Understanding the optimal timing of delivery in late preterm pre-eclampsia to reduce adverse pregnancy outcomes in low and middle income countries

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Acknowledgements

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Prof Andrew Shennan exemplifies what it means to be a mentor, and an ally. I don't think there are many Professors who would agree to take an 18-hour night train across India to reach a trial site, but this typifies his sense of adventure; always fun, and always up for a new challenge. Despite his monumental contributions to his field, he is always humble, always curious, and personifies kind, and compassionate leadership. I cannot thank him enough, not just for providing me with the opportunity of a lifetime, but for making the journey so much fun, and for his constant encouragement, and support.

Prof Lucy Chappell is a stellar role model. She uses her incredible intellect and ability to make a tangible difference to the lives of others. Although she excels in both academia and policy-making, watching her interact with women in clinic, it is easy to see her warmth and humanity shining through. She embodies what it means to provide woman-centred care, and she works tirelessly to promote the visibility of those women around her. I will not forget her whirlwind 48 hour tour of the Copperbelt in Zambia, just one example of her commitment, and willingness to make time for others. I am so grateful for everything that she has taught me.

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For all the women, and their babies, who participated in the CRADLE-4 Trial

and

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Abstract

Background

Pre-eclampsia is a progressive and unpredictable complication of pregnancy and is a leading cause of maternal and perinatal death globally. The majority of these deaths occur in low and lower-middle income countries, particularly countries in Sub-Saharan Africa and South Asia. Delivery of the fetus and placenta is currently the only curative treatment option for pre-eclampsia. The timing of delivery must be carefully balanced in order to optimise both maternal and perinatal outcomes. Too early, and complications associated with early preterm birth may lead to adverse neonatal outcomes. Too late, and the disease may progress, causing serious complications such as maternal death, stroke, eclampsia, placental abruption, fetal growth restriction, and stillbirth. Accurately detecting pre-eclampsia and predicting the onset of complications is challenging, particularly in settings where resources are limited. There is a lack of evidence to guide clinicians regarding the optimal time of delivery for late preterm pre-eclampsia (between 34^{+0} and 36^{+6} weeks' gestation), and an urgent need to evaluate interventions in regions where the main disease burden lies, rather than high income countries where fatal and serious outcomes are rare.

Methods

In this thesis, I evaluate the impact of planned delivery for pre-eclampsia between 34^{+0} and 36^{+6} weeks' gestation on pregnancy outcomes in a low and lower-middle income setting. Prior to this, I conducted a systematic review and individual participant data meta-analysis of the current available evidence on planned delivery for late preterm pre-eclampsia, and evaluated the longer-term infant outcomes from a trial in the UK comparing planned delivery to expectant management for late preterm pre-eclampsia. I assessed the feasibility of conducting a timing of delivery trial across sites in India and Zambia, via a mixed-methods feasibility and acceptability study, and explored the language barriers to informed consent in Zambia via a qualitative study. I designed a protocol for a randomised controlled trial (CRADLE-4), comparing planned delivery to expectant management, in women

with pre-eclampsia without severe features between 34^{+0} and 36^{+6} weeks' gestation, across nine sites in India and Zambia. I coordinated the interventional phase of this trial between December 2019 and March 2022. The primary maternal outcome was a composite of maternal mortality or morbidity with a superiority hypothesis. The primary perinatal outcome was a composite of one or more of: stillbirth, neonatal death, or neonatal unit admission of more than 48 hours, with a non-inferiority hypothesis (margin of 10% difference). I analysed maternal and perinatal short-term clinical outcomes between the two management groups, by intention to treat, with an additional per-protocol analysis for the perinatal outcome.

Results

The systematic review identified six randomised controlled trials, all conducted in high income countries. These were included in the individual participant data meta-analysis which demonstrated that, in high income settings, planned delivery from 34 weeks onwards, for pre-eclampsia without severe features, significantly reduces the risk of a composite maternal outcome of maternal morbidity or mortality. Planned delivery was also found to reduce the risk of an infant being born small for gestational age. However, short-term perinatal respiratory morbidity was increased by planned delivery. Two-year follow-up of infants in the largest timing of delivery trial to date (901 women across 46 maternity units in England and Wales) found a small difference in neurodevelopmental scores between the two management groups; however, the average score for infants in both groups was within the normal range.

As part of the CRADLE-4 feasibility study, I explored the disease burden associated with pre-eclampsia across four proposed trial sites in India and Zambia, alongside current management of pre-eclampsia and the acceptability of late preterm delivery to women, their families, and healthcare providers. The high prevalence of pre-eclampsia related complications observed in these settings established a need to evaluate the proposed intervention (planned delivery). I identified several barriers and facilitators to implementing the interventional phase of the trial which

informed design of the main trial protocol. The CRADLE-4 Trial enrolled 565 women with late preterm pre-eclampsia across nine sites in India and Zambia. 284 women were allocated to planned delivery and 281 women were allocated to expectant management. Planned delivery was associated with a non-significant reduction in the composite maternal outcome (adjusted risk ratio 0·91, 95% CI 0·79 to 1·05). In the planned delivery group, the incidence of the primary perinatal outcome was 58 (19%) compared to 67 (22%) in the expectant management group. The adjusted risk difference for non-inferiority was -3·39% (90% CI -8·67 to +1·90; p=<0·0001 [non-inferiority]). I was therefore able to demonstrate non-inferiority of planned delivery compared to expectant management. Planned delivery was associated with a significant reduction in severe maternal hypertension (aRR 0.83, 95% CI 0.70 to 0.99) and stillbirth (aRR 0.25, 95% CI 0.07 to 0.87).

Conclusion

This thesis provides new evidence to demonstrate that planned delivery for late preterm pre-eclampsia, at sites in India and Zambia, is safe, and reduces the risk of stillbirth by 75%. Although planned delivery was not associated with a statistically significant reduction in the composite outcome of maternal mortality or morbidity, individual components were all in the direction favouring planned delivery, and a significant reduction in the incidence of severe maternal hypertension was observed. This is consistent with the synthesis of evidence from trials conducted in high income countries, which demonstrated clear maternal benefit associated with planned delivery. The pragmatic trial design, preceded by a thorough assessment of the context and community, means that the findings are likely to be generalisable to other similar settings. However, the impact of planned delivery in a broader range of settings, including more rural areas, will be important to understand prior to implementation on a wide scale. The insights gained during the feasibility and acceptability study highlight the need for continued community engagement, in order to improve awareness and understanding around pre-eclampsia and address the wider social determinants of maternal and infant health. Overall, these findings demonstrate that planned delivery for pre-eclampsia from 34 weeks onwards is an intervention that has the potential to substantially reduce perinatal mortality and

maternal morbidity, in the regions of the world where improvements in maternal and infant health are most urgently required.

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List of abbreviations

IPD: Individual participant data

NICE: National Institute for Health and Care Excellence

ISSHP: International Society for the Study of Hypertension in Pregnancy

ACOG: American College of Obstetricians and Gynecologists

WHO: World Health Organization

UK: United Kingdom

LIC: Low income country

LMIC: Lower-middle income country

ALT: Alanine transaminase

AST: Aspartate aminotransferase

PLGF: Placental growth factor

PREP: Prediction of complications in early-onset pre-eclampsia

fullPIERS/miniPIERS: Pre-eclampsia integrated estimate of risk

CAB: Community advisory board

DMC: Data monitoring committee

TSC: Trial Steering committee

SAE: Serious adverse event

HIV: Human immunodeficiency virus

AIDS: Acquired immunodeficiency syndrome

PMTCT: Prevention of Mother to Child Transmission

HELLP syndrome: Haemolysis, elevated liver enzymes, and low platelet count syndrome

SGA: Small for gestational age

REDCap: Research Electronic Data Capture Tools

CRF: Case report form

IEC: Information, Education, Communication

Statement of own contribution

In Chapter 3, I present the results of an IPD (individual participant data) meta-analysis. I conceived of the IPD meta-analysis alongside Lucy Chappell, Henk Groen and Andrew Shennan, and wrote the study protocol with their support. I performed the systematic literature review, with Jessica Fleminger as the second review author. I led analysis of the individual participant dataset, supported by a statistician (Paul Seed). I wrote the published paper, revising the manuscript in response to feedback from co-authors, editors, and reviewers.

