up to infant hospital discharge	196/471 (42%)	159/475 (34%)	Risk ratio 1·25 (1·05, 1·48) 0·0107	Risk ratio 1·26 (1·08, 1·47) 0.0034
			Risk difference 0·08 (0·02, 0·15)	Risk difference 0·07 (0·02, 0·13)
Per protocol analysis				
Composite of perinatal deaths, and Neonatal Unit admissions up to infant hospital discharge	155/342 (45%)	155/470 (33%)	Risk ratio 1·37 (1·15, 1·64) 0.0005	Risk ratio 1·40 (1·18, 1·66) <0·0001
			Risk difference 0·12 (0·05, 0·19)	Risk difference 0·11 (0·05, 0·17)

Data are n (%).

*Adjusted for centre, singleton/ twin pregnancies, severity of hypertension in 48 hours prior to enrolment, parity, previous caesarean section and gestational age at randomisation.

Table 3: Secondary maternal outcomes post randomisation

	Planned delivery (n=448)	Expectant management (n=451)	Adjusted risk ratio* (95% CI)
Maternal morbidity composite outcome	68 (15%)	90 (20%)	0·76 (0·59, 0·98)
Systolic BP >=160 mmHg	267 (60%)	313 (70%)	0·85 (0·77, 0·94)
Progression to severe pre-eclampsia	287 (64%)	334 (74%)	0·86 (0·79, 0·94)
Placental abruption	4 (1%)	4 (1%)	1·00 (0·37, 2·67)
Antihypertensive medication prior to delivery	381 (85%)	405 (90%)	0·95 (0·91, 0·99)
Onset of labour			
Spontaneous	2 (0%)	19 (4%)	0·11 (0·02, 0·50)
Induced	304 (68%)	275 (61%)	1·11 (1·01, 1·23)
Pre-labour caesarean section	140 (31%)	152 (34%)	0·93 (0·76, 1·13)
PROM and augmentation	1 (0%)	4 (1%)	
Indication for delivery (non-exclusive)†			
Spontaneous labour <37 weeks' gestation	2 (0%)	19 (4%)	
Trial allocation to planned delivery arm	445 (100%)	0 (0%)	
Reaching 37 weeks' gestation	8 (2%)	188 (42%)	
Uncontrolled maternal hypertension	26 (6%)	111 (25%)	
Maternal haematological abnormality	3 (1%)	23 (5%)	
Maternal biochemical abnormality	19 (4%)	57 (13%)	
Fetal compromise on ultrasound scan	16 (4%)	50 (11%)	
Fetal compromise on cardiotocography	33 (7%)	64 (14%)	
Severe maternal symptoms	9 (2%)	48 (11%)	
Other (with none of the above)	0 (0%)	2 (0%)	
Maternal complications prior to discharge			
Confirmed thromboembolic disease	0 (0%)	0 (0%)	-
Confirmed sepsis (positive blood or urine cultures)	2 (0%)	6 (1%)	0·36 (0·07, 1·74)

Data are n (%). CI: confidence intervals· BP: blood pressure; PROM: prelabour rupture of membranes.

*Adjusted for centre, singleton/ twin pregnancies, severity of hypertension in 48 hours prior to enrolment, parity, previous caesarean section and gestational age at randomisation.

† Indications for delivery were pre-defined in the protocol.

Table 4: Secondary perinatal outcomes post randomisation (by intention to treat analysis)

	Planned Delivery (n=471)	**Expectant management (n=475)**	**Adjusted effect measure* (95% CI)**
Stillbirth	0 (0%)	0 (0%)	-
Neonatal deaths within 7 days of delivery	0 (0%)	0 (0%)	-
Neonatal death before discharge	0 (0%)	0 (0%)	-
Median (IQR) gestational age at delivery (days)	252 (246 to 257)	257 (251 to 260)	-3 (-3·5, -2·5)
Mode of delivery			
Spontaneous vaginal	169 (36%)	139 (29%)	1·21 (1·04, 1·41)
Assisted vaginal	40 (9%)	47 (10%)	0·87 (0·61, 1·26)
Caesarean section	260 (55%)	289 (61%)	0·92 (0·84, 1·01)
Median (IQR) birth weight (g)	2405 (2070 to 2753)	2480 (2150 to 2910)	-85 (-137, -33)
Median (IQR) birth weight centile†	35 (17 to 61)	30 (13 to 61)	4·2 (-0·4, 8·7)
Birth weight <10th centile	74 (16%)	95 (20%)	0·79 (0·58, 1·09)
Birth weight <3rd centile	20 (4%)	27 (6%)	0·77 (0·43, 1·38)
Median (IQR) Apgar score at 5 minutes post birth	10 (9 to 10)	10 (9 to 10)	0 (-1.1, 1.1)
Median (IQR) umbilical arterial pH Umbilical arterial pH collected	7·26 (7·20 to 7·20) 281 (60%)	7·25 (7·20 to 7·30) 266 (56%)	0·00 (-0·01, 0·01)
Number of infants admitted to neonatal unit	196 (42%)	159 (34%)	1·26 (1·08, 1·47)
Principal recorded indication for neonatal unit admission‡			
Prematurity	83/196 (42%)	40/159 (25%)	
Respiratory disease	47/196 (24%)	41/159 (26%)	
Hypoglycaemia	21/196 (11%)	31/159 (20%)	
Jaundice	12/196 (6%)	11/159 (7%)	
Infection suspected/confirmed	9/196 (5%)	12/159 (8%)	
Intrauterine growth restriction/ Small for gestational age infant	8/196 (4%)	10/159 (6%)	
Other	16/196 (8%)	14/159 (9%)	
Need for respiratory support	45 (10%)	48 (10%)	0·97 (0·60, 1·57)
Need for supplementary oxygen before	60 (13%)	49 (10%)	1·26 (0·89, 1·79)

discharge			
Median (IQR) days supplemental oxygen required	1 (1 to 2)	2 (1 to 3)	
Total neonatal unit stay			
Median (IQR) days in neonatal unit Number (%) admitted for at least one day	6 (3 to 11) 181 (39%)	6 (3 to 12) 153 (33%)	0 (-1·32, 1·32)
Category of care during neonatal unit stay (separation of baby from mother)			
Median (IQR) days in intensive care Number (%) admitted	2 (1 to 3) 27 (6%)	3 (1 to 4) 19 (4%)	-1·3 (-18, 16)
Median (IQR) days in high dependency care Number (%) admitted	2 (1 to 3) 51 (11%)	2 (1 to 4) 33 (7%)	-0·5 (-1·5, 0·5)
Median (IQR) days in special care Number (%) admitted	6 (2 to 10) 168 (36%)	6 (2 to 11) 143 (31%)	0 (-1·4, 1·4)
Category of care during other postnatal stay (baby alongside mother)			
Median (IQR) days in transitional care Number (%) admitted	5 (2 to 8) 40 (9%)	5 (4 to 6) 16 (3%)	0·5 (-14, 15)
Median (IQR) days in postnatal care Number (%) admitted	3 (2 to 5) 350 (75%)	3 (2 to 4) 384 (82%)	0·5 (0·28, 0·72)

Data are n (%) unless otherwise stated. Effect measures are risk ratios for categorical variables (risk in planned delivery group/ risk in expectant management group) and median differences for continuous variables (median in planned delivery group - median in expectant management group). CI: confidence intervals; IQR: interquartile range· n/N (%) indicates that the denominator only includes participants with a relevant measurement for that variable.

*Adjusted for centre, singleton/ twin pregnancies, severity of hypertension in 48 hours prior to enrolment, parity, previous caesarean section and gestational age at randomisation.

† Birth weight centile calculated using the Stata add-in function zanthro using the British 1990 Growth Reference (reanalysed 2009).

‡ Full list of other indications for Neonatal Unit admission given in Supplementary Table 4.

Table 5: Health economic evaluation of costs

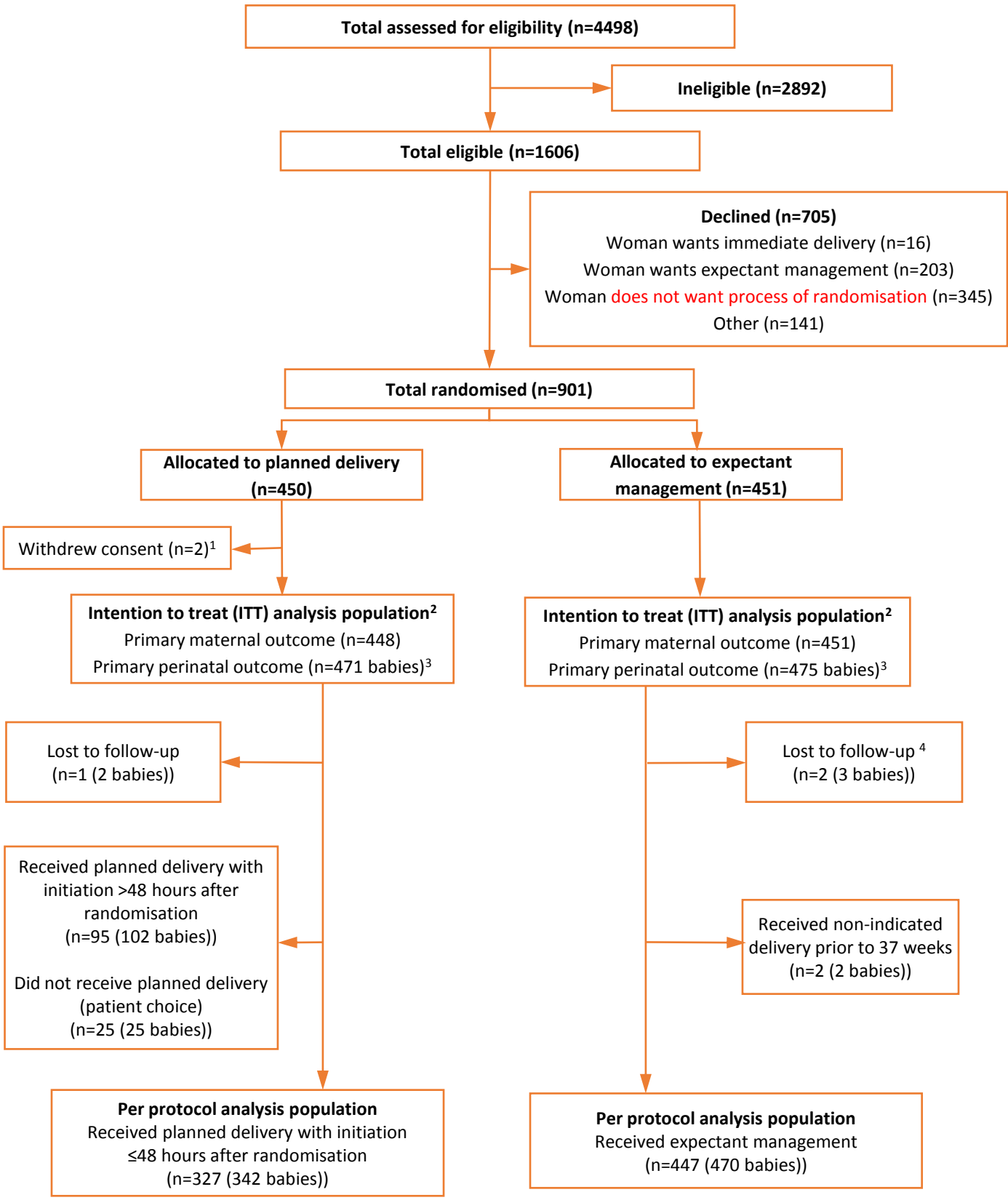
Cost component	Planned Delivery	Expectant Management	Adjusted effect measure* (95% CI)
	n=448	**n=451**	
Antenatal Inpatient	£1261 (72)	£2892 (139)	
Labour and delivery	£6087 (172)	£5468 (184)	
Maternal ITU and HDU	£422 (55)	£610 (69)	
Maternal Outpatient	£68 (12)	£292 (27)	
Maternal Transfer	£30 (21)	£65 (52)	
Total Maternal costs	£8238 (199)	£9866 (267)	
	n=471	**n=475**	
Infant Intensive Care	£198 (52)	£362 (182)	
Infant High Dependency care	£239 (43)	£203 (49)	
Infant Special Care	£1402 (127)	£1257 (124)	
Infant normal and transitional care	£1515 (69)	£1401 (65)	
Total Infant costs	£3354 (156)	£3223 (234)	
Total: Maternal and Infant costs	£11,574 (302)	£13,090 (389)	£1478 (£2354 to £605) P=0·001

Data are mean (standard error) unless shown otherwise.

* Adjusted for centre, singleton/ twin pregnancies, severity of hypertension in 48 hours prior to enrolment, parity, previous caesarean section and gestational age at randomisation.

Figure

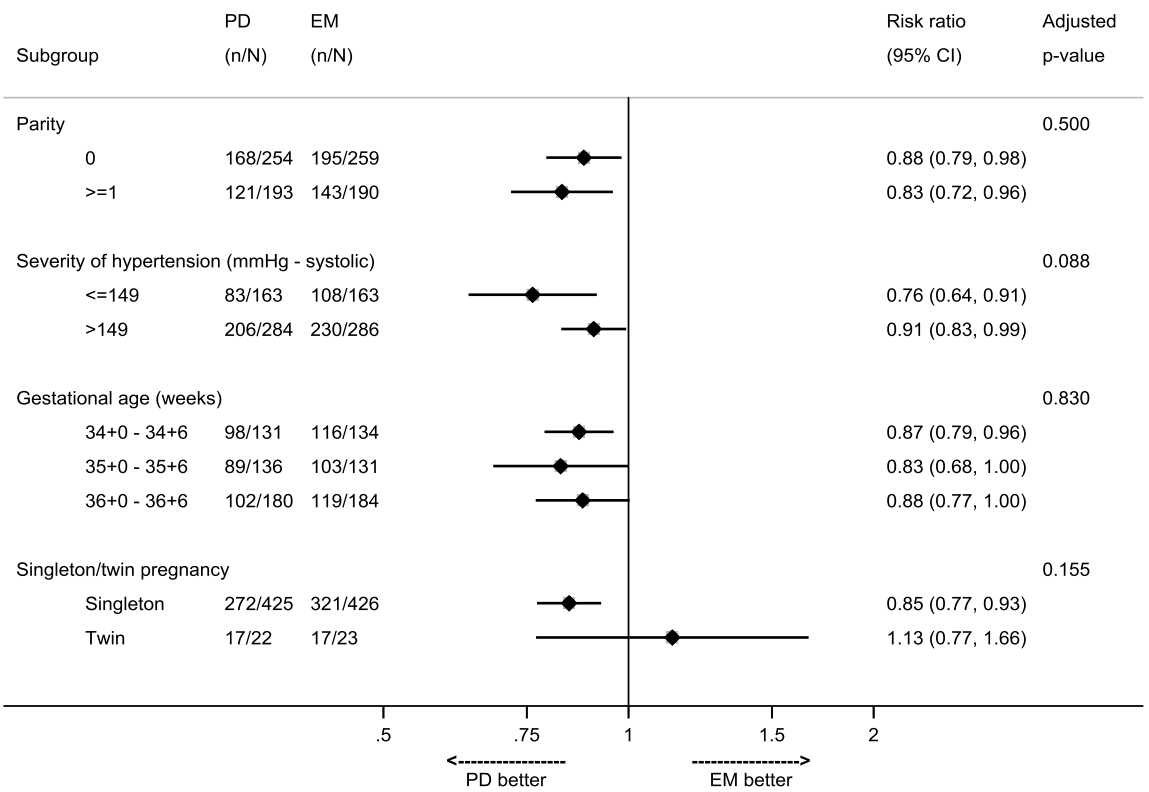
Figure 1: CONSORT flow diagram of participants

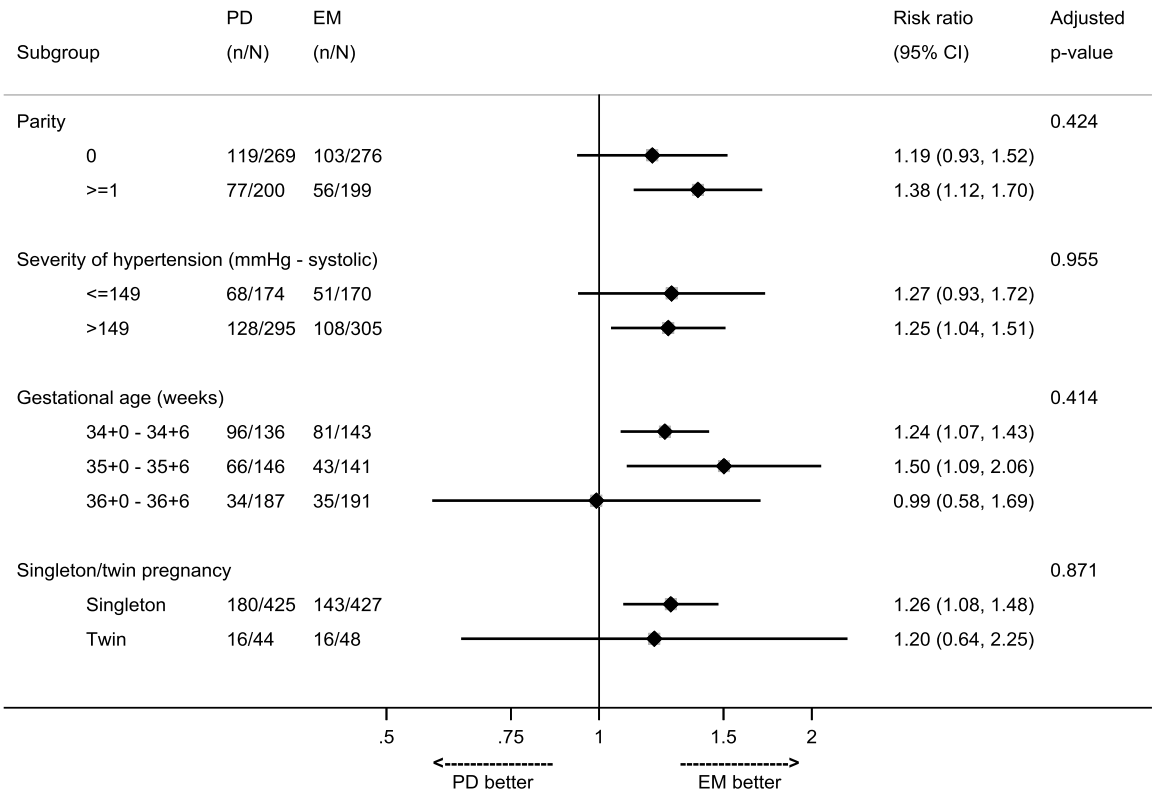


Notes:

1. These women withdrew from the trial and withdrew consent for data already collected to be used so are excluded from all analyses. One of these woman withdrew before initiation of delivery, the other withdrew after receiving planned delivery within 48 hours.
2. Analysis populations are based on intention to treat (ITT) (i.e. all participants as randomised) for all tables unless otherwise stated.
3. Includes all babies of all mothers included in the primary maternal outcome.
4. 1 woman in this group has documented delivery prior to 37 weeks (on electronic health records) but no further information available

Figure 2: Forest plot for sub-group analysis (Intention to Treat population) of primary maternal outcome (top panel) and primary perinatal outcome (bottom panel) comparing Planned Delivery (PD) with Expectant Management (EM). p-values compare risk ratios across the different sub-groups of each factor.





Response to editors' and reviewers' comments for THELANCET-D-19-04782

1. Please indicate after each of the reviewers' points the text changes which have been made (if any) and the line number on the revised manuscript at which your change can be found. [Line numbers can be added to your word document using the 'page layout' tab. Please select continuous numbers.]

A. We have done this, using line numbers from the tracked changes version.

2. When interpreting editorial points made by reviewers, please remember we will edit the final manuscript if accepted.

A. We acknowledge that further editing will be undertaken if accepted.

3. Please indicate any authors who are full professors.

A. We have edited the author list to indicate full professors.

4. Please list the highest degree for each author (one degree only, please).

A. We have done this. Marcus Green does not have a degree.

5. Please check that all author name spellings and affiliations are correct.

A. We have checked these. In addition, we request addition of four authors being moved from the acknowledgements section to the main authorship section. These are three statisticians who worked on the project (MG, VC, JT), and the trial manager (AP), all based at the NPEU CTU when undertaking this work.

6. For randomised trials please follow the CONSORT reporting guidelines and CONSORT for abstracts and include a CONSORT checklist with your resubmission.

A. We have included a CONSORT checklist with our submission.

7. Please ensure that the title of the paper is non-declamatory (ie, it describes the aim of study rather than the findings) and that it includes a description of the study type (eg, a randomised controlled trial).

A. We have done this.

8. Please limit the summary to pre-defined primary endpoints and safety endpoints.

A. We have done this.

9. For RCTs, please state the trial registration number.

A. We have done this (Abstract and Methods)

10. At the end of the methods section please state the role of the funder in: data collection, analysis, interpretation, writing of the manuscript and the decision to submit. Please also state which author(s) had access to all the data, and which author(s) were responsible for the decision to submit the manuscript etc.

A. We have added the role of the funder and authors as indicated.

11. Please explain any deviations from the protocol.

A. We have stated that 'There were no substantial changes to the published study design or methods or outcomes[7] after commencement of the trial' and have included the published protocol in our uploaded files.

12. Please report all outcomes specified in the protocol.

A. We have reported all outcomes as specified in the protocol, dividing secondary outcomes into those specified as tested and those as descriptive, as listed in the Statistical Analysis Plan.

13. If any exploratory outcomes are reported that were not pre-specified, please make it clear that these analyses were post-hoc.

A. We have not included post-hoc analyses.

14. Please use rINNs for drug names. For genes and proteins, authors can use their preferred terminology so long as it is in current use by the community, but should provide the preferred human name from Uniprot for proteins and HUGO for genes at first use to assist non-specialists.

A. Not applicable

15. For drug studies, please ensure that details of doses, route of delivery, and schedule are included.

A. Not applicable

16. For the main outcome measures, please include a result for each group, plus a point estimate (eg, RR, HR) with a measure of precision (eg, 95% CI) for the absolute difference between groups, in both the Summary and the main Results section of the paper.

A. We have done this for all outcomes except for ones where we prespecified that no statistical testing would be performed in the Statistical Analysis Plan.