In Chapter 4, I present the two-year follow-up of infants in the PHOENIX Trial. I joined the project management group of this multi-centre, randomised controlled trial in December 2020, contributing to interpretation of the statistical analysis of the long-term outcomes, which was performed by the trial statistician, Melanie Greenland. I wrote the published paper, as joint first author with Melanie Greenland, revising the manuscript in response to feedback from co-authors, editors, and reviewers.

Chapters 5 to 8 of this thesis are based around a Medical Research Council funded project entitled "CRADLE-4: Can Reduction of Adverse pregnancy outcomes occur with planned delivery vs. expectant management in pre-eclampsia?" I joined the CRADLE-4 Trial in October 2018 shortly after funding was awarded. I was responsible for undertaking all research management from this point onwards, including achieving ethics approval in the UK, India and Zambia for both phases (Appendix 10).

In Chapter 5, I designed the study protocol for the CRADLE-4 feasibility and acceptability study, including the focus group and interview topic guides, the case notes audit tool, and the REDCap database for data collection. I coordinated this six-month study, conducting stakeholder interviews and facilitating focus group discussions alongside four Zambian research assistants (Mercy Kopeka, Josephine

Miti, Christine Jere, Chipo Kanyika). I undertook the qualitative and quantitative analysis of this study, and wrote the published paper, revising the manuscript in response to feedback from co-authors, editors, and reviewers.

In Chapter 6, I secured seed funding for the Lost in Translation study and designed the study protocol. I facilitated the Lost in Translation Phase 1 workshop, performed the content analysis of recruitment materials and conducted the key informant interviews. I facilitated the focus group discussions alongside three Zambian translators (Abel Banda, Gilbert Mwila, Zwangendaba Jere). I undertook the qualitative analysis of this study and wrote the submitted manuscript, revising it in response to feedback from co-authors, editors, and reviewers.

In Chapter 7, I designed the main CRADLE-4 Trial protocol, using my findings from the CRADLE-4 feasibility study to adapt the initial outline protocol. This included designing the participant information materials and consent forms, designing the MedSciNet database, and defining primary and secondary outcome measures. The trial statistician (Paul Seed) wrote the statistical analysis plan, which is presented in the Appendix. I wrote the published trial protocol, revising the manuscript in response to feedback from co-authors, editors, and reviewers.

I coordinated the interventional phase of the CRADLE-4 Trial which included training research assistants, setting up trial sites, coordinating data collection, regular site visits, cross-checking all data for quality and completeness, monitoring trial progress and recruitment, organising monthly project management group meetings and reporting annually to the trial steering committee and data monitoring committee. I designed the monthly site resources audit and coordinated data collection for this, in addition to the women's experiences questionnaire, which I designed. I drafted the CRADLE-4 manuscript tables, cleaned the dataset and analysed the data with the trial statistician (Paul Seed). I wrote the published results paper presented in Chapter 8, revising the manuscript in response to feedback from co-authors, editors, and reviewers. I secured uplift funding to aid dissemination of the trial

findings and co-facilitated the policy lab on 14th February 2023 alongside Chileshe Mabula-Bwalya.

Publications and presentations arising from this work

Papers published

Beardmore-Gray, A., Vousden, N., Seed, P. T., Vwalika, B., Chinkoyo, S., Sichone, V., Kawimbe, A. B., Charantimath, U., Katageri, G., Bellad, M. B., Lokare, L., Donimath, K., Bidri, S., Goudar, S., Sandall, J., Chappell, L. C., Shennan, A. H. (2023). Planned delivery or expectant management for late preterm pre-eclampsia in low-income and middle-income countries (CRADLE-4): a multicentre, open-label, randomised controlled trial. *The Lancet*, *402*(10399), 386-396. https://doi.org/10.1016/S0140-6736(23)00688-8

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Contributions to other relevant published work

Hunter, R., Beardmore-Gray, A., Greenland, M., Linsell, L., Juszczak, E., Hardy, P., Placzek, A., Shennan, A., Marlow, N., Chappell, L. C., & Group, P. S. (2022). Cost-Utility Analysis of Planned Early Delivery or Expectant Management for Late Preterm Pre-eclampsia (PHOENIX). *Pharmacoecon Open*, *6*(5), 723-733. https://doi.org/10.1007/s41669-022-00355-1

Hurrell, A., Beardmore-Gray, A., Duhig, K., Webster, L., Chappell, L., & Shennan, A. (2020). Placental growth factor in suspected preterm pre-eclampsia: a review of the evidence and practicalities of implementation. *BJOG: An International Journal of Obstetrics & Gynaecology*, *127*(13), 1590-1597. https://doi.org/https://doi.org/10.1111/1471-0528.16425

Academic Presentations and Awards

Oral presentations

RCOG Annual academic meeting: Can planned delivery for late preterm pre-eclampsia reduce adverse pregnancy outcomes compared to expectant management in two low and lower-middle income settings? London, UK, February 2023. (First author, presented by departmental colleague due to a pre-existing commitment)

British Maternal and Fetal Medicine Society Annual Conference: Can planned delivery for late preterm pre-eclampsia reduce adverse pregnancy outcomes compared to expectant management in two low and lower-middle income settings? Birmingham, UK, November 2022. (Presenting author)

British Association of Perinatal Medicine Annual Conference: Two-year follow-up of maternal and infant outcomes after planned early delivery or expectant management for late preterm pre-eclampsia (PHOENIX): a randomised controlled trial. Virtual, October 2021. (Presenting author)

International Society for the Study of Hypertension in Pregnancy 22nd World Congress: Two-year infant and maternal outcomes after planned delivery or expectant management for late preterm pre-eclampsia (PHOENIX): a randomised controlled trial. Virtual, September 2021. (Presenting author) **Awarded Young Investigator Award**.

FIGO Africa Regional Kigali Congress: CRADLE-4 Phase 1: The feasibility and acceptability of planned early delivery in pre-eclampsia in a Low and Middle-Income Setting. Virtual, December 2020. (Presenting author)

International Society for the Study of Hypertension in Pregnancy European Conference: The acceptability of planned early delivery in pre-eclampsia to women and their families in India and Zambia. Lund, Sweden, October 2019. (Presenting author)

Neonatal Society Jubilee Meeting: Can Planned early delivery between 34 and 36^{+6} weeks' gestation improve perinatal outcomes for women with pre-eclampsia in low and middle-income countries. Cambridge, UK, June 2019. (Presenting author)

Poster presentations

International Society for the Study of Hypertension in Pregnancy 22nd World Congress: Planned early delivery or expectant management for the prevention of adverse pregnancy outcomes in pre-eclampsia (PHOEBUS): a meta-analysis of individual participant data from randomised controlled trials. Poster presentation, September 2021.

RCOG Annual Academic Meeting: Planned early delivery for late preterm pre-eclampsia in a low and middle-income setting: a feasibility study. Poster presentation, February 2021. **Awarded Best Poster Pitch Presentation (Global Health)**

Chapter 1 Introduction

1.1. The global burden of pre-eclampsia

1.1.1. Maternal mortality

Every day, it is estimated that 800 women die from preventable causes related to pregnancy and childbirth.(World Health Organization, 2023) Whilst disparities in care exist everywhere, almost all of these deaths (95%) occur in low and lower-middle income countries.(World Health Organization, 2023) Women living in Sub-Saharan Africa and South Asia face a disproportionately high risk of dying, with these regions accounting for approximately 87% of the estimated global maternal deaths in 2020.(World Health Organization, 2023) Hypertensive disorders including pre-eclampsia account for 14% of all maternal deaths worldwide, second only to haemorrhage as the leading direct cause of mortality.(Say et al., 2014) This contribution is even greater (16% of all maternal deaths) in Sub-Saharan Africa.(Say et al., 2014) If we are to meet the Sustainable Development Goal target 3.1 of reducing the global maternal mortality ratio to less than 70 per 100,000 live births by 2030, we must focus on interventions that address the major causes of maternal death in regions where they are most needed.

1.1.2. Neonatal mortality and stillbirth

A similar trend is seen for perinatal mortality; Sub-Saharan Africa has the highest neonatal mortality rate in the world (27 deaths per 1,000 livebirths), followed by Central and Southern Asia (23 deaths per 1,000 livebirths).(World Health Organization, 2022a) Preterm birth and intrapartum complications (such as birth asphyxia) are the leading cause of most neonatal deaths, and could be prevented by better access to good quality care immediately before, during, and after birth.(World Health Organization, 2022a)

Figure 1-1 highlights the discrepancy in global stillbirth rates, with an estimated three quarters of the 2.6 million annual stillbirths occurring in Sub-Saharan Africa or Southern Asia. However, inconsistences in reporting of stillbirths and difficulties in

collecting timely and accurate data (more than 40% of low and lower-middle income countries do not produce usable stillbirth data) make it difficult to compare or monitor trends.(Hug, 2020)

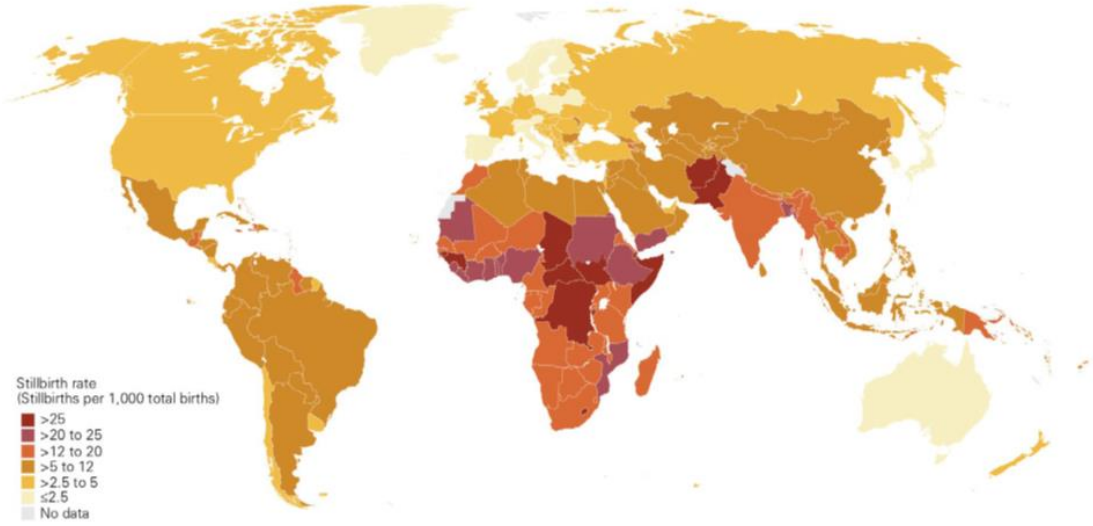


Figure 1-1 Stillbirth rate by country, 2019 (United Nations Inter-agency Group for Child Mortality Estimation (UN IGME). 2020)

1.1.3. Epidemiology

Pre-eclampsia complicates around 3-5% of pregnancies.(Chappell et al., 2021) This figure is based on a systematic review which reported on the incidence of hypertensive disorders of pregnancy during the period 2002-2010.(Abalos et al., 2013) Whilst it remains the most comprehensive and accurate study to date, representing nearly 39 million women from 40 countries, there was a wide variation noted across regions and a notable lack of data from the majority of countries in Africa, as shown in Figure 1-2.

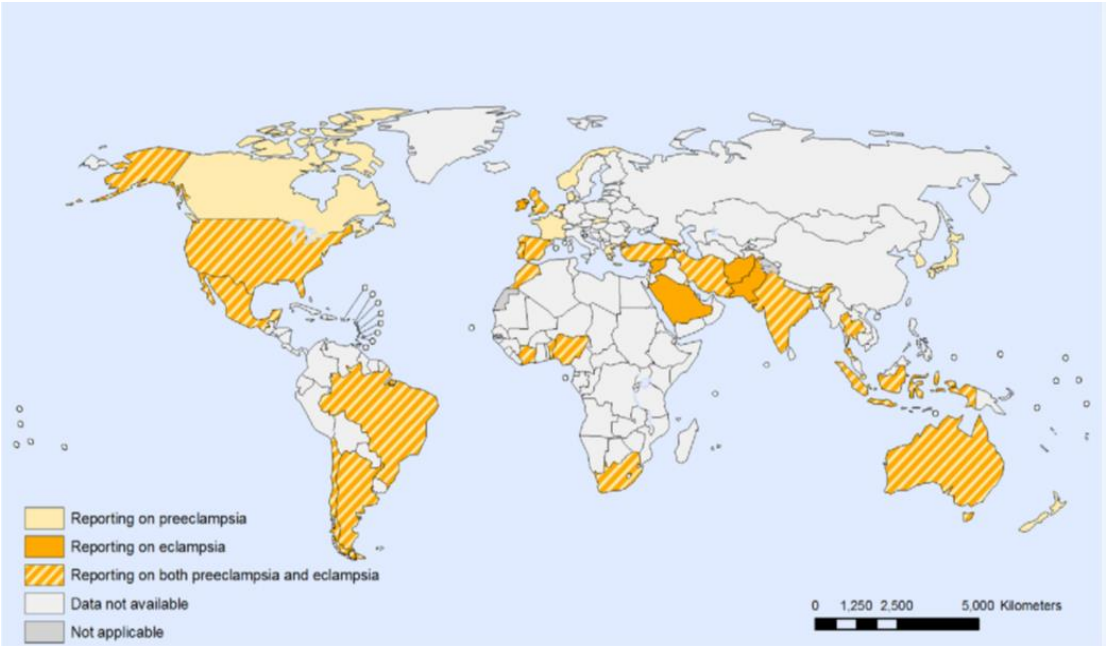


Figure 1-2 Countries reporting on pre-eclampsia/eclampsia, 2002-2010 (Abalos et al., 2013)

Furthermore, national data on pre-eclampsia and/or eclampsia were available from only seven countries, none in Sub-Saharan Africa or South Asia.(Abalos et al., 2013) This bias in regional representation, with 94.6% of the women included in this review being from the USA, makes it difficult to ascertain a true global estimate of the incidence of pre-eclampsia. Estimates for the incidence of pre-eclampsia ranged from 1.0% in the Eastern Mediterranean region to 5.6% in the African region (data available from four countries), with the crude incidence of eclampsia estimated to be 2.9% in the African region. The scarcity of data and underreporting in this region means the true incidence may be much higher. This was highlighted by a recent systematic review and meta-analysis of 82 studies across 24 African countries which estimated the prevalence of hypertensive disorders of pregnancy in Africa to be approximately 10.0%, with pre-eclampsia reported as the most common type (5.3%).(Noubiap et al., 2019)

Estimating the number of maternal deaths attributable to pre-eclampsia presents a similar challenge. Globally, pre-eclampsia is estimated to cause at least 42,000 maternal deaths (Chappell et al., 2021) and 500,000 perinatal deaths, including approximately 200,000 stillbirths,(Lawn et al., 2016) every year. However, in

countries where deaths related to pre-eclampsia are highest, and thus accurate data are most needed, they are often not available. For example, in the latest World Health Organization (WHO) systematic analysis of global causes of maternal death conducted by Say and colleagues, the authors note that of the ten countries with the highest maternal mortality ratio in 2010, data were available for only one.(Say et al., 2014) Relevant to the context of this thesis, India was categorised as one of the countries where vital registration data were available but not considered good quality, and Zambia was categorised as a country with no data available. Well-functioning civil registration and vital statistics systems are dependent upon countries having the appropriate legislation in place, the resources to implement it, and effective coordination between multiple different organisations.(AbouZahr et al., 2015) Furthermore, they require engagement from individuals, families, civil servants, and healthcare professionals. It is well acknowledged that in under-funded and over-stretched healthcare systems accurate birth and death registration is a challenge, particularly collecting accurate data on cause of death, with maternal death no exception. This has been attributed to delayed and complex presentations to healthcare facilities, women dying outside a healthcare facility or upon arrival, poor documentation, and a lack of time or training.(Aukes et al., 2021; Vousden et al., 2020) Good quality population-level data are critical to improving health outcomes and therefore the limited data available on maternal deaths in the countries where they are highest creates an additional barrier to addressing the underlying causes.(Phillips et al., 2015)