17. p-values should be exact, but no longer than 4 decimal places (eg p<0.0001). Two decimals are acceptable in tables for non-significant p-values

A. We have replaced the p-values in Table 2 (and corresponding text) and Table S9 with exact values.

18. Please provide absolute numbers to accompany all percentages. Percentages should be rounded to whole numbers unless the study population is very large (>10 000 individuals).

A. We have replaced all percentages with whole numbers.

19. Please give 95% confidence intervals for hazard ratios/odds ratios.

A. Not applicable

20. For means, please provide standard deviation (or error, as appropriate).

A. We have done this

21. Please provide interquartile ranges for medians.

A. We have done this

22. Please provide numbers at risk for Kaplan-Meier plots and ensure that plots include a measure of effect (eg, log-rank p); estimates should be reported with 95% CIs.

A. Not applicable

23. Please ensure that the Discussion contains a section on limitations of the study.

A. We have done this.

24. Please provide the text, tables, and figures in an editable format. See link above this list for details of acceptable formats for figure files.

A. We have done this.

25. Our production system is not compatible with Endnotes. Please convert to normal text.

A. We have converted to static text.

26. If accepted, only 5-6 non-text items (figures, tables, or panels) can be accommodated in the print edition; additional material can be provided in a web appendix. Please indicate which items can go in a web appendix.

A. We have provided a web appendix for supplementary items. Depending on the editors' preferences, we can move the last line of Table 5, which is the tested comparison of health economic costs, into one of the other Tables, and include the rest of the health economic evaluation (untested) into the Supplementary Appendix.

27. Please provide a research in context panel with 3 parts: Evidence before this study (which includes a description of how you searched for evidence and how you assessed the quality of that evidence); Added value of the study; and Implications of all the available evidence.

A. We have done this.

28. At the end of the manuscript, please summarise the contribution of each author to the work.

A. We have done this.

29. At the end of the manuscript please summarise the declaration of interests for each author.

A. We have done this.

30. If you have not yet done so, please return all signed authorship statements and conflict of interest forms. We also require signed statements from any named person in the acknowledgements saying that they agree to be acknowledged.

A. We are finalising all the forms and will forward them.

31. For any personal communication, please provide a letter showing that the person agrees to their name being used.

A. Not applicable

32. As corresponding author, please confirm that all authors have seen and approved of the final text.

A. I confirm that this is the case.

33. If your author line includes a study group, collaborators' names and affiliations may be listed at the end of the paper or in the appendix. Additionally, if you wish the names of collaborators within a study group to appear on PubMed, please upload with your revision a list of names of all study group members presented as a two-column table in Word. First and middle names or initials should be placed in the first column, and surnames in the second column. Names should be ordered as you wish them to appear on PubMed. The table will not be included in the paper itself - it's simply used to make sure that PubMed adds the names correctly.

A. We have included a list of collaborators as indicated.

34. Please note our guideline length for research articles is 3500 words and 30 references. For RCTs, the text can be expanded to 4500 words.

A. The text is within the word limit.

35. From July 1, 2018, all submitted reports of clinical trials must contain a data sharing statement, to be included at the end of the manuscript or in an appendix (please provide as a separate pdf). Data sharing statements must indicate:

- *Whether data collected for the study, including individual participant data and a data dictionary defining each field in the set, will be made available to others; *What data will be made available (deidentified participant data, participant data with identifiers, data dictionary, or other specified data set); *Whether additional, related documents will be available (eg, study protocol, statistical analysis plan, informed consent form); *When these data will be available (beginning and end date, or "with publication", as applicable); *Where the data will be made available (including complete URLs or email addresses if relevant); *By what access criteria data will be shared (including with whom, for what types of analyses, by what mechanism - eg, with or without investigator support, after approval of a proposal, with a signed data access agreement - or any additional restrictions).
- Clinical trials that begin enrolling participants on or after Jan 1, 2019, must include a data sharing plan in the trial's registration. If the data sharing plan changes after registration, this should be reflected in the statement submitted and published, and updated in the registry record. For reports of research other than clinical trials, data sharing statements are encouraged but not required. Mendeley Data (https://eur03.safelinks.protection.outlook.com/?url=https%3A%2F%2Fdata.mendeley.com&data=01%7C01%7Clucy.chappell%40kcl.ac.uk%7C97f95e31bb2a45d05bc208d717992fe5%7C8370cf1416f34c16b83c724071654356%7C0&sdata=5wetA6iZKnzytVY5%2FICJ8GLzIqbuMionJZBGzufkS%2Bs%3D&reserved=0) is a secure online repository for research data, permitting archiving of any file type and assigning a permanent and unique digital object identifier (DOI) so that the files can be easily referenced. If authors wish to share their supporting data, and have not already made alternative arrangements, a Mendeley DOI can be referred to in the data sharing statement.

A. We have included a data sharing statement.

Reviewer #1: Thanks for allowing me to review the manuscript THELANCET-D-19-04782 "Planned early delivery or expectant management for late preterm pre-eclampsia: a randomised controlled trial (PHOENIX trial).

The editors should know that I have been involved in HYPITAT I and HYPITAT II, and that the Phoenix and HYPITAT teams have the intention to share data in an IPD.

First, I want to congratulate the authors who did a fantastic job by recruiting so many women in such a relatively short time. The research network in the UK is leading worldwide in pragmatic trials (we have a waiting list for journal club in Melbourne), and PHOENIX is going to be yet another landmark trial.
The study randomized 901 women with pre-eclampsia between 34-37 weeks, and found that planned delivery reduces maternal morbidity and severe hypertension, with more neonatal unit admissions related to prematurity, but no indicators of greater neonatal morbidity.

The study is well designed and executed, and is the largest in its size worldwide.

1.1 Criticism could be that the co-primary perinatal outcome contains NICU admission. If the conclusion is that planned delivery results in "more neonatal unit admissions related to prematurity, but no indicators of greater neonatal morbidity" than why not limit the primary outcome to greater neonatal morbidity".

A. We appreciate the reviewer's point that it could be a clearer message to focus on neonatal morbidity only, but we do not think that we could change the primary outcome at this stage. At trial inception there was no validated measure of neonatal morbidity that represented the potential harms of both groups (planned delivery and expectant management). As we understood at the time that there was no routine admission for prematurity, neonatal unit admission appeared to be appropriate. We have clarified in the manuscript that neonatal unit admission may have been driven by clinical practice related to arbitrary gestational age thresholds rather than clinical condition of the infant, in view of the lack of associated morbidity:
Discussion (line 344):
As adjudication of multi-organ neonatal morbidity is complex and subjective, and no widely accepted validated measure of neonatal morbidity is currently available, we chose neonatal unit admission (involving separation of the baby from the mother), supported by our lay representatives, and intending that this would capture underlying neonatal morbidity. Although UK clinical practice guidelines do not recommend routine admission of an infant based solely on gestational age after 34 weeks of pregnancy, admission solely for prematurity in this trial suggests different real-world clinician behaviour, despite no differences in objective measures of direct neonatal morbidity being demonstrated.
And
Discussion (line 396)
Additional prolongation of pregnancy by five days (in the expectant management group) may move an infant out of a notional group where admission is dictated by a guideline (for example based on a gestational age threshold), rather than by clinical need.

Detailed comments

Abstract
1.2 Interpretation: I would put more stress on leaving women a choice.
A. We have edited the manuscript as follows (and edited other words from the abstract to reduce word count):
Abstract (line 65)

Interpretation
There is strong evidence to suggest that planned delivery reduces maternal morbidity and severe hypertension, with more neonatal unit admissions related to prematurity, but no indicators of greater neonatal morbidity, compared to expectant management. This trade-off should be discussed with women with late preterm pre-eclampsia to allow shared decision making on timing of delivery.

1.3 Introduction: line 72; suggest to add reference to HYPITAT 1; Lancet. 2009 Sep 19; 374(9694): 979-988.

A. We have added the reference as suggested:
Introduction (line 80)
'…since maternal and fetal risks can be significantly reduced without any additional risks from such an intervention.[5]

1.4 Line 94: add the trial registration number

A. We have added as follows:
Methods (line 242):
The trial is registered with the ISRCTN registry, number 01879376.

1.5 Participants: The description of the eligibility suggests that women with HELLP syndrome, severe thrombocytopenia etc. could be included, Were there not more inclusion criteria in place?

A. We have edited the manuscript as follows to make the inclusion criteria clearer:
Methods (line 112)
Current practice by national guidelines in use during the trial was for immediate delivery of a woman with persistent severe features of pre-eclampsia (including Haemolysis, Elevated Liver enzymes, Low Platelets syndrome), who would thus not be eligible for the trial.

1.6 Was there a measurement of cervical ripeness (vaginal examination, cervical length measurement) in place.

A. We collected information on cervical assessment prior to randomisation and have added this information to Table 1 as follows:
Table 1:
Cervical assessment (prior to randomisation)

Bishop's score <2	*2 (0.4)*	*2 (0.4)*
Bishop's score 2-6	*7 (1.6)*	*4 (0.9)*
Not assessed	*439 (98.0)*	*445 (98.7)*

1.7 I can live with the primary outcomes (I have to), but I would suggest for further studies to replace neonatal admission to intensive care by true neonatal morbidity. I can understand the choice of the authors here.

A. We agree that using a validated measure of neonatal morbidity would be ideal. Whilst there was no such validated composite measure of morbidity available at the time of trial design, the anticipated publication in 2019 or 2020 of neonatal core outcome sets (protocol published at https://bmjpaedsopen.bmj.com/content/1/1/e000048) may help this. The difficulty remains that capturing measures of morbidity across multiple organ systems using varying disease definitions will always be challenging.

Results:

1.8 I miss a paragraph where the authors describe how 'planned delivery' was executed. How many IOL? How many unripe cervix? Balloon or Prostaglandins?

A. We have made this clearer in the following paragraph in the Methods, and have checked that we have reported the relevant information in the Tables:
Methods (line 128)
Interventions
We allocated women to planned initiation of delivery within 48 hours of randomisation (to allow for corticosteroid administration to accelerate fetal lung maturation, and neonatal cot availability if necessary), usually by induction of labour (unless there was an additional specific indication for pre-labour Caesarean section) or to expectant management (usual care), with delivery at 37 weeks' gestation or sooner as clinical needs dictated in accordance with the UK national guidelines4 (as assessed by the clinician responsible for her care) for maternal indications (e.g. uncontrolled hypertension, abnormal blood results), or fetal compromise, or eclampsia or other clinical crisis. Individual decisions around mode of induction and delivery and Use of corticosteroids for fetal lung maturity was left to the discretion of the individual clinician, with the trial protocol advising that all options should be discussed with the pregnant woman and her needs and preferences taken into account.

In Table 3, we report the proportion of deliveries by onset:

Induced:	*304 (68·0%) vs. 275 (61·1%); aRR 1·11 (1·01, 1·23)*
Pre-labour caesarean section:	*140 (31·3%) vs. 152 (33·8%); aRR 0·93 (0·76, 1·13)*

In Supplementary Table 3, we report the method of induction:

Method of induction if induced (non-exclusive)		
Prostaglandin gel/pessary	*275/304 (90·5)*	*238/275 (86·6)*
Foley catheter	*13/304 (4·3)*	*7/275 (2·6)*
Artificial rupture of membranes	*133/304 (43·8)*	*120/275 (43·6)*
Syntocinon	*99/304 (32·6)*	*90/275 (32·7)*
Other	*1/304 (0·3)*	*3/275 (1·1)*

1.9 How many planned CS? What were the reasons for the emergency CS?

A. We have reported the onset of delivery as a maternal outcome (Table 3) and the actual mode of delivery as a perinatal outcome (Table 4), as twins can have different modes of delivery, but the onset relates to the woman. We have reported the indication for delivery in Table 3 and had not separated this out into indication for delivery by various modes of delivery (e.g. by emergency Caesarean section).

Discussion

1.10 I would be more neutral in discussing the results. 40% of the woman was beyond 36 weeks at randomization, hence a delay of 5 days was the maximum achievable. Most importantly, the information should be used to allow women to make a choice.

A. We have edited the manuscript to acknowledge this limitation:
Discussion (line 358)
Although it is acknowledged that for women enrolled after 36 weeks' gestation, expectant management would only be for a maximum of seven days, immediate planned delivery would still represent a change in clinical care from usual practice and the research uncertainty remained at trial conception. The proportion of women enrolled at 36 weeks' gestation was similar (and even slightly lower) than that enrolled in a similar trial,[13] and maternal benefit shown even at this gestation.
We have further emphasised the importance of shared decision-making in the abstract, as we agree with the reviewer that this information should be used to inform women's choices.

Figure 1:

1.11 Woman wants immediate delivery (n=16). Woman wants expectant management (n=203) Woman wants not to be randomised (n=345) I would change the wording, as all these women do not want to be randomized.

A. We have clarified as follows in the Figure box, as we intended to mean that the woman did not want her delivery plans to be decided by a randomisation process:
Figure 1:
Woman does not want process of randomisation

I strongly recommend publication.

Ben W Mol
Melbourne

Reviewer #2: The PHOENIX trial protocol has been presented previously (Chappell et al, Trials 2019), and the present well-written paper presents the result of this well-planned and well-performed RCT study across 46 maternity units in the UK (England and Wales).

2.1 As maternal health outcomes in preeclampsia are likely to improve when delivering the dysfunctional placenta, today's guidelines in most countries with a well-functioning health care system recommend delivery from week 37 of pregnancy when a preeclampsia diagnosis is verified, as health outcomes for the baby are reassuring. As for pregnancies below 34 weeks, the current evidence points to total (fetal) health benefits of prolonging the pregnancy in preeclampstic pregnancies, under close surveillance, as long as there are reassuring maternal and fetal surveillance data.
It is however uncertain what is the best clinical approach for preeclampsia diagnosed between 34 and 37 weeks of pregnancy. One previous publication from 2015 (HYPITAT-II: Broekhuijsen K et al, Lancet 2015) was smaller, and showed a non-significant reduction in maternal adverse outcomes in late preterm preeclampsia. A recent individual participant data "meta-analysis" by Bernardes TP et al (Ultrasound in obstetrics and gynecology 2019) indicated however a likely maternal benefit with deliver before GW 37 in some women with PE.
The current study by Chappell and coworkers is therefore be highly welcomed by the global obstetric communities. They aimed to determine whether planned delivery in women with pre-eclampsia between 34+ 0 and 36+ 6 weeks' gestation reduces maternal adverse outcomes without substantial worsening of neonatal or infant outcomes, compared with the current practice of expectant management to 37 weeks' gestation.
Their results point to less risk of maternal severe outcomes when a preeclamptic pregnancy diagnosed between 34 +0 and 36+6 s not prolonged, but rather planned to deliver within the next 2 days. As expected, they found a higher referral rate to NICU, as prematurely delivered babies are more likely to have respiratory distress symptoms. However, it is reassuring that the total neonatal morbidities were not increased for the active delivery group. Women in the expectant management group had a 5 day median additional prolongation of pregnancy, and over half of them had an indicated delivery before 37 weeks' gestation, with three quarters meeting the criteria for progression to severe pre-eclampsia. This suggests that more of the women in the prolongation group might be in need of more acute delivery methods. In line with this, the study showed that women in the planned delivery group had significantly more vaginal deliveries, which is likely beneficial for her future obstetric history (including less risk of invasive placentas in a scare uterus). The study showed that planned delivery had lower costs than expectant management in this UK healthcare setting, which is likely due to no increase in fetal morbidity severity as well as shorter observation time of the woman that was actively delivered, with less severe maternal morbidities).
The conclusions of the authors are balanced and wise, including shared decision making with the preeclamptic woman: "In conclusion, our trial supports offering initiation of delivery in women with late preterm pre-eclampsia. The trade-off of lower maternal morbidity and severe hypertension against higher neonatal unit admissions, albeit without additional respiratory or other morbidity, should be discussed with women with late preterm pre-eclampsia to allow shared decision making on timing of delivery" . This study findings are likely to be generalizable to similar healthcare settings.

A. We thank the reviewer for their thoughtful comments supporting our interpretation and their views on generalisability.

I have no major objections, but some minor comments and questions to the authors regarding this impressive study:

2.2 Table 1: could the authors indicate rates of overweight/obesity (not only mean BMI +/-SD at booking), as these are well-known risk factors for preeclampsia (PE)?

A. We have added this information to Supplementary Table 2 as follows (and are happy to swap it for median BMI (in Table 1) if the editors would prefer:

Body mass index (kg/m^2)	Planned delivery (n = 448)	Expectant management (n = 451)
18.0-24.9	4 (1%)	4 (1%)
25.0-29.9	126 (28%)	114 (25%)
30.0-34.9	120 (27%)	146 (32%)
35.0-39.9	161 (36%)	153 (34%)
≥40.0	37 (8%)	34 (8%)

2.3 Table 2: could the authors indicate rates for ART/IVF for the 2 groups (again well-known risk factors for preeclampsia)?

A. We acknowledge that this is a risk factor for pre-eclampsia, but we did not collect this information as we did not anticipate that it would influence our interpretation of the trial intervention.

2.4 The authors may comment on the fact that their patients had high rate of PE risk factors. Although the numbers are lower, was there any indication of which risk groups could have better or worse outcomes after a planned delivery versus expectant management? Did any of the high PE risk subgroups benefit more or less from active delivery?

a. What would the conclusions have been the same if only looking at primipara without other risk factors for PE?
b. Does Figure 2 suggest that women with DC/DA twins and PE (34-37 weeks) are less likely to benefit (maternal and neonatal outcomes) from planned delivery compared to expectant management?
c. What about women with superimposed PE; those with CTH(11%), is there any reason to assume they had same, better or worse effects of active delivery (as aspirine has no effect on these women (when screened positive in the ASPREE trial at first trimester screening) in reducing preterm PE?

A. We agree that it is a very interesting question as to whether there are sub-groups that might benefit more or less from planned delivery. We pre-specified the planned sub-group analyses in the protocol and have presented these in Figure 2 and Supplementary Figure 1. As the statistical test for interaction was not significant for any sub-groups, we have tried not to over-interpret visual inspection of the Forest plots in these Figures. We are planning further exploratory analyses (that would not usually be reported in the main manuscript), but we consider that it will be even more informative if conducted as individual patient data meta-analyses with data from other similar trials (such as HYPITAT-2). We will include both of the reviewer's suggested sub-groups (primipara, women with chronic hypertension) in that planned IPD.

2.5 "Research in context": pleas insert the appropriate reference to the cited Cochrane review of 2017.

A. We have followed the Lancet instructions for authors: 'Research in context panels should not contain references; key studies mentioned here should be referenced in the main text.' We have checked that we have referenced this Cochrane review in the main text (reference 13).

2.6 Women with prematurely delivered PE have epidemiologically the highest risk among women with previous PE for several NCDs, including CVD (cardiovascular disease): Would the authors like to speculate whether a more rapid delivery of the women with preterm preeclampsia also could improve her long-term health outcomes, such as CVD, as the stress of her

cardiovasculature is shorter than if not actively planned to deliver? The same question goes for the infant, warranting a long-term (but extremely challenging) follow-up of such excellent RCTs. Are the authors planning such a study?

A. We have two such studies planned: we offered women eligible for the PHOENIX trial enrolment into a nested study (named PHOEBE), in which we have undertaken maternal echocardiography at 6 months post-partum to assess the effect of pre-eclampsia on the woman's heart (details listed on http://www.isrctn.com/ISRCTN01879376) and we have offered long-term follow-up of the infants born to women in PHOENIX. Results of these studies will be disseminated when available, but follow-up and analysis is still ongoing.

Reviewer #3: The present, open-label, multicentre, RCT was conducted to examine the efficacy and safety of planned delivery compared with expectant management i.e. usual care among women with late preterm pre-eclampsia (34-37 weeks' gestation) in relation to a composite maternal morbidity and SBP>=160 mmHg and a composite perinatal outcome. The trial participants were recruited in 46 maternity units in the UK between September 2014 and December 2018. The trial findings showed a reduced risk of maternal morbidity in the planned delivery arm with increased risk of perinatal outcomes, although the perinatal outcomes were mostly due to admission to neonatal unit related to prematurity and not perinatal death. The manuscript is very well written and the Discussion is very thorough. The authors may wish to consider the following comments:

3.1 Abstract: It would be worth mentioning how multiple testing was handled in the analysis and what factors were included in the models considering that adjusted risk ratios were reported with the name of the statistical model used for the analysis. Considering that the perinatal outcomes endpoint was a non-inferiority endpoint, this should be highlighted and the per-protocol result should be reported in the Abstract because the intention to treat result is potentially biased towards the null i.e. biased towards achieving non-inferiority.

A. The abstract word count is restricted, and so it is difficult to include such level of detail about the statistical modelling process in the abstract, without omitting important summary information from elsewhere. We have followed CONSORT guidelines for abstracts (http://www.consort-statement.org/checklists/view/32--consort-2010/67-abstract), but we can include this additional information in the Abstract at the editors' request. We have edited the Abstract to indicated that the perinatal outcome was based on a non-inferiority hypothesis and that the results of the PP analysis were similar to the ITT analysis as follows (we can add further numbers for the PP analysis in the Results if the editors wish). We have ensured that we have reported adjustment variables as footnotes in the tables, and we have also edited the text in the main Methods section as shown below:

[Abstract] Methods
In this UK parallel-group, non-masked, multi-centre, randomised controlled trial, we compared planned delivery against expectant management (usual care) with individual randomisation in women with late preterm pre-eclampsia from 34 to 37 weeks' gestation and a singleton or dichorionic diamniotic twin pregnancy. The co-primary maternal outcome was a composite of maternal morbidity or recorded systolic blood pressure ≥160 mmHg with a superiority hypothesis. The co-primary perinatal outcome was a composite of perinatal deaths or neonatal unit admission up to infant hospital discharge with a non-inferiority hypothesis. Analyses were by intention to treat, together with a per protocol analysis for the perinatal outcome. The trial was prospectively registered (ISRCTN Registry, number 01879376).