1.2. Clinical features of pre-eclampsia

1.2.1. Diagnosis

Pre-eclampsia is broadly defined as new onset hypertension after 20 weeks' gestation with evidence of one or more of proteinuria, maternal organ dysfunction, or uteroplacental dysfunction. Superimposed pre-eclampsia may present as worsening hypertension or deteriorating renal function in women with pre-existing disease. Hypertension is defined as a systolic blood pressure of 140mmHg or greater, and/or a diastolic blood pressure of 90mmHg and above. Significant

proteinuria may be defined as urine dipstick proteinuria of 1+ and above, a spot urinary protein: creatinine ratio of 30mg/mmol or greater, or a 24 hour urinary protein of 300mg or more. Different guidelines include varying definitions of maternal organ dysfunction, for example, ACOG (American College of Obstetricians and Gynecologists) guidelines recommend different thresholds to diagnose renal and liver involvement compared to NICE (National Institute for Health and Care Excellence) and ISSHP (International Society for the Study of Hypertension in Pregnancy) guidelines, and do not include fetal growth restriction as part of their diagnostic criteria.(Brown et al., 2018; National Institute for Health and Care Excellence, 2019; The American College of Obstetricians and Gynecologists, 2020) These differences have been summarised in a recently published seminar on pre-eclampsia.(Chappell et al., 2021) The most recent ISSHP guidelines state that proteinuria is not a prerequisite for the diagnosis of pre-eclampsia, if other clinical features (such as maternal biochemical abnormalities or fetal growth restriction) of the disease are present.(Brown et al., 2018) However, in low-resource settings the availability of laboratory facilities (Wilson et al., 2018) and obstetric ultrasound (Kim et al., 2018; Papageorghiou et al., 2016) is limited, therefore diagnosis of pre-eclampsia relies predominantly upon blood pressure measurement, dipstick urinalysis, and maternal symptoms. Even these assessments may not always be performed, highlighted by a comparison of antenatal care coverage across 91 low and middle income countries, which found that nearly a third of women did not have their blood pressure checked or their urine tested at any point during their pregnancy.(Arsenault et al., 2018) A comparison of the diagnostic capabilities according to ISSHP criteria between high income and low income settings is shown in Table 1-1.

Table 1-1 Comparison of diagnostic capabilities (√ indicates typically capable to detect, ~ indicates reduced capability to detect)

ISSHP Diagnostic criteria	**High income setting**	**Low income setting**	**Comment**
Gestational hypertension (persistent de novo hypertension that develops at or after 20 weeks' gestation defined as systolic BP ≥ 140mmHg and/or diastolic BP ≥ 90 mmHg on repeated readings taken over a few hours	√	√	BP monitors available but in limited supply in many low income settings (Leslie et al., 2017)
And one or more of:			
1. Proteinuria	√	√	Whilst quantitative assessment of proteinuria is the gold standard in high income settings, visual dipstick urinalysis is used throughout low income settings. Reagent strips are often out of stock (Leslie et al., 2017) and reserved only for those women found to be hypertensive
2. Other maternal organ dysfunction, including:			
Acute kidney injury (creatinine ≥ 90 µmol/L; 1mg/dL)	√	~	Lack of laboratory reagents limit ability to detect this
Liver involvement (elevated transaminases e.g. ALT or AST >40 IU/L) with or without right upper quadrant or epigastric abdominal pain	√	~	Lack of laboratory reagents limit ability to detect this
Neurological complications (such as eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, persistent visual scotomata)	√	√	Diagnosis predominantly based on clinical symptoms and signs
Haematological complications (thrombocytopenia – platelet count below 150, 000/µL, Disseminated intravascular coagulation, haemolysis)	√	~	Lack of laboratory reagents limit ability to detect this
3. Uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery Doppler wave form analysis, or stillbirth)	√	~	Limited access to obstetric ultrasound makes this difficult to detect

1.2.2. Pathophysiology

The clinical signs and symptoms of pre-eclampsia are manifestations of a common pathway, underpinned by uteroplacental malperfusion, with growing recognition that this represents a syndrome comprising multiple phenotypes rather than a distinct disease.(Myatt, 2022; Myatt & Roberts, 2015) Uteroplacental malperfusion leads to stressed syncytiotrophoblast tissue in the placenta, which then triggers maternal endothelial dysfunction and systemic vascular inflammation. This is commonly viewed as a two stage process, whereby stage one involves the initial development of a deficient placenta, leading to the second stage of diffuse maternal endothelial dysfunction and organ involvement. These stages may take place over the course of several months, in the case of early-onset pre-eclampsia, or several weeks in the case of late-onset pre-eclampsia. Uteroplacental malperfusion may occur due to abnormal placentation, or due to an inability of the placenta to meet the demands of pregnancy.(Burton et al., 2019) Different causal pathways are implicated, influenced by maternal genetics, comorbidities, and fetal factors such as multiple pregnancy. Figure 1-3 outlines the two stage model of pre-eclampsia, highlighting the different phenotypes associated with early-onset and late-onset placental dysfunction. Different theories regarding the underlying cause of placental dysfunction persist, with some placing greater emphasis on suboptimal maternal cardiovascular performance as the primary driver of placental malperfusion,(Melchiorre et al., 2022) whereas others focus more on immunological factors leading to inadequate remodelling of the uterine spiral arteries by fetal trophoblast tissue, creating resistance to placental blood flow.

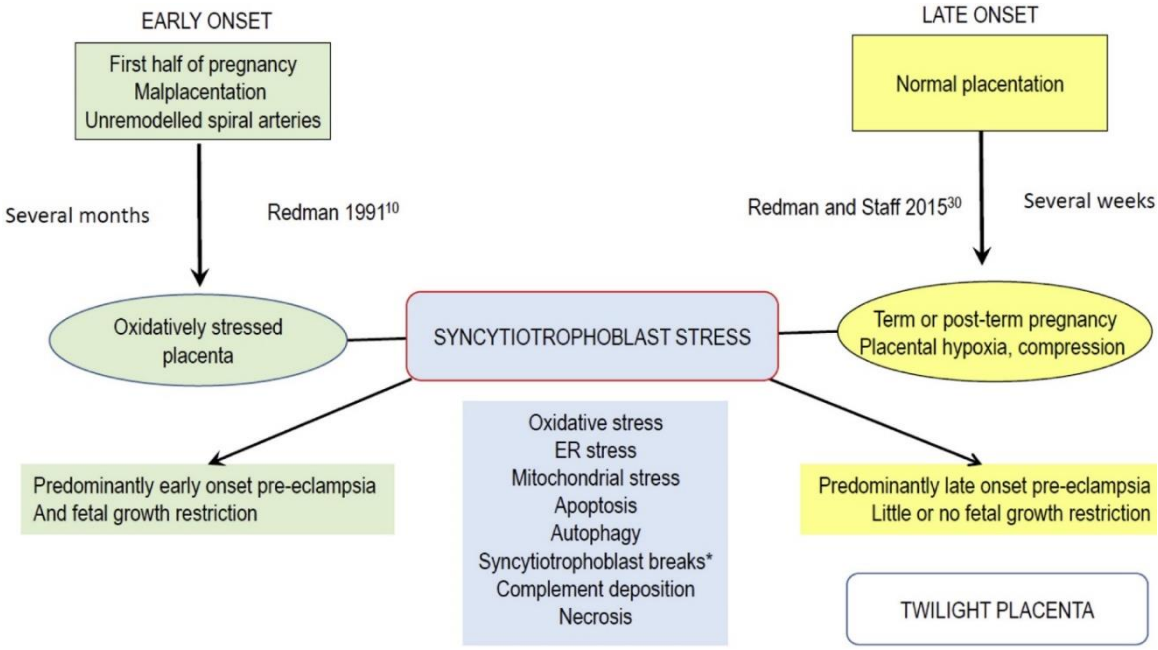


Figure 1-3 Two stage model of pre-eclampsia - early and late placental dysfunction (Redman et al., 2022)

The factors which predispose to this defective placentation are complex, and not fully understood. Epidemiological evidence supports a genetic component, with a family history of pre-eclampsia and Black ethnicity both recognised as risk factors for developing the disease.(Ayorinde & Bhattacharya, 2017; Roberts & Cooper, 2001; Urquia et al., 2014) When discussing the increased frequency of pre-eclampsia observed in Black women, it is important to distinguish between ethnicity/race, which is a social construct influenced by socio-economic and political factors, and ancestry, which more accurately describes genetic origin.(Borrell et al., 2021) However, African women and women with African ancestry have a higher incidence of pre-eclampsia compared to women with European ancestry, which cannot be explained by socio-economic or environmental factors alone.(Nakimuli et al., 2014) Efforts to identify specific susceptibility genes via genome-wide association studies have identified variants in the fetal genome near the FLT1 gene (which codes sFlt-1) associated with pre-eclampsia, however these are based on European populations, and therefore limited by the exclusion of women with African ancestry.(McGinnis et al., 2017; Osafo et al., 2022) Apolipoprotein L1, known to be associated with chronic kidney disease,(Rosset et al., 2011) and to

provide innate immunity against African sleeping sickness,(Pays & Vanhollebeke, 2009) may be associated with pre-eclampsia and is currently being investigated further as part of a case-control study in Ghana.(Osafo et al., 2022) The interaction between maternal natural killer (NK) cells and fetal HLA-C molecules has also been identified as an important influence on the function of invading trophoblast cells, and therefore placental development. Maternal NK cells use killer-cell immunoglobulin-like receptor (KIR) to recognise the fetal HLA-C molecules, with certain combinations protecting against pre-eclampsia and others increasing the risk of deficient placentation and therefore the development of pre-eclampsia, illustrated by Figure 1-4.