[Abstract] Findings
Between 29 September 2014 and 10 December 2018, 901 women were recruited across 46 maternity units. 450 women (448 women and 471 infants analysed) were allocated to planned delivery, and 451 women (451 women and 475 infants analysed) to expectant management. The incidence of the co-primary maternal outcome was significantly lower in the planned delivery group (64·7%) compared to the expectant management group (75·3%); adjusted risk ratio 0·86 (95% CI 0·79 to 0·94); p<0·01. The incidence of the co-primary perinatal outcome was significantly higher in the planned delivery group (41·8%) compared to the expectant management group (33·5%); adjusted risk ratio 1·26 (95% CI 1·08 to 1·47); p<0·01. The results from the per protocol analysis were similar. There were nine serious adverse events in the planned delivery group and twelve in the expectant management group.

Methods (line 221):

No adjustment of co-primary outcomes was made for multiplicity.[13]

3.2 Considering that 900 women were recruited at 46 centres there would be an average of 20 women recruited at each centre. Would these numbers be enough to achieve the stratification according to five variables in addition to centre?

A. Randomisation was performed using a probabilistic (prospective allocation based on accruing information) minimisation algorithm to ensure approximate balance across strata on marginal totals, unlike classic stratified permuted block randomisation (conducted in advance and not based on accruing information), and therefore we considered that these criteria were not necessarily strictly applicable. In addition, we monitored the randomisation schedule at regular intervals as per NPEU CTU_SOP ST102 4.0 Randomisation Procedures, and the DMC also monitored the randomisation at their annual meetings. We can confirm that good balance across arms for each of the stratification factors, as demonstrated in Table 1.

3.3 The statistical analysis section should describe whether multiple testing due to having co-primary endpoints was adjusted for and what approach was taken. If this was not accounted for, a justification is needed as to why this was not planned.

A. Our approach fundamentally adheres to the concept that a clinical trial is a focused scientific research question, the result of which and interpretation thereof are considered sometimes in terms of one or two key outcomes. These outcomes are considered as a whole picture and interpreted likewise. Rigidly adjusting for multiplicity can be counter-intuitive (especially to the reader) in so far as diluting what is often corroborating evidence. In addition, no one could reasonably expect us to conduct two separate clinical trials, one looking at the woman's outcomes, the other at the infant's outcomes, but in that case, there would be no question of adjustment. Women and their infants need to be considered together. Statistical adjustment for multiple comparisons invokes debate among methodologists, and there is no consensus. While some would use such an adjustment, others would never apply adjustments (Rothman et al Epidemiology 1990). We do not fall into the latter camp, but are not making confirmatory claims. As stated in the European Medicines Agency's guideline on multiplicity issues in clinical trials, 'as a general rule it can be stated that control of the study-wise type I error is a minimal prerequisite for confirmatory claims' (https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-multiplicity-issues-clinical-trials_en.pdf). As both co-primary outcomes are important clinical aspects of this research question that needed to be considered on balance, we did not adjust for multiple testing. We have added this (with a reference) to the Methods as follows:
Methods (line 221)
95% confidence intervals are presented for all primary and secondary outcomes. No adjustment of co-primary outcomes was made for multiplicity.[13]

3.4 Was there a plan on how to interpret the results from the co-primary endpoints? Considering they are co-primary, one understands that they are of equal importance and in the event of conflicting results, i.e. the results of the co-primary endpoints do not support the same conclusion, one expects that there should have been a plan for the interpretation of the results. Although the perinatal endpoint was analysed using the intention to treat and per-protocol populations and the authors acknowledgment that the per-protocol analysis is needed for the non-inferiority analysis, the authors seem to favour the intention to treat result. However, this is likely to be biased towards the null. Why would we believe the RR of 1.26 and not the 1.40? these are not necessarily similar, at least from a clinical point of view. I realise that the perinatal outcome result ended up being a superiority result but all these issues together makes it difficult to draw robust conclusions without being planned in the protocol. As a statistician I may have missed some clinical issues, however, would not one expect a higher risk of prematurity and

admission to the neonatal unit in the planned delivery arm considering the higher likelihood of preterm delivery?

A. The reviewer will be aware that it is common in perinatal trials (as well as clinical practice) to consider the perspective of the woman and the infant, and thus to have two co-primary outcomes. At inception of the trial, we chose neonatal unit admission to try and represent the potential disadvantages to the infant of both groups – being delivered earlier vs. risks of ongoing pre-eclampsia, in the face of clinical guidelines that do not mandate admission (and therefore increased admission was not automatically anticipated.
It is difficult to pre-specify interpretation of every possible scenario, as in practice, clinicians and women may put different weight on benefits and risks of interventions. This underpins our conclusion that these data should be used to enable shared decision-making with a woman with pre-eclampsia. This are many similar instances in maternity care, where a woman will make her own decision depending on her perception of this trade-off; common examples include considering vaginal birth after a previous Caesarean section, induction of labour vs. expectant management at term gestation etc.

3.5 The numbers needed to treat are reporting in the results and this should be mentioned in the statistical analysis section. Why the numbers needed to treat is reported for the maternal outcome while risk difference is reported for the perinatal outcome? Why not report the numbers needed to harm for the perinatal outcome? This would be more consistent and important to interpret the results in a more balanced way. I could not find the numbers needed to treat analysis in the protocol, was this a post-hoc calculation?

A. We initially considered that readers might want to see these, but we have now removed them from the Tables as these were not pre-specified in the protocol, as pointed out.

3.6 Table 3: what is the basis of reporting the risk ratios for some outcomes but not others? Was this based on number of events? This does not seem to be the case because the confirmed sepsis risk ratio is based on 2 cases in the treatment arm. The same applies to Table 4.

A. We have reported the risk ratios for the secondary outcomes that we pre-specified (in the Statistical Analysis Plan) that would be tested. We have moved the non-tested outcomes to the Supplementary Tables to make this clearer.

Reviewer #4: This is an important clinical question to answer by a randomized trial. The trial is well-designed however there are major flaws with inclusion criteria and in selection of primary outcome.

4.1 The study is designed to address late preterm preeclampsia, but the authors do not mention whether the patients had preeclampsia or preeclampsia with severe features. Indeed, there is considerable overlap in included subjects if one is make results generalizable to definitions by various international Organizations. For example , many of the patients included for expectant management had indications for delivery using ACOG Criteria (Task Force on Hypertension in Pregnancy 3013, and ACOG practice Bulletin on gestational hypertension-preeclampsia 2019. Such examples include EFW < 10th percentile (15%) are not candidates for expectant management after 34 weeks' gestation, a serum creatinine of > 90 micromole/L (> 1.1 mg/dl), AST> 70 IU/l.

A. We recognise that there are different strategies for managing women in various healthcare settings. We are not aware of a robust evidence base that determines optimal management for women with late preterm pre-eclampsia (whether planned delivery or expectant management) and sought to address this with the trial. This approach is reflected in the widely adopted guidelines of the International Society for the Study of Hypertension in pregnancy; in its most recent guidelines (2018), it states: 'Women with onset of pre-eclampsia between 34 and 37 weeks' gestation should be managed with an expectant conservative approach, as below.' We have made this context clearer in the manuscript as follows:
Introduction (line 87)
In the absence of definitive new evidence, this advice has been maintained in the most recent management recommendations from the International Society for the Study of Hypertension in Pregnancy, published in 2018,[6] used to inform current practice in many countries worldwide.

4.2 83% of patients were receiving at least one oral antihypertensive medication, and 35% were receiving at least 2 medications. Using guidelines by ACOG ,many of these will be considered to have severe disease requiring delivery at 34 weeks. In the US, antihypertensives are not used in those with SBP< 160 or in DBP < 105 mm Hg.

A. We accept that there are different national guidelines, as mentioned above, but are aware that many countries other than the US have adopted the International Society for the Study of Hypertension in Pregnancy guidelines (including Europe, Australasia, Japan, Canada etc.). We noted the current international guidelines recommend delivery for the following indications:

Delivery is necessary when one or more of the following indications emerge:
i. Inability to control maternal blood pressure despite using 3 or more classes of antihypertensives in appropriate doses.
ii. Maternal pulse oximetry<90%.
iii. Progressive deterioration in liver function, creatinine, haemolysis or platelet count.
iv. Ongoing neurological features such as severe intractable headache, repeated visual scotomata, or eclampsia.
v. Placental abruption.
vi. Reversed end-diastolic flow in the umbilical artery Doppler velocimetry, a non-reassuring CTG, or stillbirth.

The women included in our trial did not therefore meet the requirement for immediate delivery (and it was an explicit criterion that anticipated need for delivery in the next 48 hours would exclude a woman). We have not added all the indications listed above to the manuscript as we have included reference to the national guidelines in use, but are happy to edit the manuscript further if the editors think it would be useful to provide further context.

We anticipate that this trial will further inform the evidence base for all guidelines, including those of the US. We have edited the manuscript as follows:
Discussion (line 333)
Findings are likely to be generalisable to similar healthcare settings, as it was undertaken in a large number of maternity units across England and Wales, with diverse representation of women both in demographic terms and disease spectrum and with recommendations for expectant management and indications for delivery in clinical practice similar in our trial (which followed UK national guidelines[4]) and current international guidelines.[6]

4.3 Selection of both primary outcomes is a major limitation of the study. This probably was done to limit the sample size , but it is not clinically a relevant outcome. For maternal outcome ,the differences between the 2 groups are driven mainly by an isolated recording of a single systolic BP> 160 mm Hg between randomization and delivery. This is self fulfilling considering that 82% of patients in expectant group were enrolled while hospitalized , and the protocol required measurement of BP at least 4 X / day. Frequent recordings of BP are more likely to identify an isolated elevation that has no clinical relevance. Also, the likelyhood of having such a value will depend on whether anti-hypertensive medications are being used, type of medication, frequency, and dose. In countries where management of women with pre-eclampsia without severe features follow ACOG guidelines, the recommendation is to monitor BP only 2x/week. Thus, their results will not be applicable. In addition, another factor driving their primary outcome in absence of severe systolic BP> 160 is hepatic dysfunction. Again, this finding is most likely to be identified because of their protocol requiring blood testing at least 3 x / week. In contrast, ACOG recommendation is for once weekly. indeed , as evident in their results, there were no clinical implications for an isolated severe systolic BP or for hepatic dysfunction. In fact , there were no differences in clinically meaningful outcomes such as abruption, eclampsia, pulmonary edema, or acute renal failure between groups.

A. We note in the manuscript that both components of the primary outcome were reduced, with a greater reduction in the maternal morbidity composite outcome (15·2% in planned delivery group vs. 20·0% in expectant management group; RR 0·76 (0·59, 0·98). The recent paper describing a US cohort in which 96% of stroke-related pre-eclampsia deaths were associated with systolic hypertension ≥160mmHg (Judy et al 2018, referenced in the manuscript) suggests that elevated blood pressure at this level is not of 'no clinical relevance'. We note that in point 4.1 above the reviewer states that the ACOG guidelines identify women with ALT >70IU/L as requiring delivery, but that in this point there are 'no clinical implications' of such a laboratory finding. It is difficult to reconcile the two statements. Timely delivery of such women is likely to avoid major clinical complications such as pulmonary oedema or acute renal failure, and so cannot be criticised on clinical grounds. We have clarified this in the manuscript as follows:
Discussion (line 351)
Choice of a maternal outcome that reflects the multi-organ manifestations of pre-eclampsia is also challenging, particularly as no intermediate complication exists between severe systolic hypertension (relatively common) and stroke (very rare in high-income healthcare settings), and treatment paradox may mean that women are (appropriately) delivered on the basis of moderate deterioration in biochemical parameters before severe complications occur.

4.4 For the primary neonatal outcome they found differences in admission to Neonatal Unit even though there were no differences in neonatal morbidity. This maybe related to sample size and the inclusion of large number of women with GA > 36 weeks. Indeed, using a similar design with different inclusion criteria, HYPITAT-2 found significantly lower rates of RDS in expectant group. where all babies with this diagnosis required CPAP >24 hours, surfactant or both.(lancet june 20, 2015). moreover, early delivery in women with late preterm hypertension / preeclampsia is associated with poorer neurodevelopmental outcomes in their children at 2 years of age(Am J

Obstet Gynecol August 2019). It is important to emphasize that the risks of RDS and other neonatal complications is markedly reduced in those born at 34 weeks compared to those born at 37 weeks. TIn HYPITAT-2, the rate of RDS in immediate delivey at < 35 weeks was 12.7% whereas it was 2.4% in those at >- 36 weeks. This will have significant clinical implications for infants delivered in low-resource countries if the results of trial are misinterpreted suggesting. these babies have significant long-term respiratory and neurologic morbidities. immediate delivery at 34 weeks.

A. We are surprised that the reviewer considers that there are large numbers of women with GA >36 weeks, when the distribution (around 30% at 34+ weeks, 30% at 35+ weeks, 40% at 36+ weeks) reflects the expected prevalence, and is still less than half of women included (and less than the proportion in the HYPITAT-II trial). We have highlighted the differences between our trial and the HYPITAT-2 trial in the Discussion as follows:
Discussion (line 376)
This trial has similar findings of a reduction in maternal adverse outcomes to a previous smaller study,[14] but that trial included only 352 women with late preterm pre-eclampsia, and the reduction was not statistically significant. However, our trial found no difference in respiratory morbidity (as a secondary outcome) and much higher antenatal corticosteroid use (60%), in contrast to the previous trial which reported increased respiratory distress syndrome in those with planned delivery, with lower corticosteroid use (8%) and a longer interval to delivery in the expectant management group likely related to inclusion of women with chronic or gestational hypertension.[14]

We agree that the findings should be considered cautiously in low income settings, where the balance of risk of planned delivery and expectant management may be different, particularly in light of the much higher proportion of stillbirths in women with pre-eclampsia (ref Nathan et al). We have edited the manuscript to make this clearer:
Discussion (line 409):
The benefits and risks of planned delivery in women with late preterm pre-eclampsia may vary in low resource healthcare settings and require further evaluation, although the potential disadvantages of increased prematurity would need to be balanced against a much high incidence of stillbirth in women with pre-eclampsia managed expectantly, such as that reported in a South African setting.[20]

4.5 Finally , the recent ACOG guidelines recommend similar management and timing of delivery for women with a diagnosis of gestational hypertension or preeclampsia without severe features. if the results of the trial are disseminated , it will lead to a significant increase in late preterm births with no maternal benefit.

A. We agree with the reviewer that the results of the trial should not automatically be extrapolated to women with gestational hypertension and have clarified this in the manuscript as follows:
Discussion (line 413)
The trial findings relate to women with late preterm pre-eclampsia and should not be extrapolated to women with chronic or gestational hypertension, in whom the likelihood of developing maternal morbidity is lower.

4.6 In summary, the trial is under powered to answer this important question, and the conclusions might not be generalizable.

A. As we have shown a significant difference in both co-primary outcomes (and in both the components of the primary outcome), we are unclear why the reviewer thinks this trial might have been underpowered. We appreciate that the US guidelines recommend planned delivery (albeit without an evidence base to support the recommendation), but consider that this trial

will be of interest to the many other countries around the world where international guidelines are more commonly used.

Reviewer #5:

5.1 Composite Outcomes: The composite maternal outcome comprises many components that vary in severity from minor things to stoke and death. The more serious components have zero or very low incidence and the composite is dominated by minor components. It would be helpful if the maternal morbidity composite outcome data given in Table 3 could be stratified according to severity.

A. We have ordered the components of the primary outcome by systems (central nervous system, cardiorespiratory system etc., in the same way that it was originally reported when determined by Delphi consensus and first published in the Lancet (von Dadelszen et al Lancet 2011). We are happy to take editorial guidance on reordering by severity if that is preferred.

5.2 Expectant Management: The protocol states that in the expectant management group 'If the woman has mild hypertension (blood pressure140/90 to 149/99 mmHg), care would be as follows:

_ Admission to hospital

_ Measure blood pressure at least 4× 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 and bilirubin.'

In the paper there is no mention of not treating 'mild hypertension (blood pressure140/90 to 149/99 mmHg)'.

It is notable also that the current NICE guidelines state that 'Offer pharmacological treatment if BP remains above 140/90 mmHg' so the control group in this study does not constitute current expectant management.

The protocol of not treating 'mild blood hypertension' in the control group should be stated and there should be some discussion of the consequences of this on the outcome of the trial.

With reference to the current NICE guidelines, there should be some discussion relevance of the findings of this study to settings where 'mild hypertension' were treated according to NICE.

A. We have further clarified in the manuscript that we were using the NICE 2010 guidelines, in place for the duration of the trial, in which treatment was recommended with BP >150/100mmHg. The guidelines to which the reviewer is referring were published on 25 June 2019 (https://www.nice.org.uk/guidance/ng133/history), and this is apparent in the NICE guideline document where the section on threshold for initiation of treatment is shown as having been updated in 2019.

Treatment of pre-eclampsia

1.5.5 Offer women with pre-eclampsia the tests and treatments listed in table 2. [2019]

https://www.nice.org.uk/guidance/ng133/chapter/Recommendations#management-of-pre-eclampsia

As the intervention relates to timing of delivery rather than blood pressure threshold for initiation of antihypertensive treatment, we do not anticipate that introduction of the 2019 NICE guidelines will impact on the interpretation of the trial.

Reviewer #7:
In general I congratulate the study group for a wonderfully conducted trial. All information needed is present and clearly presented.
I have a few remarks however regarding the final conclusions.

7.1 The conclusion supports the planned delivery management stronger than the data in my opinion justify. The outcome measure of severe maternal morbidity includes a blood pressure higher than 160 which in itself can be questioned as an outcome measure. If no other severe outcomes result from this (transient) high blood pressure, does it justify the increase in neonatal morbidity and increased number of non spontaneous delivery. In my opinion the message would be stronger if only the maternal morbidity outcome would be highlighted. This is still significant and far more relevant. But this difference is 4.5% resulting in a NNT of 22.

A. We have made it clear in the manuscript that there was no excess neonatal morbidity, only increased neonatal unit admissions, which appear to have resulted from unexpected clinical practice relating to using gestational age, rather than clinical need, as a driver to admission.
Discussion (line 318)
In this randomised controlled trial in women with late preterm pre-eclampsia, planned delivery reduced maternal morbidity (including severe systolic hypertension), but led to more neonatal unit admissions for the baby, principally for a listed indication of prematurity and without an excess of respiratory or other morbidity, intensity of care or length of stay.

We note that the intervention of 'non-spontaneous delivery' resulted in a higher proportion of vaginal deliveries, and as another reviewer has pointed out, this 'is likely beneficial for her future obstetric history (including less risk of invasive placentas in a scarred uterus)'. In the expectant management group, only 4.2% of women had spontaneous onset of labour and over half required expedited delivery for clinical deterioration. We have aimed to report the trial in line with our pre-specified outcomes, rather than selectively reporting those most appealing. In a high-income setting, where there is no intermediate morbidity between severe systolic hypertension (relatively common) and stroke (very rare), it is difficult to choose a maternal morbidity measure that adequately captures adverse maternal outcomes. We have clarified this further in the manuscript as follows:
Discussion (line 351)
Choice of a maternal outcome that reflects the multi-organ manifestations of pre-eclampsia is also challenging, particularly as no intermediate complication exists between severe systolic hypertension (relatively common) and stroke (very rare in high-income healthcare settings), and treatment paradox may mean that women are (appropriately) delivered on the basis of moderate deterioration in biochemical parameters before severe complications occur.

7.2 Although the authors mention that the main contributor to the neonatal outcome is merely "admission", no statistical data are given regarding the outcomes mentioned in table 4. The incidence of hypoglycaemia, which can be related to long term outcome is doubled. Also the NNH regarding admission, being 12 can be useful. Data regarding worse outcome in late preterm babies become more and more clear and this effects these children lifelong.

A. We wonder if the reviewer has misread the table as the intervention (planned delivery) was associated with halving (not doubling) of hypoglycaemia as an indication for admission. We have not tested every indication for admission as they were not pre-specified (and we chose to avoid endless multiple testing). We have longer term follow-up on the infants planned.

7.3 Women might judge NNT of 22 regarding their own outcome compared to a NNH of 12 for their babies different than the conclusion the authors draw. So the conclusion in my opinion should be that expectant management results in an increase of severe maternal morbidity with a NNT

of 22, more spontaneous deliveries but a decrease in neonatal NICU admissions with a NNH of 12 and increased costs. Long term effects are currently unclear. These result can be helpful in discussion the management with pregnant women and their partners.

A. We are unclear about the reviewer's interpretation of our findings as there was an increase in neonatal admissions, but lower costs (rather than decreased admissions and higher costs as the reviewer suggests). We have checked our manuscript for accuracy and confirmed that we have stated it as such:
Discussion (line 324)
Planned delivery has lower costs than expectant management in the UK healthcare setting.

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Planned early delivery or expectant management for late preterm pre-eclampsia: a randomised controlled trial (PHOENIX trial).

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Summary

Background

In women with late preterm pre-eclampsia ~~between 34 and 37 weeks' gestation~~ the optimal time to initiate delivery is unclear, as limitation of maternal disease progression needs to be balanced against infant complications ~~for the infant related to ongoing expectant management or planned early delivery~~.

Methods

In this UK parallel-group, non-masked, multi-centre, randomised controlled trial, we compared planned delivery against expectant management (usual care) with individual randomisation in women with late preterm pre-eclampsia from 34 ~~up~~ to 37 weeks' gestation and a singleton or dichorionic diamniotic twin pregnancy. The co-primary maternal outcome was a composite of maternal morbidity ~~with the addition of~~ or recorded systolic blood pressure ≥160 mmHg with a superiority hypothesis. The co-primary perinatal outcome was a composite of perinatal deaths or neonatal unit admission up to infant hospital discharge with a non-inferiority hypothesis. Analyses were by intention to treat, together with a per protocol analysis for the perinatal outcome. The trial was prospectively registered ~~with the~~ (ISRCTN Registry, number 01879376).

Findings

Between 29 September 2014 and 10 December 2018, 901 women were recruited across 46 maternity units. 450 women (448 women and 471 infants analysed) were allocated to planned delivery, and 451 women (451 women and 475 infants analysed) to expectant management. The incidence of the co-primary maternal outcome was significantly lower in the planned delivery group (64·7%) compared to the expectant management group (75·3%); adjusted risk ratio 0·86 (95% CI 0·79 to 0·94); p=0.0005~~<0·01~~. The incidence of the co-primary perinatal outcome was significantly higher in the planned delivery group (41·8%) compared to the expectant management group (33·5%); adjusted risk ratio 1·26 (95% CI 1·08 to 1·47); p=0.0034~~<0·01~~. The results from the per protocol analysis were similar. There were nine serious adverse events in the planned delivery group and twelve in the expectant management group.

Interpretation

There is strong evidence to suggest that planned delivery reduces maternal morbidity and severe hypertension, with more neonatal unit admissions related to prematurity, but no indicators of

greater neonatal morbidity, compared to expectant management. This trade-off should be discussed with women with late preterm pre-eclampsia to allow shared decision making on timing of delivery.

Introduction

Pre-eclampsia is a multisystem disorder of pregnancy, characterised by placental and maternal vascular dysfunction and associated with substantial morbidity and mortality for the mother and infant. Adverse outcomes of pre-eclampsia include maternal stroke, renal and hepatic injury, and fetal growth restriction, and maternal and perinatal death.[1] Around 10% of pregnant women develop hypertension, and 2-3% pre-eclampsia, characterised by hypertension and manifestations of multi-organ disease.[2]

Standard management of pre-eclampsia involves maternal and fetal assessment, and subsequent consideration of timely delivery to minimise maternal and perinatal morbidity, taking into consideration gestational age, progression of maternal disease and fetal well-being. After 37 weeks' gestation, most national guidelines recommend prompt delivery for a woman with pre-eclampsia,[3,4] since maternal and fetal risks can be significantly reduced without any additional risks from such an intervention.[5] In women with late preterm pre-eclampsia (between 34 and 37 weeks' gestation), the optimal time for delivery is less clear, as limitation of maternal disease progression needs to be balanced against complications for the infant either related to ongoing expectant management (including needing emergency delivery, worsening growth restriction and stillbirth) or those related to planned earlier delivery (infant immaturity and associated complications). Current usual practice in the UK for women with late preterm pre-eclampsia is for expectant management until 37 weeks' gestation, with delivery sooner if the clinical scenario changes and there is concern over impending severe pre-eclampsia and associated complications. In the absence of definitive new evidence, this advice has been maintained in the most recent management recommendations from the International Society for the Study of Hypertension in Pregnancy, published in 2018,[6] used to inform current practice in many countries worldwide.

This aim of this trial was to compare planned earlier initiation of delivery with expectant management (usual care) in women with pre-eclampsia between 34 and 37 weeks' gestation in the UK healthcare setting, in order to determine whether planned delivery reduces maternal adverse outcomes without substantial worsening of neonatal or infant outcomes.

Methods

Trial design

In this parallel-group, non-masked, multi-centre, randomised controlled trial, we compared planned delivery against expectant management (usual care) with individual randomisation using a 1:1 allocation ratio. There were no substantial changes to the published study design or methods or outcomes[7] after commencement of the trial.

Participants

A pregnant woman was eligible if she was between 34^{+0} and 36^{+6} weeks of gestation, had a diagnosis of pre-eclampsia or superimposed pre-eclampsia (as defined by International Society for the Study of Hypertension in Pregnancy),[8] with a singleton or dichorionic diamniotic twin pregnancy and at least one viable fetus, was aged 18 years or over, and able to give written informed consent. Women with any other co-morbidity (including pre-existing hypertension, diabetes) or with a previous caesarean section or any fetal position were eligible. The only exclusion criterion to participation in the study was a prior decision to deliver within the subsequent 48 hours. Current practice by national guidelines in use during the trial was for immediate delivery of a woman with persistent severe features of pre-eclampsia (including Haemolysis, Elevated Liver enzymes, Low Platelets syndrome), who would thus not be eligible for the trial.

The trial was approved by the South Central - Hampshire B Research Ethics Committee (no. 13/SC/0645).

Interventions

We allocated women to planned initiation of delivery within 48 hours of randomisation (to allow for corticosteroid administration to accelerate fetal lung maturation, and neonatal cot availability if necessary), usually by induction of labour (unless there was an additional specific indication for pre-labour Caesarean section) or to expectant management (usual care), with delivery at 37 weeks' gestation or sooner as clinical needs dictated in accordance with the UK national guidelines[4] (as assessed by the clinician responsible for her care) for maternal indications (e.g. uncontrolled hypertension, abnormal blood results), or fetal compromise, or eclampsia or other clinical crisis. Individual decisions around mode of induction and delivery and ~~U~~use of corticosteroids for fetal lung maturity was left to the discretion of the individual clinician, with the trial protocol advising that all options should be discussed with the pregnant woman and her needs and preferences taken into account.

Outcomes

Outcomes were recorded on the web-based trial database through case-note review by trained researchers after maternal and infant primary hospital discharge. The co-primary maternal outcome was a composite of maternal morbidity of fullPIERS[9] outcomes: (maternal death; central nervous system (eclampsia, Glasgow coma score <13, stroke or reversible ischaemic neurological deficit, transient ischaemic attack, cortical blindness or retinal detachment, posterior reversible encephalopathy); cardiorespiratory (positive inotropic support, infusion of a third parenteral antihypertensive drug, myocardial ischaemia or infarction, SpO2 <90%, ≥50% FiO2 for >1 hr, intubation (other than for caesarean section), pulmonary oedema); haematological (transfusion of any blood product, platelet count $<50\times10^9$ per L, with no transfusion); hepatic (hepatic dysfunction, hepatic haematoma or rupture); renal (acute renal insufficiency (creatinine >150 µmol/L; no pre-existing renal disease) or acute renal failure (creatinine >200 µmol/L; pre-existing renal disease, dialysis); placental abruption), with the addition of recorded systolic blood pressure ≥160mmHg post-randomisation (on any occasion), and its presence or absence was independently countersigned by the site principal investigator or delegate. The co-primary perinatal outcome was a composite of perinatal deaths (antenatal/ intrapartum stillbirths or deaths within seven days of delivery) or neonatal unit admissions (physical separation of baby from the mother) prior to infant hospital discharge. Secondary outcomes are as listed in the published protocol:[7] maternal: individual components of the composite primary outcome, use of anti-hypertensive drugs, progression to severe pre-eclampsia, defined as systolic blood pressure ≥160 mmHg, platelet count $<100 \times 10^9$/L and abnormal liver function enzymes (ALT or AST >70 IU/L), 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 and mode of delivery, confirmed thromboembolic disease, confirmed sepsis, primary and additional indications for delivery, placental abruption and perinatal: stillbirth, neonatal death, admissions to neonatal unit, number of nights in each category of care, total number of nights, birth weight, birth weight centile, birth weight <10th and <3rd centile, gestational age at delivery, Apgar score at 5 min post-birth, umbilical arterial and venous pH at birth, need for supplementary oxygen prior to discharge, number of days when supplemental oxygen is required, need for ventilation support, abnormal cerebral ultrasound scan, confirmed sepsis, necrotising enterocolitis, seizures, encephalopathy, hypoglycaemia, other indications and main diagnoses resulting in neonatal unit admission, exclusively breastfed at discharge from the neonatal unit) and health resource use outcomes. The primary indication for neonatal unit admission was allocated as part of usual clinical care practice by a clinical neonatologist (not involved in the trial), from a pre-specified list of exclusive admission reasons, on an electronic clinical database used nationwide in England and Wales. The category of neonatal care (intensive care, high dependency

care, special care) followed nationally defined guidance, with days in each category of care individually recorded on the national electronic clinical patient database.[10]

Sample Size

Superiority hypothesis in maternal outcome

Assuming an expected adverse maternal outcome incidence of 43% in the expectant management (usual care) group, based on data from the PELICAN study[11] a sample size of 850 women would demonstrate a relative risk reduction of 25% to 32·25% (deemed clinically important) in the planned delivery group with a 2-sided 5% significance level and 90% power. With 5% loss of women in follow-up, the overall target for recruitment was 900 women (450 per group).

Non-inferiority hypothesis in neonatal outcome

Assuming a composite adverse neonatal outcome incidence of 24% in the expectant management group,[11] and assuming a sample size of 850 women would result in approximately 860 infants (430 per group, allowing for twin births). 93% power would be achieved to detect a non-inferiority margin of no less than 10% (judged as clinically relevant) and 78% power to detect a margin of no less than 8%.

Randomisation

Randomisation was performed using a probabilistic minimisation algorithm to ensure approximate balance within the following groups: study centre, singleton/ twin pregnancies, severity of hypertension in 48 hours prior to enrolment (highest systolic blood pressure with or without medication: <150mmHg, 150-159mmHg, ≥160mmHg), parity (previous delivery of a baby past 24 weeks), previous caesarean section, and gestational age at randomisation (34, 35, 36 weeks). Randomisation was managed via a secure web-based randomisation program provided by MedSciNet.

Allocation concealment and masking

The minimisation algorithm was implemented by a MedSciNet database programmer, with balance and predictability monitored by the independent National Perinatal Epidemiology Unit Clinical Trials Unit statistician during the trial. The intervention was not masked from women or clinicians, due to the nature of the intervention.

Implementation

Site research teams approached women to confirm eligibility and provided verbal and written information. A trained clinician (obstetrician or obstetric physician) obtained written informed consent. A research team member entered baseline data on a web-based database and then performed randomisation, communicating the results directly to the woman. All other aspects of pregnancy management were expected to be in accordance with the UK national guidelines[4] at the discretion of the responsible clinician. Research teams undertook standard assessment of safety, with reporting of serious adverse events following usual governance procedures.

Statistical Analysis

The primary analysis for all maternal outcomes was by intention to treat with participants analysed in the groups to which they were assigned regardless of protocol non-compliances. The primary analysis for all perinatal and infant outcomes was by both an intention to treat and a per protocol analysis, since the hypothesis under examination for these outcomes was a non-inferiority hypothesis.

All outcomes were analysed adjusting for minimisation factors (as listed above) at randomisation.[12] Binary outcomes were analysed using mixed effect Poisson regression with a robust variance estimator and presented as adjusted risk ratios with associated confidence intervals. Site was treated as a random effect, and all other minimisation factors as fixed effects. For perinatal outcomes, mother's identification was nested within site to take account of clustering within twins. For continuous outcomes, differences in medians and associated confidence intervals were estimated using quantile regression. In these models, site was treated as a fixed effect, and robust standard errors were used. 95% confidence intervals are presented for all primary and secondary outcomes. No adjustment of co-primary outcomes was made for multiplicity.[13]

Ancillary analyses

Pre-specified subgroup analyses were performed for co-primary outcomes, using the statistical test of interaction, based on criteria selected for minimisation: parity (0 and ≥1 previous pregnancy), highest systolic blood pressure in the 48 hours prior to enrolment (<150 and ≥150 mmHg), gestation at the time of randomisation (34/ 35/ 36 weeks) and singleton/ twin pregnancy. To allow for clinical and logistical delays, a pre-specified sensitivity analysis was carried out on the co-primary outcomes excluding women (and infants) randomised to the planned delivery arm where initiation of delivery was more than 96 hours post-randomisation.

Economic Analysis

Data on mother and infant inpatient care and mode of delivery were costed using the National Schedule of Reference costs.[14] Descriptive statistics are reported including mean cost per participant and 95% confidence intervals constructed using bootstrapping. The time-horizon of the analysis is from recruitment until hospital discharge following labour. Comparative difference in costs was calculated using linear regressions and adjusted for centre, singleton/ twin pregnancies, severity of hypertension in 48 hours prior to enrolment, parity, previous caesarean section and gestational age at randomisation.

The trial is registered with the ISRCTN registry, number 01879376.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Participant flow, recruitment and numbers analysed

Between 29 September 2014 and 10 December 2018, of 1,606 women found to be eligible, 901 women (56%) were recruited, across 46 maternity units in England and Wales (Supplementary Table 1). 450 women were allocated to planned delivery, and 451 women to expectant management (usual care). For the intention to treat analysis, data from 448 women and 471 infants (two women withdrew, with consent to use all data withdrawn) in the planned delivery group, and 451 women and 475 infants in the expectant management group were included. Follow-up to maternal and infant discharge continued until January 2019. One woman was lost to follow-up in the planned delivery group, and two women in the expectant management group. Recruitment ended after 901 women had been enrolled.

Baseline data

Baseline characteristics were similar between the two groups, with groups well balanced on minimisation factors (Table 1, Supplementary Table 2).

Outcomes

The proportion with the primary maternal outcome was statistically significantly lower in the planned delivery group (64·7%) compared to the expectant management group (75·3%); adjusted risk ratio 0·86 (95% CI 0·79 to 0·94); p=0.0005~~<0·01~~. The proportion with the primary perinatal outcome was significantly higher in the planned delivery group (41·8%) compared to the expectant management group (33·5%); adjusted risk ratio 1·26 (95% CI 1·08 to 1·47); p=0.0034~~<0·01~~ (Table 2).

In women allocated to planned delivery, a significant reduction in both components of the primary adverse maternal outcome was found, as was progression to severe pre-eclampsia (Table 3). Other than two women who had spontaneous onset of labour, all other women in the planned delivery group received the trial intervention, although this was not always achieved within 48 hours as intended. Of women allocated to planned delivery, 73% (327 of 448) had delivery initiated within 48 hours (Figure 1). In women allocated to expectant management, 53·9% had medically indicated delivery prior to 37 weeks' gestation and only two women were delivered prior to 37 weeks' gestation without an additional medical indication. Additional maternal secondary outcomes are shown in Supplementary Table 3. Intervals between randomisation and initiation of delivery are shown in Supplementary Table 4.

Median gestational age at enrolment was identical, but women allocated to planned delivery delivered at 252 days of gestation compared to 257 days in the expectant management group (adjusted median difference -3 (95% CI -3·5 to -2·5) days) and were significantly more likely to achieve a spontaneous vaginal delivery (36·0% vs. 29·3%; adjusted risk ratio 1·21 (95% CI 1·04, 1·41). There were no stillbirths or neonatal deaths in either group. There were more infants admitted to the neonatal unit in the planned delivery group (41·8%) compared to the expectant management group (33·5%); adjusted risk ratio 1·26 (95% CI 1·08 to 1·47); the principal recorded indication for admission was 'prematurity'. There was no evidence of differences in the proportions requiring supplementary oxygen or additional respiratory support, and no evidence of differences in the intensity of neonatal care or length of stay for the infant (Table 4). Additional perinatal secondary outcomes are shown in Supplementary Table 5. A planned per protocol analysis gave similar results for the perinatal outcomes (Supplementary Tables 6, 7).

Health economic analysis showed that total maternal and infant costs were lower in the planned delivery arm (mean £11,574, standard error £302) compared to the expectant management arm (mean £13,090, standard error £389), with an adjusted cost saving of £1478 (95% CI £2354 to £605; p=0·001) (Table 5).

There were similar numbers of serious adverse events in both groups: nine in the planned delivery group compared to 12 in the expectant management group (Supplementary Table 8). Two serious adverse events in each group were judged possibly related to the intervention in each group; one serious adverse event was judged probably related to the intervention in the expectant management group. All other serious adverse events were deemed unrelated to the intervention. There was one maternal death (in the expectant management group), considered unrelated to the trial allocation.

In planned sub-group analyses, there was no statistically significant interaction of gestational age at randomisation, singleton/ twin pregnancy, highest systolic blood pressure prior to enrolment and parity and the incidence of the primary maternal or perinatal outcome (Figure 2, Supplementary Figure 1). A planned sensitivity analysis including women or infants randomised to the planned delivery arm with initiation of delivery before 96 hours had little impact on the results (Supplementary Table 9).

Discussion

In this randomised controlled trial in women with late preterm pre-eclampsia, planned delivery reduced maternal morbidity (including severe systolic hypertension), but led to more neonatal unit admissions for the baby, principally for a listed indication of prematurity and without an excess of respiratory or other morbidity, intensity of care or length of stay. Women in the expectant management group at this gestation had a median additional prolongation of pregnancy (from enrolment to delivery) of five days, and over half of these women had indicated delivery before 37 weeks' gestation, with three quarters subsequently meeting the criteria for progression to severe pre-eclampsia. Women in the planned delivery group had significantly more vaginal deliveries. In this healthcare setting, there were no stillbirths or neonatal deaths. Planned delivery has lower costs than expectant management in the UK healthcare setting.

Strengths of the trial include a sufficiently large sample of women specifically with late preterm pre-eclampsia, in whom the benefits and risks of planned delivery may be different from those with gestational or chronic hypertension in pregnancy, related to the likelihood of progression to severe features of the disease and need for medically indicated emergency delivery. The trial was conducted to rigorous standards, with a pre-specified protocol without changes. Findings are likely

to be generalisable to similar healthcare settings, as it was undertaken in a large number of maternity units across England and Wales, with diverse representation of women both in demographic terms and disease spectrum and with recommendations for expectant management and indications for delivery in clinical practice similar in our trial (which followed UK national guidelines[4]) and current international guidelines.[6] Over half of eligible women approached agreed to participate in the trial, indicating agreement of equipoise in this scenario.

Limitations of the trial include the challenge of finding a perinatal outcome that adequately represented the potential risks of both groups, (related to intervention in the planned delivery group and to ongoing pre-eclampsia in the expectant management group), as there are potential harms from continuing pregnancy as well as initiating earlier delivery. As adjudication of multi-organ neonatal morbidity is complex and subjective, and no widely accepted validated measure of neonatal morbidity is currently available, we chose neonatal unit admission (involving separation of the baby from the mother), supported by our lay representatives, and intending that this would capture underlying neonatal morbidity. Although UK clinical practice guidelines do not recommend routine admission of an infant based solely on gestational age after 34 weeks of pregnancy, admission solely for prematurity in this trial suggests different real-world clinician behaviour, despite no differences in objective measures of direct neonatal morbidity being demonstrated. Choice of a maternal outcome that reflects the multi-organ manifestations of pre-eclampsia is also challenging, particularly as no intermediate complication exists between severe systolic hypertension (relatively common) and stroke (very rare in high-income healthcare settings), and treatment paradox may mean that women are (appropriately) delivered on the basis of moderate deterioration in biochemical parameters before severe complications occur. The incidences of maternal and perinatal primary outcomes were higher than anticipated based on previous studies, but this did not limit the interpretation of the analysis. Although it is acknowledged that for women enrolled after 36 weeks' gestation, expectant management would only be for a maximum of seven days, immediate planned delivery would still represent a change in clinical care from usual practice and the research uncertainty remained at trial conception. The proportion of women enrolled at 36 weeks' gestation was similar (and even slightly lower) than that enrolled in a similar trial,[15] and maternal benefit shown even at this gestation.

Sources of bias

We considered sources of possible bias for the trial. Selection bias was unlikely due to the randomisation process including robust allocation sequence concealment, such that probability of

determining next allocation was unlikely. Performance and detection bias were possible, as it was not possible to mask the intervention to clinicians or women and data collectors (as timing of delivery was contained within maternity records where morbidity was recorded). Every primary maternal outcome was additionally signed off by each site principal investigator, and we used a primary neonatal outcome (independently recorded by the attending clinical team) to minimise bias where possible. There was minimal attrition in both groups. We have reported all pre-specified secondary outcomes, interpreting them cautiously.

Comparison with other studies

This trial has similar findings of a reduction in maternal adverse outcomes to a previous smaller study,[15] but that trial included only 352 women with late preterm pre-eclampsia, and the reduction was not statistically significant. However, our trial found no difference in respiratory morbidity (as a secondary outcome) and much higher antenatal corticosteroid use (60%), in contrast to the previous trial which reported increased respiratory distress syndrome in those with planned delivery, with lower corticosteroid use (8%) and a longer interval to delivery in the expectant management group likely related to inclusion of women with chronic or gestational hypertension.[15] Systematic reviews of planned early delivery in women with pregnancy hypertension to date have been constrained by insufficient numbers to draw definitive conclusions for specific groups of women where the benefit and risk balance may differ (i.e. those with late preterm pre-eclampsia),[16,17] but a recent individual patient data meta-analysis suggested that some women in these groups may benefit from earlier delivery.[18] Developing accurate validated prognostic tools to best identify those at highest risk remains challenging and infant follow-up is useful to further evaluate the longer term outcomes[19] with such strategies.

Interpretation

In women with late preterm pre-eclampsia, planned delivery is associated with improved maternal outcomes, but more neonatal unit admissions for prematurity (though not respiratory or other morbidity, higher intensity of neonatal care or duration of stay), compared to expectant management. Whilst UK guidance does not recommend routine admission for prematurity alone, individual clinicians may vary in their thresholds for neonatal unit admission. Additional prolongation of pregnancy by five days (in the expectant management group) may move an infant out of a notional group where admission is dictated by a guideline (for example based on a gestational age threshold), rather than by clinical need. Increased use of transitional care arrangements (where a baby stays with its mother but with enhanced surveillance and care in a postnatal setting) may be

particularly beneficial in these babies and avoid unnecessary separation of the baby from its mother. For women with pre-eclampsia at this gestational age, prolongation of pregnancy may only be for a few days; over half of these women require indicated delivery, potentially necessitating emergency management. Rates of vaginal delivery are similar to those reported from a large US study of women with early preterm pre-eclampsia,[20] suggesting that these results can be extrapolated across similar settings. The increase in spontaneous vaginal births with planned delivery may be judged an important advantage by women and clinicians, particularly for future pregnancies. It is notable that there were no stillbirths or neonatal deaths in this setting, and one maternal death was likely related to comorbidities in association with pre-eclampsia, rather than trial allocation. The benefits and risks of planned delivery in women with late preterm pre-eclampsia may vary in low resource healthcare settings and require further evaluation, although the potential disadvantages of increased prematurity would need to be balanced against a much high incidence of stillbirth in women with pre-eclampsia managed expectantly, such as that reported in a South African setting.[21] The trial findings relate to women with late preterm pre-eclampsia and should not be extrapolated to women with chronic or gestational hypertension, in whom the likelihood of developing maternal morbidity is lower.

In conclusion, our trial supports offering initiation of delivery in women with late preterm pre-eclampsia. The trade-off of lower maternal morbidity and severe hypertension against higher neonatal unit admissions, albeit without additional respiratory or other morbidity, should be discussed with women with late preterm pre-eclampsia to allow shared decision making on timing of delivery.