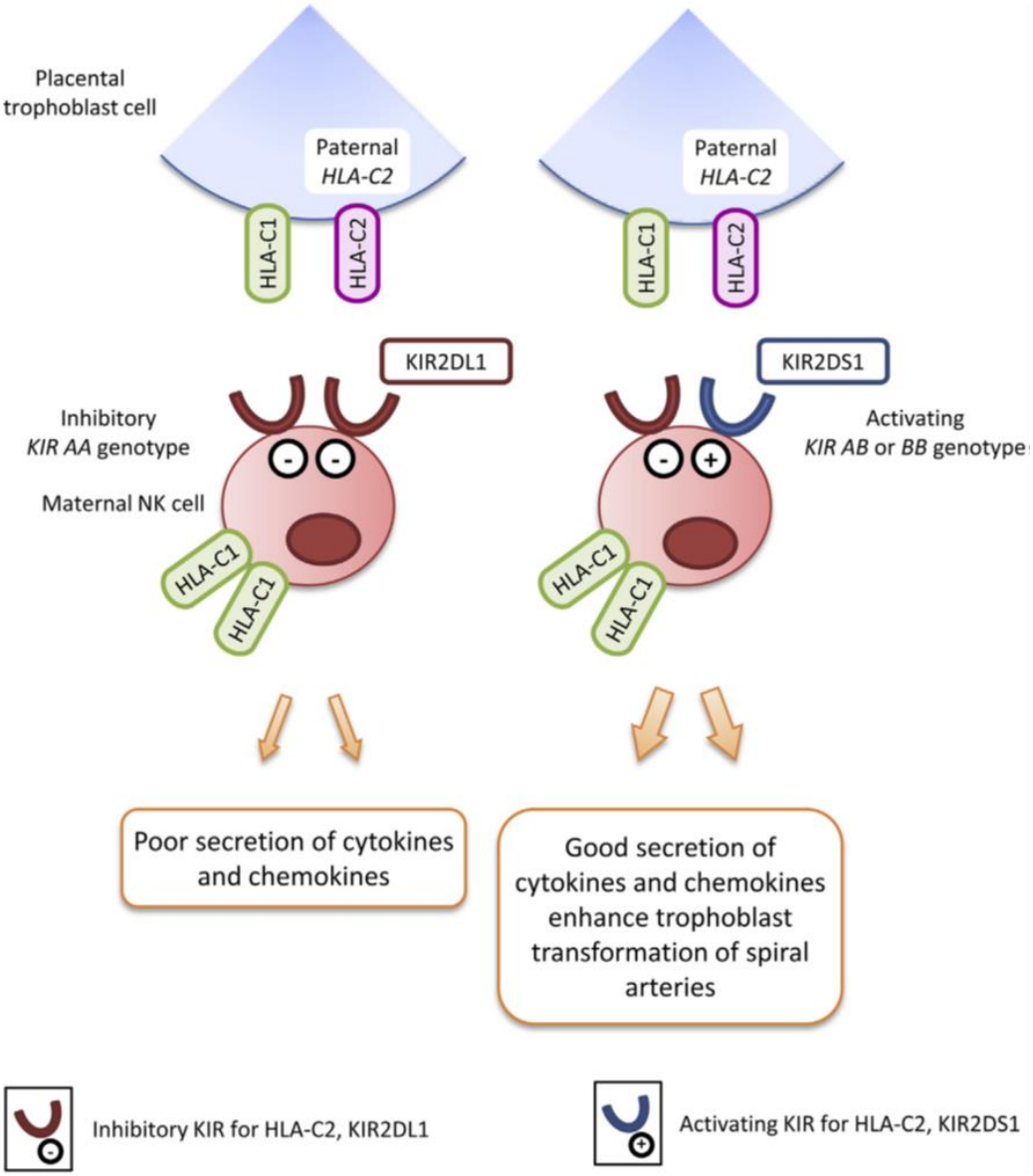


Figure 1-4 Maternal KIR/fetal HLA-C interactions at the site of placentation (Nakimuli et al., 2014)

Nakimuli and colleagues have shown that the combination of a maternal KIR AA genotype with a fetal HLA-C2 allele is associated with an increased risk of pre-eclampsia.(Nakimuli et al., 2015) Based on a case-control study at a tertiary hospital in Uganda, the authors of this study report that the probability of a Ugandan women having a fetus carrying a C2 variant is 55% compared with 40% for a European woman (UK population). The most frequent maternal KIR genotype in this Ugandan population, was found to be KIR AA.(Nakimuli et al., 2013) Although larger studies are needed to confirm these findings, it is possible that an increased

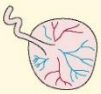
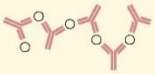
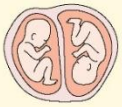
frequency of fetal HLA-C2 alleles and maternal KIR AA genotypes in African populations may contribute to the higher incidence of pre-eclampsia seen in Sub-Saharan Africa. It has been hypothesised that the increased frequency of this more inhibitory combination of maternal NK cells and fetal HLA alleles, which confers an advantage over certain pathogens, but is disadvantageous for placentation, may be due to competing evolutionary pressures, requiring human populations to balance the need for successful reproduction, against the need for survival against infectious diseases.(Hirayasu et al., 2012; Penman et al., 2016) These findings highlight the importance of studying the pre-eclampsia syndrome in the populations most affected. By conducting clinical research and establishing biobanks such as the PROVE and PREPARE initiatives (Bergman et al., 2021; De Oliveira et al., 2018) in low and middle income countries, we can gain vital insights into the underlying causes and risk factors for the disease, which may ultimately lead to advances in prediction and prevention of pre-eclampsia.

In addition to the genetic predisposition to pre-eclampsia seen in African populations, the burden of non-communicable diseases in Sub-Saharan African and South Asia is growing, particularly in countries that have moved through the epidemiological transition. Women with comorbidities such as obesity, diabetes, cardiovascular disease, and chronic hypertension are more likely to have pre-existing endothelial dysfunction and are therefore at higher risk of developing pre-eclampsia. The rising prevalence of these conditions is therefore likely to increase the burden of pre-eclampsia related morbidity and mortality in low and lower-middle income countries, particularly when a lack of resources means management of such chronic conditions may not be optimal at the start of pregnancy.(Souza et al., 2014; Vos et al., 2020)

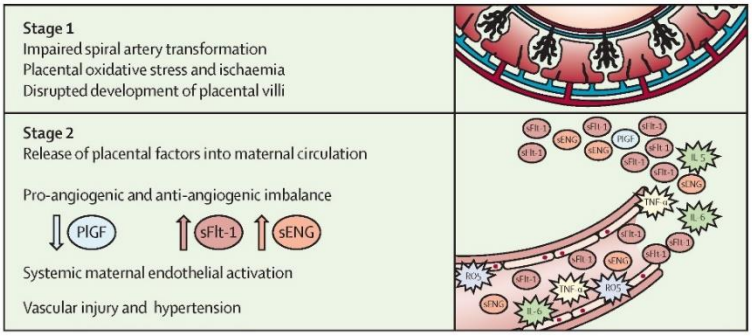
1.2.3. Complications

Pre-eclampsia may result in serious complications for the women and infant, as outlined in Figure 1-5.