Research in context

Evidence before this study

At conception of this study (in 2012), there were no published randomised controlled trials evaluating planned delivery against expectant management for women with late preterm pre-eclampsia between 34 and 37 weeks, although some women with mild pre-eclampsia may have been included in the HYPITAT-1 trial, in women with pregnancy hypertension from 36 weeks' gestation. A Cochrane systematic review on this topic, updated on 15 January 2017, concluded that 'For women suffering from hypertensive disorders of pregnancy after 34 weeks, planned early delivery is associated with less composite maternal morbidity and mortality. There is no clear difference in the composite outcome of infant mortality and severe morbidity; however, this is based on limited data (from two trials) assessing all hypertensive disorders as one group. Further studies are needed to look at the different types of hypertensive diseases and the optimal timing of delivery for these conditions.'

Added value of this study

The trial reported here is considerably larger (901 women) than the number of women with late preterm pre-eclampsia in previous trials (352 and 183 women). Previous trials have not impacted on clinical practice as there was continued uncertainty over the trade-off between maternal benefit and perinatal harms. The trial reported here is large, multicentre and represents contemporaneous management of women with late preterm pre-eclampsia. The neonatal endpoint chosen reflects potential harms from both the intervention (planned early delivery) and ongoing pre-eclampsia (in the expectant management arm).

Implications of all the available evidence

The results of this trial, taken together with smaller trials published since the trial started, support a lower threshold for considering planned delivery in women with late preterm pre-eclampsia. This benefit appears to be greater in women with pre-eclampsia (compared to women in other studies with gestational or chronic hypertension alone). Whilst planned delivery may result in more babies being admitted under current guidelines to a neonatal unit, the observed lack of associated morbidity and provision of alternative care strategies that avoid separation of the baby from the mother (such as transitional care) should enable management of these women to be optimised.

Other information

Registration

ISRCTN registry, ID: ISRCTN01879376. Prospectively registered on 25 November 2013.

Protocol

The full protocol is published.[7]

Funding and role of funding source

The trial was funded by the National Institute for Health Research Health Technology Assessment Programme. LCC is funded by the National Institute for Health Research Professorship, RP-2014-05-019. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care. The study sponsor and funders have had no input into study design; collection, management, analysis and interpretation of data; writing of the report; or the decision to submit the report for publication (beyond usual governance activities) and will not have any such input in the future.

Declaration of interests

The authors' institutions received funding from the National Institute for Health Research for this work. No conflicts of interests are reported.

Author contributions

~~All authors~~ LCC, PB, MEG, RH, PH, EJ, NM, JS, AS were involved in the study conception and in securing funding for the study. LCC and AS were co-chief investigators responsible for all aspects of the study. LL supervised the study analyses, with input from LCC. VC, MG, JT did statistical analyses. AP made a substantial contribution to the running of the trial. RMH did the health economic analysis. LCC wrote the article. All authors reviewed, contributed to and approved the final version of the manuscript.

Data sharing

The dataset will be available to appropriate academic parties on request from the Chief Investigator (Prof Lucy Chappell) in accordance with the data sharing policies of King's College London and the National Perinatal Epidemiology Unit Clinical Trials Unit, with input from the Co-investigator group where applicable.

Acknowledgements

We thank the independent Trial Steering Committee: Jane Norman (chair), Simon Gates, Alison Leaf, Katie Lean, Stavros Petrou, Jacqui Williams, and the independent Data Monitoring Committee: Diana Elbourne (chair), Phil Bennett, Jon Dorling.

We thank Ursula Bowler, ~~Virginia Chiocchia,~~ Angela Garrett, ~~Melanie Greenland,~~ Eleanor Hendy, ~~Anna Placzek,~~ Pauline Rushby, Laura Scholz, Jenie Sparkes, Sue Tohill, ~~John Townend,~~ Zarko Alfirevic and Stephen Robson, all the participating women, site research midwives and doctors for their contribution to the trial.

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Table 1: Maternal demographic and pregnancy characteristics at trial entry

Characteristic	Planned delivery (n=448)	Expectant management (n=451)
Maternal age (years)	30·6 ± 6·39	30·8 ± 6·30
Ethnicity		
White	313 (70%)	311 (69%)
Mixed	10 (2%)	23 (5%)
Asian	60 (13%)	50 (11%)
Chinese	0 (0%)	1 (0%)
Black	58 (13%)	52 (12%)
Other	5 (1%)	13 (3%)
Unknown	2 (0%)	1 (0%)
Deprivation Index quintile 5 (most deprived)*	161/425 (38%)	160/428 (37%)
Parity†: nulliparous	254 (57%)	260 (58%)
Parity†: multiparous	194 (43%)	191 (42%)
Previous caesarean section†	77/194 (40%)	78/191 (41%)
History of pre-eclampsia	85/194 (44%)	92/191 (48%)
Body mass index at booking (kg/m^2)	29·8 ± 7·3	29·8 ± 7·2
Smoking at booking	53 (12%)	50 (11%)
Systolic BP at booking (mmHg)	118·7 ± 14·4	119·6 ± 13·7
Diastolic BP at booking (mmHg)	72·7 ± 10·2	73·4 ± 10·4
Pre-existing chronic hypertension	51 (11%)	53 (12%)
Pre-existing chronic renal disease	6 (1%)	4 (1%)
Pre-pregnancy diabetes	25 (6%)	28 (6%)
Gestational diabetes	62 (14%)	53 (12%)
Aspirin prescribed during pregnancy	170 (38%)	189 (42%)
LMWH prescribed during pregnancy	125 (28%)	117 (26%)
At randomisation		
Median (IQR) gestational age (weeks)	35·6 (34·7 to 36·3)	35·6 (34·7 to 36·3)
Gestational age category†		
34^{+0} to 34^{+6} weeks	131 (29%)	135 (30%)
35^{+0} to 35^{+6} weeks	137 (31%)	132 (29%)
36^{+0} to 36^{+6} weeks	180 (40%)	184 (41%)
Number of live fetuses‡		

Singleton	425 (95%)	427 (95%)
Dichorionic diamniotic twin	23 (5%)	24 (5%)
Highest systolic BP in previous 48 hours (mmHg)	154·5 ± 14·5	155·2 ± 15·4
Highest diastolic BP in previous 48 hours (mmHg)	95·7 ± 9·5	95·8 ± 10·1
Highest BP in previous 48 hours†		
<=149 mmHg	163 (36%)	163 (36%)
150-159 mmHg	121 (27%)	123 (27%)
>=160 mmHg	164 (37%)	165 (37%)
Urinary protein-creatinine ratio measured	434 (97%)	441 (98%)
Median (IQR) urinary protein-creatinine ratio (mg/mmol)	83 (42 to 186)	80 (42 to 172)
Fetal growth ultrasound in previous two weeks	366 (82%)	375 (83%)
Suspected fetal growth restriction on ultrasound	79/366 (22%)	85/375 (23%)
Cervical assessment (prior to randomisation)		
Bishop's score <2	2 (0%)	2 (0%)
Bishop's score 2-6	7 (2%)	4 (1%)
Not assessed	439 (98%)	445 (99%)
In-patient at time of randomisation	362 (81%)	371 (82%)

Data are n (%) or mean ± standard deviation unless shown otherwise· n/N (%) indicates that the denominator only includes participants with a relevant measurement for that variable. LMWH: low molecular weight heparin; BP: blood pressure; IQR: interquartile range.

*Deprivation quintiles calculated for participants in England only (not available for participants in Wales).

† Minimisation factors used to ensure balance at randomisation.

Table 2: Primary maternal and perinatal outcomes

	Planned delivery	Expectant management	Effect measure	Adjusted effect measure*
			Effect size (95% CI) p-value	**Effect size (95% CI) p-value**
Composite of maternal morbidity and/or recorded systolic BP >=160 mmHg post randomisation	289/448 (65%)	338/451 (75%)	Risk ratio 0·86 (0·79, 0·94) 0.0006~~<0·01~~	Risk ratio 0·86 (0·79, 0·94) 0.0005~~<0·01~~
~~**Number needed to treat**~~				~~10 (7 to 23)~~
Intention to treat analysis				
Composite of perinatal deaths, and NNU admissions up to infant hospital discharge	196/471 (42%)	159/475 (34%)	Risk ratio 1·25 (1·05, 1·48) 0·0107	Risk ratio 1·26 (1·08, 1·47) 0.0034~~<0·01~~
			Risk difference 0·08 (0·02, 0·15)	Risk difference 0·07 (0·02, 0·13)
Per protocol analysis				
Composite of perinatal deaths, and Neonatal Unit admissions up to infant hospital discharge	155/342 (45%)	155/470 (33%)	Risk ratio 1·37 (1·15, 1·64) 0.0005~~<0·01~~	Risk ratio 1·40 (1·18, 1·66) <0·0001
			Risk difference 0·12 (0·05, 0·19)	Risk difference 0·11 (0·05, 0·17)

Data are n (%).

*Adjusted for centre, singleton/ twin pregnancies, severity of hypertension in 48 hours prior to enrolment, parity, previous caesarean section and gestational age at randomisation.

Table 3: Secondary maternal outcomes post randomisation

	Planned delivery (n=448)	Expectant management (n=451)	Adjusted risk ratio* (95% CI)
Maternal morbidity composite outcome	68 (15%)	90 (20%)	0·76 (0·59, 0·98)
Systolic BP >=160 mmHg	267 (60%)	313 (70%)	0·85 (0·77, 0·94)
Progression to severe pre-eclampsia	287 (64%)	334 (74%)	0·86 (0·79, 0·94)
Placental abruption	4 (1%)	4 (1%)	1·00 (0·37, 2·67)
Antihypertensive medication prior to delivery	381 (85%)	405 (90%)	0·95 (0·91, 0·99)
~~Estimated fetal weight <10th centile~~	~~8 (1·8)~~	~~28 (6·2)~~	
~~Absent or reversed umbilical artery end diastolic flow~~	~~2 (0·4)~~	~~3 (0·7)~~	
Onset of labour			
Spontaneous	2 (0%)	19 (4%)	0·11 (0·02, 0·50)
Induced	304 (68%)	275 (61%)	1·11 (1·01, 1·23)
Pre-labour caesarean section	140 (31%)	152 (34%)	0·93 (0·76, 1·13)
PROM and augmentation	1 (0%)	4 (1%)	
Indication for delivery (non-exclusive)†			
Spontaneous labour <37 weeks' gestation	2 (0%)	19 (4%)	
Trial allocation to planned delivery arm	445 (100%)	0 (0%)	
Reaching 37 weeks' gestation	8 (2%)	188 (42%)	
Uncontrolled maternal hypertension	26 (6%)	111 (25%)	
Maternal haematological abnormality	3 (1%)	23 (5%)	
Maternal biochemical abnormality	19 (4%)	57 (13%)	
Fetal compromise on ultrasound scan	16 (4%)	50 (11%)	
Fetal compromise on cardiotocography	33 (7%)	64 (14%)	
Severe maternal symptoms	9 (2%)	48 (11%)	
Other (with none of the above)	0 (0%)	2 (0%)	
Maternal complications prior to discharge			
Confirmed thromboembolic disease	0 (0%)	0 (0%)	-
Confirmed sepsis (positive blood or urine cultures)	2 (0%)	6 (1%)	0·36 (0·07, 1·74)

Data are n (%). CI: confidence intervals· BP: blood pressure; PROM: prelabour rupture of membranes.

*Adjusted for centre, singleton/ twin pregnancies, severity of hypertension in 48 hours prior to enrolment, parity, previous caesarean section and gestational age at randomisation.

† Indications for delivery were pre-defined in the protocol.

Table 4: Secondary perinatal outcomes post randomisation (by intention to treat analysis)

	Planned Delivery (n=471)	**Expectant management (n=475)**	**Adjusted effect measure* (95% CI)**
Stillbirth	0 (0%)	0 (0%)	-
Neonatal deaths within 7 days of delivery	0 (0%)	0 (0%)	-
Neonatal death before discharge	0 (0%)	0 (0%)	-
Median (IQR) gestational age at delivery (days)	252 (246 to 257)	257 (251 to 260)	-3 (-3·5, -2·5)
Mode of delivery			
Spontaneous vaginal	169 (36%)	139 (29%)	1·21 (1·04, 1·41)
Assisted vaginal	40 (9%)	47 (10%)	0·87 (0·61, 1·26)
Caesarean section	260 (55%)	289 (61%)	0·92 (0·84, 1·01)
Median (IQR) birth weight (g)	2405 (2070 to 2753)	2480 (2150 to 2910)	-85 (-137, -33)
Median (IQR) birth weight centile†	35 (17 to 61)	30 (13 to 61)	4·2 (-0·4, 8·7)
Birth weight <10th centile	74 (16%)	95 (20%)	0·79 (0·58, 1·09)
Birth weight <3rd centile	20 (4%)	27 (6%)	0·77 (0·43, 1·38)
Median (IQR) Apgar score at 5 minutes post birth	10 (9 to 10)	10 (9 to 10)	0 (-1.1, 1.1)-
Median (IQR) umbilical arterial pH Umbilical arterial pH collected	7·26 (7·20 to 7·20) 281 (60%)	7·25 (7·20 to 7·30) 266 (56%)	0·00 (-0·01, 0·01)
Number of infants admitted to neonatal unit	196 (42%)	159 (34%)	1·26 (1·08, 1·47)
Principal recorded indication for neonatal unit admission‡			
Prematurity	83/196 (42%)	40/159 (25%)	
Respiratory disease	47/196 (24%)	41/159 (26%)	
Hypoglycaemia	21/196 (11%)	31/159 (20%)	
Jaundice	12/196 (6%)	11/159 (7%)	
Infection suspected/confirmed	9/196 (5%)	12/159 (8%)	
Intrauterine growth restriction/ Small for gestational age infant	8/196 (4%)	10/159 (6%)	
Other	16/196 (8%)	14/159 (9%)	
Need for respiratory support	45 (10%)	48 (10%)	0·97 (0·60, 1·57)
Need for supplementary oxygen before	60 (13%)	49 (10%)	1·26 (0·89, 1·79)

discharge			
Median (IQR) days supplemental oxygen required	1 (1 to 2)	2 (1 to 3)	
~~Cerebral ultrasound abnormalities found/ number tested~~	~~2/18 (11%)~~	~~1/24 (4%)~~	~~-~~
~~Sepsis confirmed~~	~~3 (1%)~~	~~2 (0%)~~	
~~Necrotising enterocolitis~~	~~0 (0%)~~	~~0 (0%)~~	~~-~~
~~Seizures~~	~~0 (0%)~~	~~0 (0%)~~	~~-~~
~~Encephalopathy~~	~~0 (0%)~~	~~0 (0%)~~	~~-~~
~~Hypoglycaemia during neonatal unit admission~~	~~80 (17%)~~	~~72 (15%)~~	
~~Exclusive breast-feeding 24 hrs prior to discharge~~	~~112 (24%)~~	~~139 (30%)~~	
Total neonatal unit stay			
Median (IQR) days in neonatal unit Number (%) admitted for at least one day	6 (3 to 11) 181 (39%)	6 (3 to 12) 153 (33%)	0 (-1·32, 1·32)
Category of care during neonatal unit stay (separation of baby from mother)			
Median (IQR) days in intensive care Number (%) admitted	2 (1 to 3) 27 (6%)	3 (1 to 4) 19 (4%)	-1·3 (-18, 16)
Median (IQR) days in high dependency care Number (%) admitted	2 (1 to 3) 51 (11%)	2 (1 to 4) 33 (7%)	-0·5 (-1·5, 0·5)
Median (IQR) days in special care Number (%) admitted	6 (2 to 10) 168 (36%)	6 (2 to 11) 143 (31%)	0 (-1·4, 1·4)
Category of care during other postnatal stay (baby alongside mother)			
Median (IQR) days in transitional care Number (%) admitted	5 (2 to 8) 40 (9%)	5 (4 to 6) 16 (3%)	0·5 (-14, 15)
Median (IQR) days in postnatal care Number (%) admitted	3 (2 to 5) 350 (75%)	3 (2 to 4) 384 (82%)	0·5 (0·28, 0·72)

Data are n (%) unless otherwise stated. Effect measures are risk ratios for categorical variables (risk in planned delivery group/ risk in expectant management group) and median differences for continuous variables (median in

planned delivery group - median in expectant management group). CI: confidence intervals; IQR: interquartile range· n/N (%) indicates that the denominator only includes participants with a relevant measurement for that variable.

*Adjusted for centre, singleton/ twin pregnancies, severity of hypertension in 48 hours prior to enrolment, parity, previous caesarean section and gestational age at randomisation.

† Birth weight centile calculated using the Stata add-in function zanthro using the British 1990 Growth Reference (reanalysed 2009).

‡ Full list of other indications for Neonatal Unit admission given in Supplementary Table 4.

Table 5: Health economic evaluation of costs

Cost component	Planned Delivery	Expectant Management	Adjusted effect measure* (95% CI)
	n=448	**n=451**	
Antenatal Inpatient	£1261 (72)	£2892 (139)	
Labour and delivery	£6087 (172)	£5468 (184)	
Maternal ITU and HDU	£422 (55)	£610 (69)	
Maternal Outpatient	£68 (12)	£292 (27)	
Maternal Transfer	£30 (21)	£65 (52)	
Total Maternal costs	£8238 (199)	£9866 (267)	
	n=471	**n=475**	
Infant Intensive Care	£198 (52)	£362 (182)	
Infant High Dependency care	£239 (43)	£203 (49)	
Infant Special Care	£1402 (127)	£1257 (124)	
Infant normal and transitional care	£1515 (69)	£1401 (65)	
Total Infant costs	£3354 (156)	£3223 (234)	
Total: Maternal and Infant costs	£11,574 (302)	£13,090 (389)	£1478 (£2354 to £605) P=0·001

Data are mean (standard error) unless shown otherwise.

* Adjusted for centre, singleton/ twin pregnancies, severity of hypertension in 48 hours prior to enrolment, parity, previous caesarean section and gestational age at randomisation.

Supplementary Table 1: Recruitment by centre

Centre	Planned delivery (n=448)	Expectant management (n=451)
St Thomas' Hospital, London	40 (9%)	40 (9%)
Darent Valley Hospital	22 (5%)	20 (4%)
St Mary's Hospital, Manchester	28 (6%)	22 (5%)
Bradford Royal Infirmary	16 (4%)	12 (3%)
West Middlesex University NHS Trust	26 (5%)	31 (7%)
Nottingham City Hospital	11 (3%)	15 (3%)
Leeds Teaching Hospitals - St James'	18 (4%)	15 (3%)
Liverpool Women's	22 (5%)	24 (5%)
Queens Medical Centre	10 (2%)	13 (3%)
Royal Victoria Infirmary	18 (4%)	21 (5%)
James Cook University Hospital	18 (4%)	19 (4%)
Sunderland Royal Hospital	17 (4%)	21 (5%)
University College Hospital	10 (2%)	14 (3%)
Birmingham Women's Hospital	11 (3%)	9 (2%)
St George's Hospital	8 (2%)	7 (2%))
Royal Stoke University Hospital	7 (2%)	7 (2%)
Western Sussex Hospitals	7 (2%)	11 (2%)
Whittington Hospital	4 (1%)	3 (1%)
ABM University Hospitals, Wales	23 (5%)	22 (5%)
Birmingham City Hospital	8 (2%)	7 (2%)
Birmingham Heartlands Hospital	6 (1%)	1 (0%)
Warrington and Halton Hospitals	2 (0%)	3 (1%)
Chesterfield Royal Hospital	5 (1%)	8 (2%)
Royal United Hospital, Bath	4 (1%)	5 (1%)
Kingston Hospital NHS Trust	16 (4%)	11 (2%)
Leighton Hospital	6 (1%)	7 (2%)
Leicester Royal infirmary	8 (2%)	8 (2%)
Shrewsbury and Telford Hospital NHS Trust	2 (0%)	3 (1%)
Royal Preston Hospital	2 (0%)	3 (1%)
Northampton General	6 (1%)	7 (1%)
Gloucestershire Royal Hospital	0 (0%)	2 (0%)
St Michael's Hospital, Bristol	2 (0%)	5 (1%)

Royal London Hospital	5 (1%)	5 (1%)
Whipps Cross Hospital	9 (2%)	7 (2%)
New Cross Hospital, wolverhampton	4 (1%)	4 (1%)
Cambridge University Hospitals	3 (1%)	0 (0%)
Chelsea and Westminster Hospital	2 (0%)	5 (1%)
Royal Bolton Hospital	4 (1%)	2 (0%)
St Helier Hospital	2 (0%)	2 (0%)
University Hospital, Lewisham	0 (0%)	2 (0%)
Luton and Dunstable	1 (0%)	0 (0%)
Epsom Hospital	2 (0%)	0 (0%)
Queen Elizabeth Hospital, Greenwich	5 (1%)	1 (0%)
Queen's Hospital, Romford	2 (0%)	2 (0%)
Croydon University Hospital	23 (5%)	25 (6%)
Broomfield Hospital, Chelmsford	3 (1%)	0 (0%)

Supplementary Table 2: Additional maternal demographic and pregnancy characteristics at trial entry