Risk factors

Genetic predisposition	Maternal characteristics (eg, age, body-mass index)	Comorbidities (eg, hypertension, diabetes)	Placental disease	Immune factors	Multifetal pregnancy
					

Pathophysiology



Multiorgan dysfunction

		Symptoms	Signs	Investigations	Complications
	Neurological	Headache and visual disturbances	Brisk reflexes and clonus	..	Eclampsia, posterior reversible encephalopathy syndrome, and intracranial haemorrhage
	Renal	..	..	Proteinuria and raised serum creatinine	Acute kidney injury
	Hepatological	Epigastric pain	Right upper quadrant tenderness	Elevated serum liver enzymes	Hepatic haematoma or rupture
	Haematological	..	Dark brown urine and petechiae	Low platelets, abnormal clotting tests, and haemolysis	Coagulopathy
	Uteroplacental and fetal	Vaginal bleeding and reduced fetal movements	Hard uterus and reduced fundal height	Fetal growth restriction	Placental abruption and intrauterine fetal death
	Cardiorespiratory	Breathlessness, chest pain, and confusion	Tachypnoea	Decreased oxygen saturation and diastolic dysfunction	Pulmonary oedema

Figure 1-5 Complications of pre-eclampsia (Chappell et al., 2021)

1.2.4. Short-term maternal outcomes

The short-term maternal outcomes related to the pre-eclampsia syndrome may involve multiple organ systems. Severe hypertension (systolic blood pressure ≥ 160mmHg) in itself is a serious complication associated with adverse maternal outcomes and should be avoided.(Magee et al., 2016) If untreated, it may progress to stroke and eclampsia as well as other rarer but serious cerebral complications such as retinal detachment, reversible ischaemic neurological deficit (RIND) and posterior reversible encephalopathy syndrome (PRES). Myocardial ischaemia and pulmonary oedema may develop, as well as renal and hepatic dysfunction. Placental abruption can also occur, leading to maternal haemorrhage and fetal hypoxia.

Associated with these complications is the risk of prolonged hospitalisation, separation of mother and infant, and the need for emergency caesarean section, which carries with it a 50-fold increase in the risk of death for women in African countries compared to women in high income countries,(Bishop et al., 2019) and may impact negatively upon women's psychological well-being.(Porter et al., 2007)

1.2.5. Long-term maternal outcomes

Whilst many of the acute clinical complications will resolve following timely delivery, women with a history of pre-eclampsia are known to be at increased risk of developing chronic conditions such as diabetes,(Engeland et al., 2011; Feig et al., 2013) chronic renal disease,(Kristensen et al., 2019) and cardiovascular disease.(Wu et al., 2017) The association between pre-eclampsia and cardiovascular disease is now recognised in the American Heart Association and the European Society of Cardiology guidelines for the prevention of cardiovascular disease in women.(Bushnell et al., 2014; Mosca et al., 2011; Visseren et al., 2021) Recently, a large UK population-based cohort study of 1.3 million women has demonstrated that women who had one or more pregnancies affected by pre-eclampsia were four times more likely to develop chronic hypertension and twice as likely to suffer a stroke or die from cardiovascular causes compared to women without hypertension in pregnancy, with differences in the cumulative incidence of cardiovascular outcomes evident as early as one year postpartum.(Leon et al., 2019) A recently published Danish cohort study showed similar findings,(Hallum et al., 2023) highlighting that women with pre-eclampsia aged 30-39 years had a five-fold and three-fold risk of acute myocardial infarction and stroke respectively, compared to women of a similar age without pre-eclampsia. The causal pathways contributing to this are a topic of ongoing research and likely multifactorial but may represent a direct effect of pre-eclampsia on the maternal vasculature, or an unmasking of a pre-existing disposition. Proactive management and timely delivery are therefore key, not just in preventing acute complications, but potentially in reducing the risk of cardiovascular disease, and other chronic conditions, in the long-term. This is especially pertinent in low and middle income countries, which account for 86% of the premature deaths due to non-communicable disease worldwide.(World Health

Organization, 2020) The majority of these deaths are preventable, if appropriate screening and treatment are in place.(Pickersgill et al., 2022; World Health Organization, 2020) However, almost half of people living with hypertension, two-thirds of whom live in low and middle income countries, are unaware they have it.(World Health Organization, 2022b) Identifying women with pre-eclampsia in these settings offers an important opportunity to target interventions to improve long-term health, which in turn benefits other key development indicators including education, economic participation, and gender equality.

1.2.6. Short-term perinatal outcomes

The adverse perinatal outcomes associated with pre-eclampsia are wide-ranging but can be broadly conceptualised as those related to the direct effects of the syndrome itself, such as fetal growth restriction, chronic hypoxia, and antepartum stillbirth, those related to preterm delivery such as respiratory distress syndrome, and those related to progression of maternal disease, such as placental abruption or eclampsia resulting in acute hypoxic injury to the fetus. There is a considerable degree of overlap, with infants that are born growth restricted at higher risk of neonatal morbidity associated with preterm birth. These risks are further compounded in settings where obstetric ultrasound is limited (making it difficult to identify fetal compromise in utero), fetal monitoring during labour is extremely difficult (due to equipment and staff constraints, with a high patient to provider ratio), and specialised neonatal care is scarce. Adverse neonatal conditions, which include birth asphyxia and birth trauma, neonatal sepsis, and preterm birth complications, remain one of the top three causes of death globally.(World Health Organization, 2020) Optimising the clinical management of women with pre-eclampsia, in order to reduce perinatal complications, is therefore key in improving neonatal outcomes, and reducing deaths overall.

1.2.7. Long-term infant outcomes

Pre-eclampsia may influence long-term infant outcomes in several different ways. Neurodevelopmental outcomes are affected by preterm birth, and fetal growth restriction. Whilst late preterm birth may be associated with an increased risk of

neurodevelopmental delay, the studies which describe this typically compare these infants with healthy controls born at term, and therefore do not accurately describe the trade off in outcomes relevant to pre-eclampsia, where the alternative to preterm delivery may be worsening growth restriction or stillbirth.(Johnson et al., 2015; Murray et al., 2017) Moreover, other factors such as parents' level of education, home environment, and socioeconomic status are likely to have a more important effect over time than gestational age at birth alone.(Zwertbroek et al., 2020) The difficulty in delineating long-term infant outcomes related to pre-eclampsia is partly due to a lack of evidence, given the logistical and financial challenges associated with long-term follow-up of research participants and their infants over a prolonged period of time. The PHOENIX Trial is the largest trial to date, in a high income setting, evaluating planned delivery or expectant management for late preterm pre-eclampsia.(Chappell, Brocklehurst, et al., 2019) In Chapter 4 of this thesis, the two-year follow-up of infant outcomes from this trial are presented. The clinical interpretation of these findings is challenging and limited by the relatively short follow-up time and loss to follow-up. In low and lower-middle income countries, there may be additional logistical barriers to overcome, such as limited postal services and frequent changes of mobile network provider, that may hinder long-term retention and follow-up of research participants. In countries such as India and Zambia, the prevalence of severe malnutrition and communicable diseases such as malaria is high.(The World Bank, 2022) These additional confounding factors may further influence childhood development,(Fink et al., 2013; Kihara et al., 2006) making it even more difficult to establish the specific impact of pre-eclampsia and preterm birth on long-term infant outcomes in these settings.

1.2.8. Prediction and prevention

The clinical course of pre-eclampsia is difficult to predict, and the development of symptoms is usually an indicator of end-stage organ damage. Most screening methods rely upon identifying maternal risk factors at the initiation of antenatal care. This enables closer monitoring and surveillance to be put in place, as well as aspirin therapy, which has been shown to reduce the relative risk of developing pre-

eclampsia by 17%, in addition to reductions in the risk of preterm birth (9%) and fetal or neonatal death (14%).(Duley et al., 2019) This is challenging in a low-resource setting, where women often do not present for antenatal care until the pregnancy is showing, at around 20 weeks' gestation. This may be due to a perceived lack of value of antenatal care, late diagnosis of pregnancy due to irregular periods, financial or logistical barriers in accessing care, or cultural preferences around declaring pregnancy.(Brighton et al., 2013) In a high income setting, placental growth factor (PLGF) based testing has been recommended as a tool to help rule in or out the diagnosis of pre-eclampsia in women with suspected disease, but not to guide decision-making on timing of delivery once pre-eclampsia has been confirmed.(Chappell et al., 2013; Duhig et al., 2019; National Institute for Health and Care Excellence, 2022) In women with confirmed pre-eclampsia, it is difficult to identify which women will go on to develop severe manifestations of the disease or which infants are at high risk of compromise, and would therefore benefit most from early obstetric intervention. Recent research has focused on the development of clinical predictive models, such as fullPIERS and PREP, which use clinical variables to predict the likelihood of a composite severe maternal outcome and may be helpful in this scenario, but trials evaluating the impact of their implementation on clinical outcomes have yet to be conducted.(Thangaratinam et al., 2017; von Dadelszen et al., 2011)

1.2.9. Management

Given the challenges described above, the mainstay of pre-eclampsia management at present still relies on early identification of the condition via routine antenatal care, with increased monitoring if the pre-eclampsia syndrome is diagnosed. UK NICE (National Institute for Health and Care Excellence) guidelines recommend that women should have their blood pressure measured and their urine checked for proteinuria at each antenatal visit,(National Institute for Health and Care Excellence, 2021) and the WHO currently recommends a minimum of eight antenatal contacts throughout pregnancy.(World Health Organization, 2016) However, this is difficult to achieve in many low and lower-middle income countries, due to multiple factors which include staff shortages, difficulty in

accessing healthcare facilities, community perceptions of antenatal care, and financial barriers.(Arsenault et al., 2018) Delayed initiation of antenatal care makes it difficult to implement preventative strategies at an optimal time and makes it difficult to accurately date the pregnancy. Uncertainty around gestational age subsequently impacts upon clinicians' ability to detect fetal growth restriction and make decisions around timing of delivery.(Papageorghiou et al., 2016)

If a woman is diagnosed with suspected pre-eclampsia (typically through detection of hypertension and dipstick proteinuria), this should prompt referral to a secondary or tertiary level healthcare facility for further management. Close monitoring is recommended including regular blood pressure surveillance (every four hours if admitted to hospital), blood testing (at least twice weekly), and assessment of fetal well-being.(Brown et al., 2018) This may include admission to hospital, where appropriate clinical management can also be implemented. This usually comprises antihypertensive medication to control blood pressure, magnesium sulfate to reduce the risk of eclampsia (and for fetal neuroprotection if delivery is planned before 32 weeks), and antenatal corticosteroids if iatrogenic preterm delivery is planned before 34 weeks.

Whilst antihypertensive medications are critical in stabilising blood pressure, they do not alter disease progression. Magnesium sulfate is recognised by the WHO and United Nations to be a priority drug, and more than halves the risk of eclampsia. However, a large Cochrane review including 15 trials was not able to show any significant difference in maternal mortality, serious maternal morbidity, stillbirth, or neonatal death associated with magnesium sulfate use compared to placebo or other anti-convulsant.(Duley et al., 2010) The MAGPIE trial, which was the largest trial in this review, enrolled 10,141 women, 85% of whom were living in low or middle income countries. The relatively small number of eclampsia cases (136) and maternal deaths (31) illustrates the challenge of demonstrating a reduction in rare, but serious, clinical outcomes.(Altman et al., 2002) Medications already used in pregnancy for other indications, including esomeprazole and metformin, have been

identified as potential disease modifying agents for pre-eclampsia,(Cluver et al., 2018) and a single centre randomised controlled trial recently demonstrated that extended release metformin can prolong gestation in women with preterm pre-eclampsia.(Cluver et al., 2021) However, larger trials are needed to replicate these findings, and delivery therefore currently remains the only definitive treatment option for pre-eclampsia, and the only intervention proven to reduce the risk of severe maternal morbidity.(Cluver et al., 2017) Indications for delivery will vary depending on gestational age. Typically, severe maternal symptoms, uncontrollable blood pressure despite maximal antihypertensive therapy, worsening renal or hepatic dysfunction, or evidence of fetal compromise may prompt intervention.

1.2.10. Factors influencing pre-eclampsia outcomes in a low-resource setting

When trying to explain the high proportion of adverse pregnancy outcomes related to pre-eclampsia in low and lower-middle income countries, there are multiple underlying factors to be explored. These exist at the level of government, the healthcare system, the local community, and the individual woman and her family, and are outlined in the following framework (Figure 1-6).

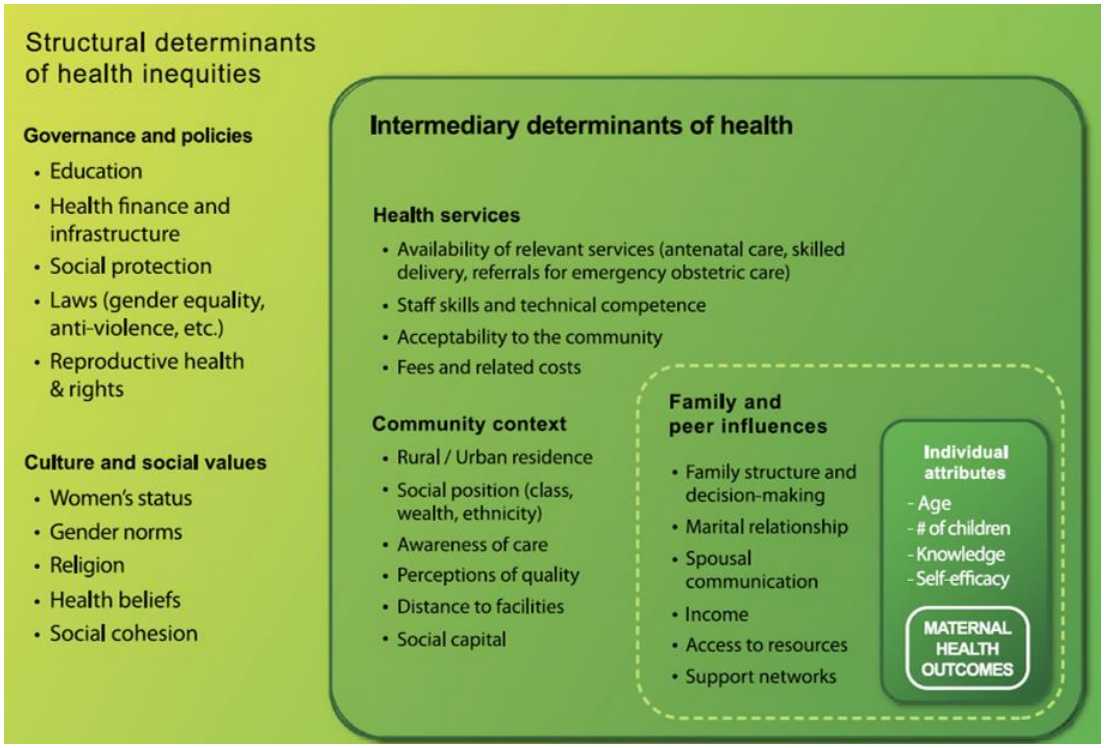


Figure 1-6 Structural determinants of health inequities (Jones et al., 2022)

Social and economic determinants of health are also key to understanding the wider context of maternity care. Factors such as age, the presence of any medical co-morbidities, nutritional status, and home environment may influence a woman's baseline health status at the start of pregnancy. Educational attainment and financial resources may impact upon a woman's decision to seek pregnancy care, and her role and position within the community in which she lives may affect her ability to make autonomous decisions relating to household spending and healthcare. Once the decision to seek care has been made, access to care may be dependent upon a number of individual, local, and systemic factors. For example, personal financial resources may limit the ability to reach care. The local infrastructure, such as geographical terrain and road quality, may make it difficult for a woman to reach a healthcare facility. Health system inadequacies may lead to poor referral systems (such as lack of transport, lack of staffing, and inability to recognise complications requiring higher level care) meaning that women are not able to access the right care, at the right time, in the right place.(Miller et al., 2016) Even once these barriers in accessing care have been removed, there remains huge variability in the quality of care that is provided.(Arsenault et al., 2018) Staffing, availability of equipment, essential drugs and blood products, the provision of specialist care (including surgical care), and appropriate knowledge and skills all impact the quality of maternity care provided and thus pregnancy outcomes. Respectful maternity care is integral to every aspect of this process, and a woman's experiences of healthcare facilities and how she was treated by healthcare professionals may in turn affect her decision to seek care in subsequent pregnancies. Differing interpretations and perceived causes of pregnancy complications, particularly pre-eclampsia and eclampsia, may also influence where and when women choose to seek care. For example, raised blood pressure has been shown to be attributed to psychosocial distress and dietary factors across a range of cultures and countries, with eclampsia often linked to spiritual manifestations.(Robbins et al., 2021) As a result, women may choose to seek care from alternative sources such as traditional healers or religious leaders, with or without input from healthcare professionals. Addressing these complex issues

requires interventions that have been designed with a low-resource environment in mind, with robust community engagement and thorough evaluation, before they can be successfully implemented on a large scale and in a sustainable manner.