	Planned delivery (n = 448)	**Expectant management (n = 451)**
Median (IQR) gestational age at booking (weeks)	10 (8 to 12)	10 (8 to 12)
Deprivation Index quintile (England only)		
1 (Least deprived)	41/425 (10%)	25/428 (6%)
2	53/425 (13%)	53/428 (12%)
3	64/425 (15%)	72/428 (17%)
4	106/425 (25%)	118/428 (28%)
5 (Most deprived)	161/425 (38%)	160/428 (37%)
Centre in Wales (quintiles not available)	23	22
Parity (previous pregnancies >=24 weeks' gestation)*		
0	254 (57%)	260 (58%)
1	104 (23%)	103 (23%)
2	49 (11%)	52 (12%)
>2	41 (9%)	36 (8%)
Mode of previous deliveries		
Total number of previous deliveries	368	335
Spontaneous vaginal delivery	241/368 (66%)	201/335 (60%)
Assisted vaginal delivery	20/368 (5%)	24/335 (7%)
Caesarean section	102/368 (28%)	110/335 (33%)
Unknown	5/368 (1%)	0/335 (0%)
Previous pregnancies <24 weeks' gestation		
0	295 (66%)	309 (69%)
1	96 (21%)	87 (19%)
2	28 (6%)	33 (7%)
>2	29 (7%)	22 (5%)
Body mass index (kg/m^2)		
<18.5	4 (1%)	4 (1%)
18.5-24.9	126 (28%)	114 (25%)
25.0-29.9	120 (27%)	146 (32%)
30.0-39.9	161 (36%)	153 (34%)
≥40·0	37 (8%)	34 (8%)
First trimester Pregnancy-associated plasma protein-A Multiple		

of the Median		
Number recorded	159 (36%)	172 (39%)
Median (IQR)	0·80 (0·51 to 1·27)	0·85 (0·51 to 1·35)
Second trimester uterine artery Doppler mean pulsatility index		
Number recorded	89 (20%)	91 (20%)
Median (IQR)	1·20 (0·94 to 1·49)	1·09 (0·88 to 1·49)
Parameters related to diagnosis of pre-eclampsia		
Highest blood pressure reading that led to diagnosis (mmHg)		
If based on single diastolic blood pressure ≥110mmHg: n (%)	53 (12%)	64 (14%)
Mean (SD) systolic blood pressure	163·8 (16·76)	166·1 (15·07)
Mean (SD) diastolic blood pressure	114·2 (6·30)	114·1 (5·24)
If based on 2 diastolic blood pressure readings >=90mmHg, mean of 2 readings: n (%)	395 (88%)	387 (86%)
Mean (SD) systolic blood pressure	149·7 (9·99)	150·0 (10·19)
Mean (SD) diastolic blood pressure	96·7 (4·37)	96·5 (4·06)
All participants: n (%)	448 (100%)	451 (100%)
Mean (SD) systolic blood pressure	151·4 (11·88)	152·3 (12·36)
Mean (SD) diastolic blood pressure	98·8 (7·30)	99·0 (7·47)
Additional parameters leading to diagnosis of pre-eclampsia (non-exclusive)		
Urinary protein-creatinine ratio >=30 (mg/mmol): n (%)	405 (90%)	407 (90%)
Median (IQR) (if >= 30 mg/mmol)	92 (50 to 188)	87 (47 to 187)
24 hr urinary protein excretion >=300 (mg/24hrs): n (%)	18 (4%)	21 (5%)
Median (IQR) (if >= 300 mg/24hrs)	550 (400 to 1000)	900 (600 to 50000)
Creatinine >90 µmol/L: n (%)	14 (3%)	11 (2%)
Median (IQR) (if >90 µmol/L)	100 (94 to 110)	99 (91 to 111)
Alanine or aspartate transaminase >70 IU/L: n (%)	19 (4%)	15 (3%)
Median (IQR) (if >70 IU/L)	107 (84 to 211)	105 (83 to 317)
Platelet count <150 x 10^9/L: n (%)	44 (10%)	43 (10%)
Median (IQR) (if <150 x 10^9/L)	130 (108 to 140)	131 (118 to 144)
Estimated fetal weight <10^{th} centile on ultrasound	61 (14%)	66 (15%)
Antihypertensive medication at study entry	359 (80%)	374 (83%)
One oral agent	240/359 (67%)	241/374 (64%)
Two or more oral agents	117/359 (33%)	132/374 (35%)

One intravenous agent	2/359 (1%)	5/374 (1%)
Aspirin prescribed during pregnancy	170 (38%)	189 (42%)
Median (IQR) gestational age aspirin first prescribed (weeks)	13 (11 to 16)	12 (11 to 16)
Low molecular weight heparin prescribed during pregnancy	125 (28%)	117 (26%)
Median (IQR) Gestational age heparin first prescribed (weeks)	33 (31 to 34)	34 (31 to 35)
Most recent proteinuria reading		
Urinary protein-creatinine ratio recorded: n (%)	434 (97%)	441 (98%)
Median (IQR) (mg/mmol)	83 (42 to 186)	80 (42 to 172)
24 hr urinary protein excretion recorded: n (%)	15 (3%)	14 (3%)
Median (IQR) (mg/24hrs)	78 (31 to 550)	107 (31 to 460)
Most recent lab parameters prior to study entry		
Median (IQR) haemoglobin (g/L)	116 (108 to 124)	117 (108 to 124)
Median (IQR) platelet count ($x10^9$/L)	213 (174 to 255)	210 (174 to 251)
Median (IQR) creatinine (µmol/L)	59 (50 to 68)	59 (51 to 67)
Median (IQR) alanine aminotransferase (U/L)	15 (10 to 22)	15 (10 to 22)
n (%)	424 (95%)	422 (94%)
Median (IQR) aspartate aminotransferase (U/L)	20 (15 to 32)	20 (15 to 24)
n (%)	51 (11%)	59 (13%)
Median (IQR) Placental growth factor (pg/ml)	16 (12 to 43)	12 (12 to 22)
n (%)	33 (7%)	28 (6%)
Median (IQR) uric acid (µmol/L)	366 (303 to 416)	357 (300 to 424)
n (%)	166 (37%)	165 (37%)
Bishop score assessed at study entry	9 (2%)	6 (1%)
<2	2/9 (22%)	2/6 (33%)
2-6	7/9 (78%)	4/6 (67%)
Fetal growth scan in last two weeks	366 (82%)	375 (83%)
Suspected fetal growth restriction	79/366 (22%)	85/375 (23%)
Indicator of fetal growth restriction (non-exclusive)		
Abdominal circumference <10^{th} centile	23 (5%)	32 (7%)
Estimated fetal weight <10^{th} centile	67 (15%)	73 (16%)
Umbilical artery pulsatility index >95^{th} centile	8 (2%)	13 (3%)
Absent or reversed umbilical artery end diastolic flow	2 (0%)	5 (1%)
Amniotic fluid index <5^{th} centile	4 (1%)	7 (2%)

In-patient at time of trial entry	362 (81%)	371 (82%)

Data are n (%) unless shown otherwise. n/N (%) indicates that the denominator only includes participants with a relevant measurement for that variable.

Supplementary Table 3: Additional secondary maternal outcomes

	Planned delivery (n=448)	Expectant management (n=451)
Components by category (non-exclusive)		
Maternal death	0 (0%)	1 (0%)
Central nervous system		
Eclampsia	3 (1%)	4 (1%)
Glasgow coma score <13	0 (0%)	0 (0%)
Stroke or reversible ischaemic neurological deficit	0 (0%)	0 (0%)
Transient ischaemic attack	0 (0%)	0 (0%)
Cortical blindness or retinal detachment	0 (0%)	0 (0%)
Posterior reversible encephalopathy	0 (0%)	0 (0%)
Cardiorespiratory		
Positive inotropic support	0 (0%)	1 (0%)
Infusion of a third parenteral antihypertensive drug	2 (0%)	0 (0%)
Myocardial ischaemia or infarction	1 (0%)	0 (0%)
SpO_2 <90%	2 (0%)	3 (1%)
>=50% FiO_2 for >1 hr	1 (0%)	0 (0·0)
Intubation (other than for caesarean section)	2 (0%)	0 (0%)
Pulmonary oedema	1 (0%)	2 (0%)
Haematological		
Transfusion of any blood product	20 (5%)	23 (5%)
Platelet count <50×10^9 per L, with no transfusion	2 (0%)	4 (1%)
Hepatic		
Hepatic dysfunction	44 (10%)	63 (14%)
Hepatic haematoma or rupture	0 (0%)	0 (0%)
Renal		
Acute renal insufficiency (creatinine >150 µmol/L; no pre-existing renal disease)	3 (1%)	4 (1%)
Acute renal failure (creatinine >200 µmol/L; pre-existing renal disease)	0 (0%)	0 (0%)
Dialysis	0 (0%)	0 (0%)
Other		

Placental abruption	4 (1%)	4 (1%)
Systolic blood pressure ≥160 mmHg post randomisation	267 (60%)	313 (70%)
Systolic blood pressure ≥160mmHg (randomisation to delivery)	203 (45%)	261 (58%)
Systolic blood pressure ≥160mmHg (delivery to post-delivery discharge)	172 (39%)	173 (39%)
Highest BP recorded: randomisation to delivery		
Mean (SD) systolic blood pressure (mmHg)	159·4 (17%)	164·4 (17%)
Mean (SD) diastolic blood pressure (mmHg)	95·0 (11%)	97·7 (12%)
Highest BP recorded: delivery to post-delivery discharge		
Mean (SD) systolic blood pressure (mmHg)	155·8 (16%)	156·6 (16%)
Mean (SD) diastolic blood pressure (mmHg)	91·5 (12%)	92·5 (12%)
Antihypertensive medication: randomisation to delivery	381 (85%)	405 (90%)
One oral agent	233/381 (61%)	185/405 (46%)
Two or more oral agents	147/381 (39%)	218/405 (54%)
One intravenous agent	17/381 (5%)	37/405 (9%)
Two or more intravenous agents	3/381 (1%)	4/405 (1%)
Anti-hypertensive drugs administered (non-exclusive)		
Hydralazine	10/381 (3%)	25/405 (6%)
Labetalol	328/381 (86%)	353/405 (87%)
Methyldopa	39/381 (10%)	61/405 (15%)
Nifedipine	162/381 (43%)	222/405 (55%)
Amlodipine	5/381 (1%)	5/405 (1%)
Atenolol	2/381 (1%)	3/405 (1%)
Diltiazem	0/381 (0%)	0/405 (0%)
Doxazosin	2/381 (1%)	6/405 (2%)
Ketaserin	0/381 (0%)	0/405 (0%)
Propranolol	0/381 (0%)	1/405 (0%)
Verapamil	0/381 (0%)	0/405 (0%)
Other	2/381 (1%)	3/405 (1%)
Progression to HELLP syndrome	7 (2%)	10 (2%)
Magnesium sulfate: randomisation to delivery	31 (7%)	69 (15%)
Low molecular weight heparin: randomisation to delivery	157 (35%)	208 (46%)
Steroids for fetal lung maturation	291 (65%)	248 (55%)
Number of doses of steroids		

1	12/291 (4%)	14/248 (6%)
2	277/291 (95%)	229/248 (92%)
3	0/291 (0%)	0/248 (0%)
>=4	2/291 (1%)	5/248 (2%)
Suspected fetal growth restriction post randomisation	13 (3%)	41 (9%)
Indicator of fetal growth restriction (non-exclusive)		
Abdominal circumference <10th centile	6	15
Estimated fetal weight <10th centile	8	28
Umbilical artery pulsatility index >95th centile	3	13
Absent or reversed umbilical artery end diastolic flow	2	3
Amniotic fluid index <5th centile	2	7
Onset of labour		
Induced	304 (68%)	275 (61%)
Method of induction if induced (non-exclusive)		
Prostaglandin gel/pessary	275/304 (91%)	238/275 (87%)
Foley catheter	13/304 (4%)	7/275 (3%)
Artificial rupture of membranes	133/304 (44%)	120/275 (44%)
Syntocinon	99/304 (33%)	90/275 (33%)
Other	1/304 (0%)	3/275 (1%)
Estimated amount of blood loss at delivery (mls)		
Mean (SD)	559·0 (583·1)	557·9 (454·8)
Median (IQR)	406 (300 to 600)	400 (300 to 650)
Confirmed maternal sepsis (positive blood or urine cultures) between randomisation and hospital discharge	2 (0%)	6 (1%)
Blood culture	1/2 (50%)	5/6 (83%)
Urine culture	1/2 (50%)	1/6 (17%)

Data are n (%) unless shown otherwise· n/N (%) indicates that the denominator only includes participants with a relevant measurement for that variable· HELLP: haemolysis, elevated liver enzymes, low platelets syndrome.

Supplementary Table 4: Process outcomes: time between randomisation to initiation of delivery and delivery

	Planned delivery (n = 448)	**Expectant management (n = 451)**
Time between randomisation and initiation of delivery (days)		
Overall		
n	447	450
Median (IQR)	1 (1 to 2)	5 (3 to 8)
By gestational age at randomisation		
34^{+0} to 34^{+6}		
n (%)	131 (29%)	135 (30%)
Median (IQR)	1 (1 to 2)	6 (2 to 11)
35^{+0} to 35^{+6}		
n (%)	136 (30%)	131 (29%)
Median (IQR)	1 (1 to 2)	6 (3 to 10)
36^{+0} to 36^{+6}		
n (%)	180 (40%)	184 (41%)
Median (IQR)	1 (1 to 2)	4 (2 to 6)
Time between randomisation and delivery (days)		
Overall		
n	447	451
Median (IQR)	2 (1 to 4)	6 (3 to 9)
By gestational age at randomisation		
34^{+0} to 34^{+6}		
n (%)	131 (29%)	135 (30%)
Median (IQR)	3 (1 to 4)	7 (3 to 12)
35^{+0} to 35^{+6}		
n (%)	136 (30%)	132 (29%)
Median (IQR)	2 (1 to 3)	7 (4 to 11)
36^{+0} to 36^{+6}		
n (%)	180 (40%)	184 (41%)
Median (IQR)	2 (2 to 4)	5 (4 to 7)

Supplementary Table 5: Additional secondary perinatal outcomes (Intention To Treat analysis)

	Planned delivery (n = 471)	Expectant management (n = 475)
Mode of delivery		
Spontaneous vaginal	169 (36%)	139 (29%)
Spontaneous vaginal (cephalic)	165 (35%)	138 (29%)
Spontaneous vaginal (breech)	4 (1%)	1 (0%)
Assisted vaginal (cephalic)	40 (9%)	47 (10%)
Assisted vaginal – vacuum	13 (3%)	19 (4%)
Assisted vaginal – forceps	27 (6%)	28 (6%)
Caesarean section	260 (55%)	289 (61%)
Pre-labour caesarean section	153 (33%)	168 (35%)
Emergency caesarean section	107 (23%)	121 (26%)
Indication for assisted vaginal delivery (non-exclusive)		
Maternal comorbidity or disease	1/40 (3%)	3/47 (6%)
Failure to progress in second stage	16/40 (40%)	17/47 (36%)
Suspected fetal distress	28/40 (70%)	30/47 (64%)
Indication for caesarean delivery (non-exclusive)		
Maternal comorbidity or disease	40/260 (15%)	78/289 (27%)
Previous caesarean delivery/uterine surgery	57/260 (22%)	57/289 (20%)
Failure to progress in first stage	39/260 (15%)	46/289 (16%)
Failure to progress in second stage	2/260 (1%)	1/289 (0%)
Suspected fetal distress	83/260 (32%)	101/289 (35%)
Failed instrumental delivery	3/260 (1%)	1/289 (0%)
Fetal presentation not cephalic	42/260 (16%)	31/289 (11%)
Twins	6/260 (2%)	9/289 (3%)
Maternal request	7/260 (3%)	1/289 (0%)
Gestational age at delivery (days)		
<37 weeks	387 (83%)	261 (55%)
Baby sex		
Boy	240 (51%)	233 (49%)
Girl	229 (49%)	242 (51%)
Umbilical artery pH <7·05	6/281 (2%)	7/266 (3%)
Umbilical arterial pH collected	281 (60%)	266 (56%)

Principal recorded indication for neonatal unit admission		
Number of babies admitted to the neonatal unit*	196	159
Preterm		
Prematurity	83 (42%)	40 (25%)
Cardiorespiratory		
Respiratory disease	47 (24%)	41 (26%)
Cardiovascular disease	0 (0%)	1 (1%)
Failed oximetry testing	0 (0%)	1 (1%)
Gastric, Hepatic, Metabolic		
Gastrointestinal tract disease	0 (0%)	0 (0%)
Jaundice	12 (6%)	11 (7%)
Hypoglycaemia	21 (11%)	31 (20%)
Other metabolic disease	0 (0%)	0 (0%)
Neurological		
Convulsions	1 (1%)	0 (0%)
Hypoxic ischaemic encephalopathy	0 (0%)	0 (0%)
Poor condition at birth	2 (1%)	3 (2%)
Neonatal abstinence syndrome	0 (0%)	0 (0%)
Other neurological disease	0 (0%)	0 (0%)
Infection		
Infection suspected/confirmed	9 (5%)	12 (8%)
Size, weight, feeding		
Intrauterine growth restriction/ Small for gestational age infant	8 (4%)	10 (6%)
Poor feeding or weight loss	4 (2%)	2 (1%)
Anomaly or trauma		
Congenital anomaly suspected/ confirmed	2 (1%)	0 (0%)
Birth trauma/ injury	0 (0%)	0 (0%)
Relating to carer		
Social issues/Foster care	0 (0%)	0 (0%)
Maternal admission/emergency	1 (1%)	2 (1%)
Specialist care		
Surgery	0 (0%)	0 (0%)
Palliative care	0 (0%)	0 (0%)

Monitoring or investigation		
Monitoring	4 (2%)	5 (3%)
Exclusively for specific investigation	0 (0%)	0 (0%)
Continuing care	2 (1%)	0 (0%)
Need for respiratory support	45 (10%)	48 (10%)
Type of respiratory support needed (non-exclusive)		
Endotracheal ventilation	10/45 (22%)	14/48 (29%)
Continuous positive airway pressure	36/45 (80%)	37/48 (77%)
High flow oxygen	12/45 (27%)	17/48 (35%)
Cerebral ultrasound scan performed	18 (4%)	24 (5%)
Abnormalities found	2/18 (11%)	1/24 (4%)
Intraventricular haemorrhage (IVH) Grade I-II	1/2 (50%)	0/1 (0%)
Intraventricular haemorrhage (IVH) causing ventricular distension	1/2 (50%)	0/1 (0%)
Other	0/2 (0%)	1/1 (100%)
Sepsis confirmed	3 (1%)	2 (0%)
Positive blood cultures	3/3 (100%)	1/2 (50%)
Cerebrospinal fluid cultures	0/3 (0%)	1/2 (50%)
Necrotising enterocolitis confirmed (Bell's stage 2 or 3)	0 (0%)	0 (0%)
Seizures	0 (0%)	0 (0%)
Diagnosed Encephalopathy	0 (0%)	0 (0%)
Diagnosed hypoglycaemia (blood glucose <2·6 mmol/L on >=2 consecutive occasions)	80 (17%)	72 (15%)
Intravenous dextrose required	32/80 (40%)	32/72 (44%)
Tube feeding required	41/80 (51%)	45/72 (63%)
Method of infant feeding 24 hrs prior to discharge		
Exclusive breast-feeding	112 (24%)	139 (30%)
Mixed feeding	174 (38%)	161 (34%)
Exclusive formula feeding	176 (38%)	168 (36%)

Data are n (%) unless shown otherwise· n/N (%) indicates that the denominator only includes participants with a relevant measurement for that variable.

*Number of babies admitted to the neonatal unit (denominator for the principal recorded indications).

Supplementary Table 6: Secondary perinatal outcomes post randomisation (by Per Protocol analysis)

	Planned delivery (n = 342)	**Expectant management (n = 470)**	**Adjusted effect measure* (95% CI)**
Stillbirth	0 (0%)	0 (0%)	-
Neonatal deaths within 7 days of delivery	0 (0%)	0 (0%)	-
Neonatal death before discharge	0 (0%)	0 (0%)	-
Median (IQR) gestational age at delivery (days)	252 (246 to 257)	258 (251 to 260)	-4·0 (-4·6, -3·4)
Mode of delivery			
Spontaneous vaginal	127 (37%)	138 (29%)	1·21 (1·01, 1·44)
Assisted vaginal	34 (10%)	46 (10%)	0·97 (0·64, 1·46)
Caesarean section	181 (53%)	286 (61%)	0·90 (0·81, 1·00)
Median (IQR) birth weight (g)	2400 (2060 to 2780)	2483 (2150 to 2912)	-109 (-167, -51)
Median (IQR) birth weight centile†	34 (17 to 61)	30 (13 to 61)	2·5 (-2·3, 7·4)
Birth weight <10th centile	53 (16%)	95 (20%)	0·77 (0·56, 1·05)
Birth weight <3rd centile	13 (4%)	27 (6%)	0·69 (0·36, 1·33)
Median (IQR) Apgar score at 5 minutes post birth	10 (9 to 10)	10 (9 to 10)	-
Median (IQR) umbilical arterial pH Umbilical arterial pH collected	7·26 (7·19 to 7·30) 201 (59%)	7·25 (7·20 to 7·30) 265 (56%)	0·00 (-0·01, 0·02)
Number of infants admitted to neonatal unit	155 (45%)	155 (33%)	1·40 (1·18, 1·66)
Principal recorded indication for neonatal unit admission*			
Prematurity	66/155 (43%)	38/155 (25%)	
Respiratory disease	34/155 (22%)	39/155 (25%)	
Hypoglycaemia	19/155 (12%)	31/155 (20%)	
Jaundice	10/155 (7%)	11/155 (7%)	
Infection suspected/confirmed	7/155 (5%)	12/155 (8%)	
Intrauterine growth restriction/ Small for gestational age infant	7/155 (5%)	10/155 (7%)	
Other	12/155 (8%)	14/155 (9%)	
Need for respiratory support	32 (9%)	46 (10%)	0·98 (0·55, 1·77)
Need for supplementary oxygen prior to discharge	47 (14%)	47 (10%)	1·41 (0·97, 2·07)
Median (IQR) supplemental oxygen required	1 (1 to 2)	2 (1 to 3)	

Cerebral ultrasound abnormalities found/ number tested	0/12 (0%)	1/20 (5%)	
Sepsis confirmed	1 (0%)	2 (0%)	
Necrotising enterocolitis	0 (0%)	0 (0%)	
Seizures	0 (0%)	0 (0%)	
Encephalopathy	0 (0%)	0 (0%)	
Hypoglycaemia during neonatal unit admission	61 (18%)	71 (15%)	
Exclusive breast-feeding 24 hrs prior to discharge	84 (25%)	139 (30%)	
Total neonatal unit stay			
Median (IQR) days in neonatal unit	6 (2 to 10)	6 (3 to 12)	-0·4 (-2·07, 1·21)
Number (%) admitted for at least one day	147 (43%)	149 (32%)	
Category of care during neonatal unit stay (separation of baby from mother)			
Median (IQR) days in intensive care	2 (1 to 3)	3 (1 to 4)	-1·4 (-27, 25)
Number (%) admitted	22 (6%)	19 (4%)	
Median (IQR) days in high dependency care	1 (1 to 3)	2 (1 to 5)	-0·6 (-3·3, 2·2)
Number (%) admitted	39 (11%)	32 (7%)	
Median (IQR) days in special care	5 (2 to 10)	6 (2 to 11)	0 (-1·7, 1·7)
Number (%) admitted	135 (40%)	139 (30%)	
Category of care during other postnatal stay (baby alongside mother)			
Median (IQR) days in transitional care	6 (2 to 8)	5 (4 to 6)	-
Number (%) admitted	26 (8%)	16 (3%)	
Median (IQR) days in postnatal care	3 (2 to 5)	3 (2 to 4)	0·25 (-0·06, 0·56)
Number (%) admitted	249 (73%)	382 (82%)	

Data are n (%) unless otherwise stated. Effect measures are risk ratios for categorical variables (risk in planned delivery group/ risk in expectant management group) and median differences for continuous variables (median in planned delivery group - median in expectant management group). CI: confidence intervals; IQR: interquartile range· n/N (%) indicates that the denominator only includes participants with a relevant measurement for that variable.

*Adjusted for centre, singleton/twin pregnancies, severity of hypertension in 48 hours prior to enrolment, parity, previous caesarean section and gestational age at randomisation.

† Birth weight centile calculated using the Stata add-in function zanthro using the British 1990 Growth Reference (reanalysed 2009).

‡ Full list of other indications for Neonatal Unit admission given in Supplementary Table 6.

Supplementary Table 7: Additional secondary perinatal outcomes (by Per Protocol analysis)

	Planned delivery (n = 342)	**Expectant management (n = 470)**
Mode of delivery		
Spontaneous vaginal	127 (37%)	138 (29%)
Spontaneous vaginal (cephalic)	125 (37%)	137 (29%)
Spontaneous vaginal (breech)	2 (1%)	1 (0%)
Assisted vaginal (cephalic)	34 (10%)	46 (10%)
Assisted vaginal – vacuum	12 (4%)	19 (4%)
Assisted vaginal – forceps	22 (6%)	27 (6%)
Caesarean section	181 (53%)	286 (61%)
Pre-labour caesarean section	92 (27%)	167 (36%)
Emergency caesarean section	89 (26%)	119 (25%)
Indication for assisted vaginal delivery (non-exclusive)		
Maternal comorbidity or disease	1/34 (3%)	3/46 (7%)
Failure to progress in second stage	13/34 (38%)	17/46 (37%)
Suspected fetal distress	25/34 (74%)	29/46 (63%)
Indication for caesarean delivery (non-exclusive)		
Maternal comorbidity or disease	25/181 (14%)	75/286 (26%)
Previous caesarean delivery/uterine surgery	30/181 (17%)	55/286 (19%)
Failure to progress in first stage	31/181 (17%)	46/286 (16%)
Failure to progress in second stage	2/181 (1%)	1/286 (0%)
Suspected fetal distress	66/181 (37%)	101/286 (35%)
Failed instrumental delivery	3/181 (2%)	1/286 (0%)
Fetal presentation not cephalic	33/181 (18%)	31/286 (11%)
Twins	2/181 (1%)	9/286 (3%)
Maternal request	5/181 (3%)	1/286 (0%)
Gestational age at delivery (days)		
<37 weeks	286 (84%)	256 (55%)
Baby sex		
Boy	176 (52%)	229 (49%)
Girl	166 (49%)	241 (51%)

Umbilical artery pH <7·05 **Umbilical arterial pH collected**	5/201 (3%) 201 (59%)	7/265 (3%) 265 (57%)
Principal recorded indication for neonatal unit admission		
Number of babies admitted to the neonatal unit*	155	155
Preterm		
Prematurity	66 (43%)	38 (25%)
Cardiorespiratory		
Respiratory disease	34 (22%)	39 (25%)
Cardiovascular disease	0 (0%)	1 (1%)
Failed oximetry testing	0 (0%)	1 (1%)
Gastric, Hepatic, Metabolic		
Gastrointestinal tract disease	0 (0%)	0 (0%)
Jaundice	10 (7%)	11 (7%)
Hypoglycaemia	19 (12%)	31 (20%)
Other metabolic disease	0 (0%)	0 (0%)
Neurological		
Convulsions	1 (1%)	0 (0%)
Hypoxic ischaemic encephalopathy	0 (0%)	0 (0%)
Poor condition at birth	2 (1%)	3 (2%)
Neonatal abstinence syndrome	0 (0%)	0 (0%)
Other neurological disease	0 (0%)	0 (0%)
Infection		
Infection suspected/confirmed	7 (5%)	12 (8%)
Size, weight, feeding		
Intrauterine growth restriction/ Small for gestational age infant	7 (5%)	10 (7%)
Poor feeding or weight loss	3 (2%)	2 (1%)
Anomaly or trauma		
Congenital anomaly suspected/ confirmed	0 (0%)	0 (0%)
Birth trauma/ injury	0 (0%)	0 (0%)
Relating to carer		
Social issues/Foster care	0 (0%)	0 (0%)
Maternal admission/emergency	0 (0%)	2 (1%)
Specialist care		

Surgery	0 (0%)	0 (0·0)
Palliative care	0 (0%)	0 (0·0)
Monitoring or investigation		
Monitoring	4 (3%)	5 (3%)
Exclusively for a specific investigation	0 (0%)	0 (0%)
Continuing care	2 (1%)	0 (0%)
Need for respiratory support	32 (9%)	46 (10%)
Type of respiratory support needed (non-exclusive)		
Endotracheal ventilation	6/32 (19%)	14/46 (30%)
Continuous positive airway pressure	27/32 (84%)	35/46 (76%)
High flow oxygen	8/32 (25%)	17/46 (37%)
Cerebral ultrasound scan performed	12 (4%)	20 (4%)
Abnormalities found	0/12 (0%)	1/20 (5%)
Intraventricular haemorrhage (IVH) Grade I-II	0/0 (0%)	0/1 (0%)
Intraventricular haemorrhage (IVH) causing ventricular distension	0/0 (0%)	0/1 (0%)
Other	0/0 (0%)	1/1 (100%)
Sepsis confirmed	1 (0%)	2 (0%)
Positive blood cultures	1/1 (100%)	1/2 (50%)
Cerebrospinal fluid cultures	0/1 (0%)	1/2 (50%)
Diagnosed Encephalopathy	0 (0%)	0 (0%)
Diagnosed hypoglycaemia (blood glucose <2·6 mmol/L on >=2 consecutive occasions)	61 (18%)	71 (15%)
Intravenous dextrose required	28/61 (46%)	31/71 (44%)
Tube feeding required	33/61 (54%)	44/71 (62%)
Method of infant feeding 24 hrs prior to discharge		
Exclusive breast-feeding	84 (25%)	139 (30%)
Mixed feeding	124 (37%)	159 (34%)
Exclusive formula feeding	128 (38%)	167 (36%)

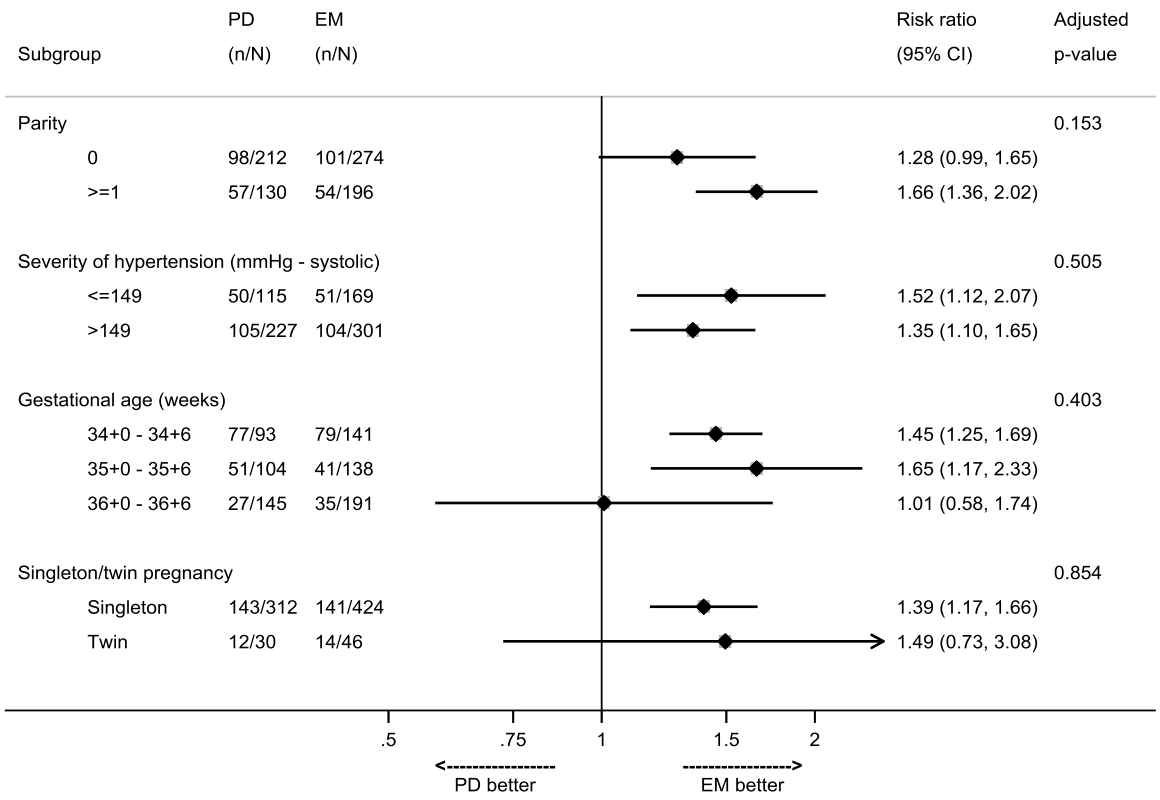
Data are n (%) unless shown otherwise· n/N (%) indicates that the denominator only includes participants with a relevant measurement for that variable.

*Number of babies admitted to the neonatal unit (denominator for the principal recorded indications).

Supplementary Table 8: Unexpected maternal and infant serious adverse events by allocation

	Planned delivery	Expectant management
Serious adverse events (SAEs)	9	12
Severity		
Mild	4	3
Moderate	2	2
Severe	3	7
Causality		
Not related	7	9
Possibly	2	2
Probably	0	1
Action taken		
Intervention stopped prior to the event started	2	5
None	7	7
Outcome		
Fatal	0	1
Not resolved	0	3
Resolved	6	7
Resolved with sequelae	1	0
Resolving	2	1
System Organ Class		
Cardiac disorders	3	3
Gastrointestinal disorders	0	1
Infections and infestations	1	0
Neoplasms benign, malignant and unspecified	0	1
Pregnancy, puerperium and perinatal conditions	4	5
Renal and urinary disorders	0	1
Respiratory, thoracic and mediastinal disorders	0	1
Vascular disorders	1	0

Supplementary Figure 1: Forest plot for sub-group analysis (Per Protocol population) of primary perinatal outcome comparing Planned Delivery (PD) with Expectant Management (EM). p-values compare risk ratios across the different sub-groups of each factor.



Supplementary Table 9: Sensitivity analysis for the primary outcome, excluding women (maternal outcome) and babies (perinatal outcome) in the planned delivery arm for whom initiation of delivery was greater than 96 hours after randomisation

	Planned delivery	Expectant management	Risk ratio (95% CI) p-value	Adjusted risk ratio (95% CI) p-value
Composite of maternal morbidity and/or recorded systolic BP >=160 mmHg post randomisation	274/429 (64%)	338/451 (75%)	0·85 (0·78, 0·93) 0.0003~~<0·01~~	0·85 (0·78, 0·93) 0.0003~~<0·01~~
Composite of perinatal deaths and NNU admissions up to infant hospital discharge	184/450 (41%)	159/475 (34%)	1·23 (1·03, 1·46) 0·0205	1·24 (1·06, 1·44) 0·00751~~1~~

Data are n (%).

*Adjusted for centre, singleton/twin pregnancies, severity of hypertension in 48 hours prior to enrolment, parity, previous caesarean section and gestational age at randomisation.

Chappell et al. Trials (2019) 20:85
https://doi.org/10.1186/s13063-018-3150-1

Trials

STUDY PROTOCOL Open Access

Planned delivery or expectant management for late preterm pre-eclampsia: study protocol for a randomised controlled trial (PHOENIX trial)

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Abstract

Background: Pre-eclampsia is a pregnancy disorder, characterised by hypertension and multisystem complications in the mother. The adverse outcomes of pre-eclampsia include severe hypertension, stroke, renal and hepatic injury, haemorrhage, fetal growth restriction and even death. The optimal time to instigate delivery to prevent morbidity when pre-eclampsia occurs between 34 and 37 weeks' gestation, without increasing problems related to infant immaturity or complications, remains unclear.

Methods/design: The PHOENIX trial is a non-masked, randomised controlled trial, comparing planned early delivery (with initiation of delivery within 48 h of randomisation) with usual care (expectant management) in women with pre-eclampsia between 34^{+0} and 36^{+6} weeks' gestation. The primary objectives of the trial are to determine if planned delivery reduces adverse maternal outcomes, without increasing the short-term harm to infants (composite of perinatal deaths or neonatal unit admissions up to infant hospital discharge) or impacting long-term infant neurodevelopmental status at 2 years corrected age (Parent Report of Cognitive Abilities-Revised).

Discussion: Current practice in the UK at the time of trial commencement for management of pre-eclampsia varies by gestation. Previous trials have shown that in women with pre-eclampsia after 37 weeks of gestion, delivery is initiated, as maternal complications are reduced without increasing fetal risks. Prior to 34 weeks of gestation, usual management aims to prolong pregnancy for fetal benefit, unless severe complications occur, necessitating preterm delivery. This trial aims to address the uncertainty for women where the balance of benefits and risks of delivery compared to expectant management are uncertain. Previous trials in this area have been undertaken, but have not provided a definitive answer, and the research question remains active. The results of this trial are expected to influence clinical practice internationally, through direct adoption and by incorporation into guidelines in countries with similar settings.

Trial registration: ISRCTN01879376. Registered on 25 November 2013.

Keywords: Pre-eclampsia, hypertension, pregnancy, perinatal

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Background

In the UK, 10–15% of pregnant women develop hypertension in pregnancy, and 2–5% pre-eclampsia. Pre-eclampsia is a multisystem disorder, characterised by placental and maternal vascular dysfunction, which is associated with substantial 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].

Timely delivery may be indicated to prevent maternal and infant morbidity. Standard management of pre-eclampsia involves close monitoring whilst taking into consideration gestational age, fetal well-being and progression of maternal disease. When a diagnosis of pre-eclampsia is made at or beyond 37 weeks' 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.

Around half (40%) of all pre-eclampsia occurs preterm (before 37 weeks), and these cases 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] increases neonatal risk (Hyaline Membrane Disease risk ratio 2.3 [95% confidence interval, CI 1.39 to 3.81] and necrotising enterocolitis risk ratio 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' gestation, without increasing problems related to infant immaturity or complications, remains unclear. Current management involves close surveillance and delivery only when evidence of impending serious morbidity becomes apparent (e.g. deteriorating maternal or fetal condition). As this may be rapid or unexpected, planned delivery (the proposed intervention) beyond 34 weeks may be valuable. Neonatal and infant mortality and morbidity (e.g. through respiratory distress syndrome) may, nonetheless, occur following delivery between 34 and 37 weeks of gestation. However, neurodevelopmental morbidity and risk of growth restriction and death may be reduced by early delivery, and adverse events related to expectant management (including placental abruption, 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, to evaluate the benefits and risks for the mother and baby, including assessment of longer-term neurodevelopmental outcomes.

This aim of this study is to compare planned delivery with expectant management (usual care) in women with pre-eclampsia between 34 and 37 weeks' gestation. This study arose from a commissioned call by the funder (National Institute for Health Research), following development of the proposal and choice of important outcomes by clinicians with patient and public involvement. 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 an NHS research ethics committee (REC) and the NHS Trust Research and Development Offices for approval.

Methods/design

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' gestation reduces maternal adverse outcomes without substantial worsening of neonatal or infant outcomes, compared with the current practice of expectant management to 37 weeks' gestation.

Primary objectives

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' gestation reduces adverse maternal outcomes based on a composite listed in the fullPIERS [5] paper with addition of recorded systolic hypertension (systolic blood pressure of ≥160 mmHg), as highlighted in the triennial Confidential Enquiry into Maternal Deaths (2006–8) [6].
- To evaluate the impact of the intervention on short- and long-term perinatal outcomes. Short-term outcomes will be assessed by a composite of perinatal deaths (antenatal or intrapartum stillbirths or neonatal deaths within 7 days, but not deaths due to congenital anomaly) or neonatal unit admissions up to time of infant hospital discharge.
- To determine the impact on infant neurodevelopmental status at 2 years of age corrected for prematurity using the Parent Report of Cognitive Abilities, Revised (PARCA-R) [7] Composite.

Secondary objectives

The secondary objectives of the study are:

- To investigate the effect of the 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)
- To assess the impact of both management strategies on health economic outcomes
- To evaluate quality of life using questionnaires immediately after randomisation and at 6 months and 2 years corrected age.

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 35 to 45 consultant-led maternity units across England and Wales. An internal pilot phase will initially be run, involving six 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. If the processes are shown to work in the internal pilot phase, recruitment to the main trial will proceed with no break and data from the internal pilot phase will be analysed together with the main trial data collected. The internal pilot will aim to recruit a total of 41 women by the end of month 6. Progression criteria (internal pilot into main trial) will be recruitment in the pilot study of at least 75% of target (31 women or more) with loss to follow-up of no more than seven women.

Selection and withdrawal of participants

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
- Pre-eclampsia defined by the International Society for the Study of Hypertension in Pregnancy 2014 [8] as (1) diastolic blood pressure ≥90 mmHg (twice, ≥4 h and <1 week apart) or (2) diastolic blood pressure ≥110 mmHg on one occasion [9] and one or more of the following: (i) proteinuria (≥0.3 g/day by 24-h urine collection or ≥ 30 mg/mmol by spot urinary protein creatinine ratio), (ii) thrombocytopenia (platelet count < 150×10^9/L), (iii) renal insufficiency (creatinine ≥90 μmol/L), (iv) impaired liver function (alanine transaminase or aspartate transaminase >70 IU/L), (v) fetal growth restriction (Estimated fetal weight EFW <10th centile confirmed by ultrasound); or 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.

Exclusion criterion

Women will be excluded from participation in the study if a decision has already been made to deliver within the next 48 h.

Recruitment, eligibility and consent

Members of the research team will provide a full verbal explanation and written description of the trial to women who meet the inclusion criteria (as above). The woman will be given sufficient time to consider the information, and to decide whether she will participate in the trial. Written informed consent will be sought from the woman and taken by an appropriately trained doctor.

Study periods

A woman's participation in the study may be from 34 weeks' gestation until their child reaches 2 years of age corrected for prematurity, a maximum duration of 28 months.

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) ongoing care and there will be no requirement for any study-related follow-up safety assessments. The intervention may be discontinued if their clinician feels it is in the baby's best interests. For a woman allocated to the expectant management group, the attending clinician will make a decision for delivery based on the National Institute for Health and Care Excellence (NICE) guidelines, with delivery planned at 37 weeks' gestation. If clinical needs dictate delivery prior to 37 weeks' gestation, this will not constitute withdrawal from the trial allocation. For a woman allocated to the planned delivery group, if the woman should decide that she does not wish to proceed with the planned delivery and instead chooses to continue to be monitored by her attending clinician, this will not constitute 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.

Assessment of outcomes

Outcomes will be recorded on the web-based database after a review of case notes by trained researchers after the discharge of the mother and baby. Confirmation of maternal outcome data (to include occurrence or not of the primary outcome) will be undertaken with an additional sign-off by the site's principal investigator for each participant.

Co-primary outcomes

Primary short-term maternal outcome

- Composite of maternal morbidity of fullPIERS [5] 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 or intrapartum stillbirths or deaths within 7 days of delivery but not deaths due to congenital anomalies) or neonatal unit admissions (physical separation of baby from the mother) prior to infant hospital discharge.

Primary long-term infant outcome

- PARCA-R composite score for neurodevelopment at 2 years of age corrected for prematurity [7].

Secondary outcomes

Secondary maternal outcomes will include assessments of:

- Individual components of the composite primary outcome, as number of women with one or more of the following: eclampsia, Glasgow coma scale <13, stroke, hypertensive encephalopathy, posterior reversible encephalopathy, cortical blindness, retinal detachment, myocardial infarction, intubation other than for a caesarean section, pulmonary oedema, ionotropic support, saturation <92%, 50% FiO2 for > 1 h, infusion of a third parenteral antihypertensive, platelets $<50 \times 10^9$/L, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome, acute fatty liver of pregnancy, hepatic dysfunction, haematoma or rupture, severe acute kidney injury (creatinine > 150 μmol/L or > 200 μmol/L in chronic kidney disease, dialysis, transfusion of blood products)
- Severe hypertension post-randomisation (systolic blood pressure ≥160 mmHg with or without medication on at least one occasion) recorded in written or electronic notes and measured by health-care professionals in clinical care
- Use of anti-hypertensive drugs recorded in written or electronic notes prescribed by health-care professionals in clinical care
- Progression to severe pre-eclampsia, defined as systolic blood pressure ≥160 mmHg, platelet count $< 100 \times 10^9$/L and abnormal liver function enzymes (ALT or AST > 70 IU/L)
- Estimated fetal weight (on ultrasound scan) <10th 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 or 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 assessments of:

- Stillbirth post-randomisation
- Neonatal death prior to hospital discharge
- Admissions to neonatal unit
- 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
- Birth weight <10th and <3rd customised/population centile
- Gestational age at delivery
- Apgar score at 5 min 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 (continuous positive airway pressure, high flow or endotracheal ventilation)

- Abnormal cerebral ultrasound scan
- Confirmed sepsis (positive blood or cerebrospinal fluid cultures)
- Necrotising enterocolitis (Bell's stage 2 and 3)
- Seizures (confirmed by electroencephalography or requiring anticonvulsant therapy)
- Encephalopathy grade (worst at any time: mild, moderate or severe)
- Hypoglycaemia (blood glucose < 2.6 mmol/L on two or more occasions)
- Other indications and main diagnoses resulting in neonatal unit admission
- Exclusively breastfed at discharge from the neonatal unit

Secondary long-term maternal outcomes will include assessments of:

- Quality of maternal physical and mental health using the validated SF-12v2® questionnaire when the infant is 6 months and 2 years of age corrected for prematurity.

Secondary health economic and quality of life outcomes will include assessments of

- Quality of life using the validated quality of life questionnaire EQ-5D-5 L [10] 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 and social care use by mother and infant at 6 months and 2 years
- EQ-5D-5 L [10] for the calculation of maternal QALYs

Trial procedures

The study procedures are shown in Fig. 1.

Informed consent

Written consent will be sought from the woman only after she has been given a full verbal explanation and written description of the trial (via the participant information leaflet; Additional file 1). Women who do not speak English will be approached only if an adult interpreter is available. Relatives may not interpret. Introductory verbal and written information should be offered to all potentially eligible women with pre-eclampsia at the study's recruiting centres. Written informed consent will be given using an informed consent form (Additional file 2) completed, signed and dated by the woman (with a countersignature by an interpreter where required) and signed by the person who obtained informed consent, who will be the principal investigator or another study doctor with delegated authority. After written informed consent has been obtained, a member of the research team will enter the baseline data onto the online database and perform randomisation, communicating the results directly to the woman. 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.

The management of pregnant women whilst in hospital should be in accordance with the NICE guidelines for the management of hypertension in pregnancy [11]. Delivery will be in accordance with standard procedures but will most likely be through induction with prostaglandins, unless contraindicated. 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

The intervention is planned delivery with minimal delay (with initiation of delivery within 48 h of randomisation to allow for steroid use and neonatal cot availability). Use of corticosteroids will be at the discretion of the individual clinician as indicated in the NICE guidelines. Postnatal care should follow NICE guidelines [11, 12].

Control (expectant management) group

Usual care is expectant management of pregnancy, as indicated by 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 on whether the woman has mild or moderate hypertension.

If the woman has mild hypertension (blood pressure 140/90 to 149/99 mmHg), care would be as follows:

- Admission to hospital
- Measure blood pressure at least 4× 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 and bilirubin.

If the woman has moderate hypertension (blood pressure 150/100 to 159/109 mmHg), care would be as for

Procedure for the intervention arm	Screening[1] (between booking and 36+6 weeks of gestation)	Randomisation (between 34+0 and 36+6 weeks of gestation)	Planned delivery[2] (within 48 hours of randomisation)	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 Assessment						✓
EQ-5D-5L[12] Questionnaire		✓			✓	✓
SF-12 v2® Questionnaire					✓	✓

Fig. 1 Schedule of participant enrolment, interventions and assessments in the trial. PARCA-R Parent Report of Cognitive Abilities, Revised, SAE serious adverse event. 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/ 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 Serious Adverse Event is reported. 12 EQ-5D-5L[10] to be given to the participant to complete immediately after randomisation

mild hypertension with the addition of the following assessments:

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

Time of delivery: adherence to protocol

Following randomisation to either the planned delivery group (intervention) or expectant management group (control), 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 so that protocol deviations can be identified and investigated.

Sample size

The sample size for the PHOENIX 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. It is also powered to ensure that a clinically relevant effect size can be detected for the short- and long-term perinatal co-primary outcomes.

Superiority hypothesis for the primary short-term 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 systolic 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 two-sided 5% significance level and 90% power in the planned delivery group. Taking into account a 5% loss of women in the follow-up, the overall target sample size for the study is 900 women (450 per group).

Non-inferiority hypothesis for the neonatal outcomes

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 a difference in incidence of no less than 10% (judged to be clinically relevant) and 78% power to detect a margin of no less than 8%.

To examine the component of perinatal death specifically, using Office for National Statistics data for all babies born in England and Wales in 2013, it is estimated that 1.6% (585/36,939) of all preterm births were perinatal deaths (stillbirth and early neonatal) [13]. 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 1.5%, a sample size of 430 in each group would achieve 90% power to detect a non-inferiority margin of a difference in incidence of no less than 2.7%. 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 a difference in incidence of no less than 9%.

Assuming a loss to follow-up at 2 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 questionnaire [7] 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 94% power to detect a non-inferiority margin of a 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. Considering the results from the INFANT trial [14] of over 46,000 higher risk women with babies of over 35 weeks' gestation, the original power calculation was revised. Using a revised standard deviation of 34, a sample size of 345 in each group will detect a non-inferiority margin of a difference in the mean PARCA-R score of no less than 9 points (1/4 of a standard deviation) with 94% power. A margin of no less than 7 points can be detected with 77% power.

In summary, a sample size of 900 women will have at least 90% power to detect: (1) a relative risk reduction of 25% (from 43% to 32%) in the primary maternal composite outcome, (2) a non-inferiority margin of a difference in the incidence of the primary short-term perinatal outcome of no less than 10% (from 24%) and (3) a non-inferiority margin of a difference in the mean 2-year PARCA-R score of ≥9 points.

Randomisation

The allocation ratio for the intervention (planned delivery) to usual care (expectant management) will be 1:1. Randomisation will be managed via a secure web-based randomisation facility hosted by MedSciNet with a 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 or twin pregnancies, severity of hypertension in the 48 h prior to enrolment (highest systolic blood pressure with or without medication: ≤149 mmHg, 150–159 mmHg, ≥160 mmHg), parity (delivery of a baby past 24 weeks' gestation), previous caesarean sections and gestational age at randomisation (34, 35 or 36 weeks). MedSciNet will write the randomisation program and hold the allocation code. Following randomisation, the obstetrician will then arrange for delivery or ongoing expectant management as indicated by the randomisation.

Masking

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

Data collection

Data collection before postnatal 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 study. Women will be asked to complete the EQ-5D-5 L [10] questionnaire at the time of randomisation, which usually takes fewer than 5 minutes.

Data collection after discharge

Questionnaires will be sent to all participants at 6 months post-delivery and 2 years of age corrected for prematurity. The 6-month and 2-year questionnaires will collect the following data: EQ-5D-5 L [10], SF-12v2® [15] and maternal and infant health and social care use after their hospital discharge. In addition, the PARCA-R questionnaire [7] will be collected at 2 years.

Data processing

All hospital trial data will be collected using bespoke electronic case report forms and entered directly into the study's electronic database by the centre's research staff. Data will be stored by single-entry only and at the point of entry, the data will undergo a number of validation checks to verify the validity and completeness. An additional sign-off of the maternal outcomes data will be performed by the site's principal investigator for each participant. Follow-up questionnaires returned by post or completed by the mother on-line will also undergo a number of validation checks at the point of entry.

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 serious adverse events (SAEs). The DMC will, if appropriate, make recommendations to the Trial Steering Committee (TSC) regarding continuance of the study or modification of the study protocol.

Adverse events

An adverse event is any untoward medical occurrence in a participant. It 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.

Serious adverse events

An SAE is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires participant hospitalisation or prolongation of existing hospitalisation
- results in persistent or a significant disability or incapacity
- is a congenital anomaly or birth defect
- is an important medical event

Expected SAEs

Expected SAEs are those events that are expected in the patient population or as a result of the routine care or 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 or 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 or infarction
- severe breathing difficulty
- pulmonary oedema
- sepsis
- admission to hospital for pre-eclampsia (if managed as an outpatient)

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.

Unexpected SAEs

An unexpected SAE is any event that meets the definition of an 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

Safety reporting procedures

SAE recording

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

Unexpected SAE reporting

Only unexpected SAEs will be reported. These will be followed up until the 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 Clinical Trials Unit of the National Perinatal Epidemiology Unit (NPEU) within 24 h of research staff at the site becoming aware of the event. An SAE occurring to a participant will be reported to the REC, which gave a favourable opinion of the study, if, in the opinion of the chief investigator, the event was related (resulted from the administration of any of the research procedures) and unexpected in relation to those procedures. Reports of related and unexpected SAEs will be submitted within 15 working days of the chief investigator becoming aware of the event, using the Health Research Authority's form for reporting an SAE. All reported SAEs will be regularly reviewed by the DMC throughout the study. The chief investigator will inform all investigators concerned of relevant information that could adversely affect the safety of participants.

Direct access to source data and documents

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

Statistical analysis

The primary analysis for all maternal outcomes will be by intention to treat with participants analysed in the groups to which they are assigned regardless of protocol non-compliance. The primary analyses for all perinatal and infant outcomes will be by intention to treat and per protocol, since the hypothesis under examination for these outcomes is a non-inferiority hypothesis. The intention-to-treat analysis will include data from all women who discontinue the intervention for any reason and data from all women who withdraw, up to the point of their withdrawal (after which no further data will be collected). The per-protocol analysis will exclude babies of women who do not receive the allocated intervention as per protocol. Non-inferiority will be concluded if the results from both populations are consistent with each other. If women in the expectant management arm are delivered prior to 37 weeks' gestation due to clinical need (i.e. with new indications for delivery by NICE guidelines [11, 12]), this will not be considered a protocol deviation. A sensitivity analysis will also be carried out excluding babies of women randomised to the planned delivery arm where initiation of delivery is more than 96 h post-randomisation. This is to allow for clinical (e.g. steroid administration) and logistical (e.g. availability of labour ward bed or neonatal unit cot) delays.

All outcomes will be analysed adjusting for minimisation factors (as listed above) at randomisation [16] where possible. Binary outcomes will be analysed using log binomial regression models. If the model does not converge, log Poisson regression models with robust variance estimation will be used [17]. Results will be presented as adjusted risk ratios with associated CIs. The site will be treated as a random effect in the model, and all other factors as fixed effects. For continuous outcomes, differences in means and associated CIs will be estimated using linear regression models assuming the residuals are normally distributed. Should this assumption be considered unmet, quantile regression methods will be used. For all primary outcomes, 95% CIs will be presented. For the analysis of perinatal outcomes, the adjusted analysis will also account for the correlation of outcomes in twins included in the trial by treating these as random effects in the model.

The frequency and content of any interim analyses, including any stopping guidelines, will be determined by an independent DMC and documented in the DMC's charter.

Further details of the short-term outcomes can be found in the statistical analysis plan (Additional file 3). A statistical analysis plan for the 2-year follow-up analysis is currently in development.

The loss to long-term follow-up is expected to be around 20% to 30% and to be associated with poor

outcomes and lower socioeconomic status. 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.

Economic evaluation

An economic evaluation from the perspective of the National Health Service (NHS) and personal social services 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, which capture health and social care resource use for mother and child in the previous 6 months. Health and social care services will be costed using national published sources (NHS reference costs and Unit Costs of Health and Social Care, Personal Social Services Research Unit, British National Formulary). QALYs for the mother will be calculated from EQ-5D-5 L [10] utility scores collected at baseline, 6 months and 2 years and the SF-12v2® [15] questionnaire also at 6 months and 2 years. Differences in infant mortality between the two groups will be captured by assuming full health up to 2 years for surviving infants. The final results of the economic evaluation analyses will be expressed as the mean incremental cost per mean QALY gained from baseline until the 2-year follow-up. Costs and QALYs in the second year will be discounted in line with NICE guidance [18]. As the analysis will be undertaken after the 2-year follow-up, a full health economic analysis plan, linking with the 2-year statistical analysis plan, is currently in development.

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. For regulatory purposes, the end of the study is defined as the date when the study database is locked. An end of study declaration will be made to the approving REC within 3 months of this date.

Early cessation

Based on interim data on the trial's outcomes, adverse event data, accumulating evidence from other trials and any 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. This will apply if any part of the protocol under investigation is either clearly indicated or contra-indicated, either for all infants or for a particular subgroup of trial participants. 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.

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) and the General Data Protection Regulation. Data entered onto electronic case report forms will be automatically transferred for storage in an electronic database held by MedSciNet on behalf of the sponsors. Participants 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 on behalf of the sponsors. The databases will be linked only by the participant's study number. This identifiable information will be collected and retained with the participant's explicit consent to enable follow-ups to be undertaken. After the 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 is restricted to a few named individuals. Authorisation to access restricted areas of the NPEU Clinical Trials Unit network is as described in the unit's security policy. Data will be processed on a workstation by authorised staff. All paper documents will be stored securely and kept in strict confidence in compliance with the Data Protection Act (1998) and the General Data Protection Regulation and all trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006. Due to the nature of pregnancy research, data will be kept for a period of no fewer than 25 years to allow follow-ups on health-related issues that may become relevant. All personal data will be held securely at all times and will not be used for any other purpose.

The dataset will be available to appropriate academic parties on request from the chief investigator in accordance with the data-sharing policies of King's College London and the NPEU Clinical Trials Unit, with input from the co-investigator group where applicable.

Retention of personal data

Personal data will be used to contact the participant, to thank them for participating in the study, to facilitate the follow-ups at 6 months and 2 years of age, to co-ordinate the follow-ups and to disseminate the results of the study to participants.

Data security

An IT security risk assessment of MedSciNet will be undertaken by the sponsor. Prior to recruitment commencing, data-sharing agreements will be produced to ensure that all study data are captured and stored as per the sponsor's security policy and in compliance with all UK data storage requirements. A similar risk assessment and data-sharing agreement will also be produced to ensure EQ-5D-5 L data captured via the EuroQol website are captured, stored and transferred to the MedSciNet database as per the sponsor's security policy.

Quality control and assurance

Site initiation and training

The site principal investigator and a local research midwife or nurse, 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 site research team will also promote the trial so that the necessary recruitment targets are reached within the timescale and they will encourage recruitment in their centre.

Site monitoring and auditing

The site research team will be responsible for the day-to-day smooth running of the trial at a recruiting site. The Clinical Trials Unit will monitor recruitment against targets, provide staff education and training, and monitor the completeness and quality of collected data. The study monitor will perform regular visits to all recruiting centres and will verify the source data for selected participants during these visits.

Throughout the trial, there will be central monitoring, overseen by the Project Management Group, DMC, TSC and Quality Assurance team to ensure there is good communication between the NPEU trial team and site staff. Trial monitoring will be conducted in accordance with the monitoring plan developed from the trial-specific risk assessment. The monitor will visit sites where anomalies are identified through central monitoring. Sites that are identified as requiring additional support will be visited by a member of the trial team or the monitor as appropriate to the particular issues.

The DMC will look regularly at protocol adherence by site and by trial arm, including randomisation processes and patterns of allocation.

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 study and will be updated as required.

Communication

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

Study website

The PHOENIX study website will provide information on the study to recruiting centres, participants and their families. Copies of all electronic case report forms, 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 page for participants will also have links to other websites that offer advice and support to people affected by pre-eclampsia.

Discussion

Current practice in the UK at the time of trial commencement for management of pre-eclampsia varies by gestation. Previous trials have shown that if delivery is initiated after 37 weeks of gestation for women with pre-eclampsia, maternal complications are reduced without increasing fetal risks. Prior to 34 weeks of gestation, usual management is to aim to prolong pregnancy for fetal benefit, unless severe complications occur that necessitate a preterm delivery. This trial aims to address the uncertainty in the balance of benefits and risks of an earlier delivery compared to expectant management. Previous trials in this area have been undertaken, but have not provided a definitive answer, and the research question remains active. The results of this trial are highly likely to influence clinical practice internationally, through a direct impact and through impacting guidelines in countries with similar settings.

Trial status

The current PHOENIX protocol is version 3.1 (5 January 2018). The trial opened to recruitment on 29 September 2014. The first participant was recruited on 29 September 2014. All 46 sites (40 NHS Trusts) were opened by 23 January 2018. Recruitment ended on 10 December 2018. Follow-up in progress until last woman and

infant have been discharged from hospital for short-term outcomes and to 2 years post-delivery for long-term outcomes (Additional file 4).

Additional files

Additional file 1: Participant information leaflet. (PDF 1587 kb)
Additional file 2: Consent form. (PDF 238 kb)
Additional file 3: Statistical analysis plan. (DOCX 187 kb)
Additional file 4: SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents. (DOC 121 kb)

Abbreviations

APEC: Action on pre-eclampsia; CI: Confidence interval; DMC: Data monitoring committee; NHS: National health service; NICE: National Institute for Health and Care Excellence; NPEU: National perinatal epidemiology unit; PARCA-R: Parent report of cognitive abilities, revised; QALY: Quality-adjusted life year; REC: Research ethics committee; SAE: Serious adverse event; TSC: Trial steering committee

Acknowledgements

We thank Catherine Rounding for her help in formatting the protocol manuscript.

Funding

The study is funded by the Health Technology Assessment programme (project reference 12/25/03) of the National Institute for Health Research. The views expressed are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care.

Availability of data and materials

Primary responsibility for preparing publications will lie with the chief investigator, Professor Lucy Chappell, who will liaise with the NPEU Clinical Trials Unit to deliver effective dissemination. All publications using data from this trial for original analyses will be submitted to the TSC for review before release. The research will be published in high-impact peer-reviewed scientific journals. There are no commercial or intellectual rights issues that would delay publication of results. The writing will be the responsibility of a writing committee drawn from the co-investigators (trial grant holders), trial co-ordinators and others substantially involved in execution, analysis and interpretation. The committee 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). No external professional writers will be used. Local principal investigators will be named formally as collaborators on the publication. Other trial personnel with significant input to the running of the trial will be named in the acknowledgements section of published research. The chief investigator will nominate and agree appropriate authorship on all publications prior to commencement of writing. Participants will be sent a summary of trial publications if they wish, with a reference to the final paper. A copy of the journal article will be made available to them on request from the chief investigator. Information will be made available on the trial website, including the final report and any publications when available.
To target the clinical community, the results of this research will be disseminated at conventional academic platforms, including presentations at prominent national and international conferences. The results will be available for inclusion in the relevant Cochrane review and in national and international guidelines. Requests for the final dataset can be made through the chief investigator in accordance with the data-sharing policies of King's College London and the NPEU Clinical Trials Unit, with input from the co-investigator group where applicable.

Declaration of Helsinki and guidelines for good clinical practice

Investigators will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (October 2008). The conduct of this study will be in full compliance with the relevant regulations and Good Clinical Practice.

Oversight committees

Project Management Group

The study will be supervised on a day-to-day basis by the Project Management Group. This group reports to the TSC and will meet at least monthly.
Members from King's College London:

- Lucy Chappell, National Institute for Health Research Professor in Obstetrics
- Andrew Shennan, Professor of Obstetrics

Members from NPEU Clinical Trials Unit, University of Oxford, Oxford:

- Edmund Juszczak, Director
- Ursula Bowler, Senior Trials Manager

Also from NPEU Clinical Trials Unit:

- senior statistician
- trial statistician
- quality assurance manager
- trial manager
- trial administrative assistant/data co-ordinator
- trial midwife co-ordinators

Co-Investigators Group

- Professor Lucy Chappell, National Institute for Health Research Professor in Obstetrics, King's College London
- Professor Andrew Shennan, Professor of Obstetrics, King's College London
- Professor Peter Brocklehurst, Professor of Women's Health, Director of the Institute for Women's Health Institute for Women's Health, University College London
- Professor Zarko Alfirevic, Professor of Fetal and Maternal Medicine, Liverpool Women's Hospital
- Professor Stephen Robson, Professor of Fetal Medicine, Newcastle University
- Professor Neil Marlow, Professor of Neonatology Institute for Women's Health, University College London
- Associate Professor Edmund Juszczak, Director, NPEU Clinical Trials Unit, University of Oxford
- Professor Jane Sandall, Professor of Social Science and Women's Health, King's College London
- Ursula Bowler, Senior Trials Manager, NPEU Clinical Trials Unit, University of Oxford
- Rachael Hunter, Senior Research Associate, Royal Free Medical School, London
- Pollyanna Hardy, Senior Statistician, NPEU Clinical Trials Unit, University of Oxford
- Marcus Green, Representative of Action on Pre-eclampsia (APEC)

Trial Steering Committee

The trial will be overseen by a TSC consisting of an independent chair and at least two other independent members who will meet at least annually.
Independent members:

- Professor Jane Norman (Chair), Professor of Maternal and Fetal Health, University of Edinburgh
- Professor Simon Gates, Professor of Clinical Trials, Warwick Clinical Trials Unit, University of Warwick
- Dr Alison Leaf, Consultant Neonatologist, University Hospital Southampton NHS Foundation Trust
- Jacqui Williams, APEC Representative
- Professor Stavros Petrou, Professor of Health Economics, Warwick Clinical Trials Unit, University of Warwick
- Katie Lean, Quality Improvement Midwife, Oxford University Hospitals NHS Trust

Non-independent members:

- Professor Lucy Chappell, National Institute for Health Research Professor in Obstetrics, King's College London

- Professor Andrew Shennan, Professor of Obstetrics, King's College London
- Associate Professor Edmund Juszczak, Director, NPEU Clinical Trials Unit, University of Oxford

Data Monitoring Committee

The DMC, which is 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 and to the funder. A charter has been completed following the recommendations of the DAMOCLES Study [19]. The committee will periodically review trial progress and outcomes and will look regularly at protocol adherence by site and by trial arm, including randomisation processes and patterns of allocation.

- Professor Diana Elbourne (Chair), Professor of Healthcare Evaluation, London School of Hygiene & Tropical Medicine
- Dr Jon Dorling, Clinical Associate Professor, University of Nottingham, and Honorary Consultant Neonatologist, Nottingham University Hospitals, NHS Health
- Professor Phillip Bennett, Professor of Obstetrics and Gynaecology, Imperial College, Hammersmith Hospital, London

Adjudication Panel

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

Sponsors

The lead sponsor is King's College London, Strand, London WC2R 2LS. The co-sponsor is Guy's and St Thomas' NHS Foundation Trust, Great Maze Pond, London SE1 9RT

The study sponsor and funders have had no input into study design; collection, management, analysis and interpretation of data; writing of the report; or the decision to submit the report for publication (beyond usual governance activities) and will not have any such input in the future.

The sponsors of the study have a specialist insurance policy that 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 any clinical treatment provided.

Authors' contributions

The protocol was drafted by LC. MG, NM, JS, RH, SR, UB, VC, PH, EJ, LL, AP, PB and AS provided comments on the initial draft and on subsequent revisions. All authors have seen and approved the final version.

Ethics approval and consent to participate

The study will start only after gaining approval from an NHS-registered REC. Additionally, approval of the appropriate trust research and development office will be sought for individual trial sites. The chief investigator or their delegate will submit and, where necessary, obtain approval from the REC and the appropriate trust research and development offices for any substantial amendments. All protocol modifications will be communicated promptly to sites once approved by the sponsor and the REC. Written informed consent will be obtained by the principal investigator or another study doctor with delegated authority.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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Received: 24 September 2018 Accepted: 18 December 2018
Published online: 28 January 2019

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Supplementary Material

Click here to download Supplementary Material: PHOENIX collaborators 2019_08_06.docx