1.3. Timing of delivery in pre-eclampsia

1.3.1. Risks and benefits

As outlined above (section 1.2.9 Management), delivery is currently the only curative treatment for pre-eclampsia. Deciding when to initiate delivery requires careful balancing of the risks and benefits for the woman and her infant. Before 34 weeks' gestation, the risks associated with early preterm delivery justify a policy of expectant management, continuing the pregnancy unless severe features of pre-eclampsia develop, which would necessitate emergency delivery at any stage of pregnancy.(Churchill et al., 2018) At 37 weeks' gestation, the WHO recommend initiating delivery for all women with pre-eclampsia, irrespective of severity, based on evidence demonstrating clear maternal benefit with no additional risk for the infant.(Cluver et al., 2017; Koopmans et al., 2009) At late preterm gestations, between 34 and 37 weeks, the balance of risks and benefits is less clear. Planned delivery at this stage may result in increased rates of respiratory distress syndrome in the neonate, or an increased risk of neurodevelopmental delay in the infant. However, continuing the pregnancy may increase the risk of both maternal and perinatal complications associated with disease progression, such as eclampsia, placental abruption, worsening fetal growth restriction and stillbirth, with these adverse outcomes also associated with neurodevelopmental delay. Figure 1-7 illustrates some of the potential short-term perinatal complications associated with either management strategy, both of which may lead to long-term neurological sequelae.

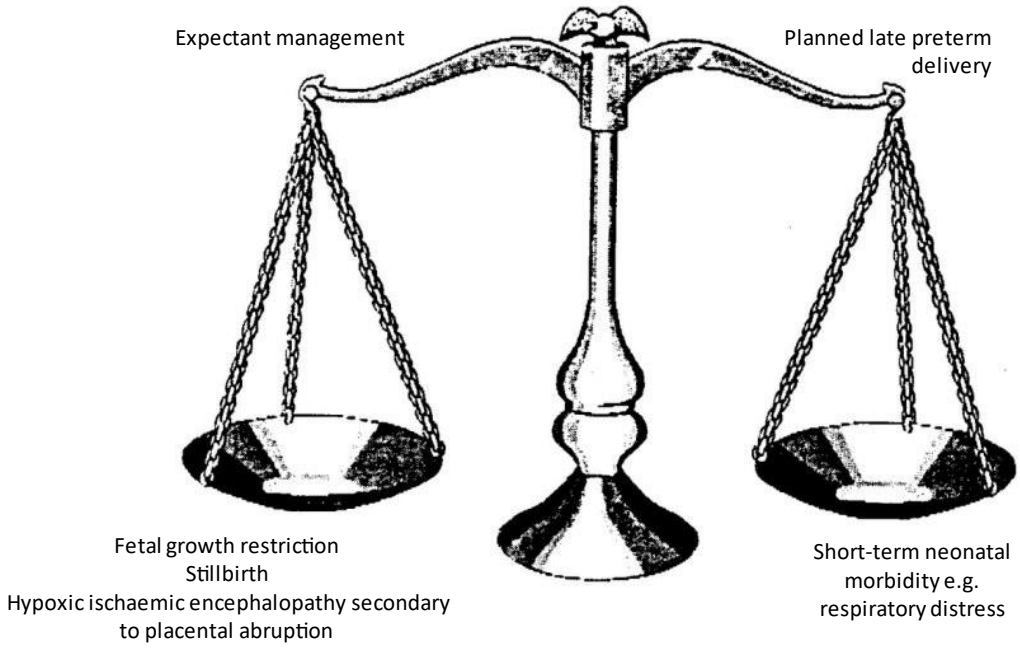


Figure 1-7 Potential short-term perinatal complications associated with expectant management versus late preterm delivery

1.3.2. Current evidence

Six trials in high income settings have evaluated the optimal timing of delivery for women with late preterm pre-eclampsia without severe features. The participant-level data from these trials is synthesised and presented in Chapter 3, as an individual participant data meta-analysis. The largest of these trials, the PHOENIX Trial, enrolled 901 women and randomly allocated women with pre-eclampsia between 34^{+0} and 36^{+6} weeks, without severe features, to planned delivery within 48 hours of randomisation or usual care (expectant management).(Chappell, Brocklehurst, et al., 2019) The investigators found a significant reduction in adverse maternal outcomes associated with planned delivery, with an increase in neonatal unit admissions, but no difference in overall indicators of neonatal morbidity between the two management groups. This differs from the findings of the HYPITAT-II trial, which evaluated planned delivery in women with any hypertensive disorder of pregnancy (including gestational hypertension and chronic hypertension) between 34 and 37 weeks.(Broekhuijsen et al., 2015) They found no significant reduction in maternal morbidity but an increase in the primary perinatal

outcome of respiratory distress syndrome. Antenatal corticosteroid use varied widely between these two trials (with greatly increased coverage in the PHOENIX Trial) and may in part explain the difference in findings. The results also highlight the need to consider pre-eclampsia as a distinct and more serious condition, in which earlier intervention is more likely to be beneficial, compared to other hypertensive disorders of pregnancy.(Bernardes et al., 2019)

1.3.3. Implications of late preterm delivery in a low-resource setting

None of the above trials evaluate planned delivery in a low or middle income country. This reflects a wider issue, indicative of a clear mismatch between the regions where clinical research takes place and where the global burden of disease lies. An analysis of all clinical trials registered from 2010 to 2019 found that only 2% of the trials were set in Sub-Saharan African countries.(Park et al., 2021) A further scoping review of maternal health trials conducted in low and middle income countries over the same period, found that only a quarter of these were targeted at a major cause of maternal mortality.(Eggleston et al., 2022) In addition to a lack of clinical research, many of the studies that have been conducted are constrained by limited funding and a lack of research infrastructure resulting in trials that are often inefficient, underpowered, and therefore unable to provide robust evidence informing a substantial change in policy or practice.(Park et al., 2021)

Given the disproportionately high burden of pre-eclampsia related mortality and morbidity in low and middle income countries, in order to improve maternal and perinatal outcomes, interventions must be evaluated in the environments and populations where they can have the greatest impact. Researchers need to focus their efforts on designing large-scale clinical trials that can be delivered efficiently and pragmatically, within the constraints of a lower resource setting. Developing clinical trial protocols that are adapted to suit the local context is extremely important, and implementing interventions developed and tested in high income settings without evaluating the context, can lead to misleading results. This is demonstrated by the ACT trial, which assessed a multi-faceted intervention to increase uptake of antenatal corticosteroids, amongst women at risk of preterm

birth, across six low and middle income countries.(Althabe et al., 2015) Antenatal corticosteroids are acknowledged as one of the most effective hospital-based interventions to reduce neonatal mortality.(McGoldrick et al., 2020) However, this trial found that the intervention was associated with a significant increase in perinatal mortality and suspected maternal infection. This was not because antenatal corticosteroids are necessarily harmful when used correctly, and indeed the recent ACTION trial which evaluated safety and efficacy of antenatal corticosteroids in five low-resource countries was stopped for benefit at the second interim analysis.(WHO ACTION Trials Collaborators et al., 2020) However, the initial ACT trial failed to take account of multiple barriers to safe and appropriate administration of antenatal corticosteroids, such as accurate gestational age determination, prediction of preterm birth, referral processes, and location of antenatal care (community vs. hospital), as well as other key factors influencing perinatal outcomes such as the availability of good quality neonatal care. This is an important lesson in why interventions developed in high income countries and healthcare systems cannot be assumed to work in the same way in low or middle income countries, and demonstrates the importance of generating robust local evidence, suited to the context.

The balance of risks and benefits of planned delivery for late preterm pre-eclampsia in a low and middle income setting, may be very different compared to a high income setting. The risks of planned delivery may be increased due to limitations on the ability to provide safe intrapartum care, such as a high woman to midwife ratio making it difficult to monitor fetal wellbeing during labour, and a lack of key resources such as ventilators and surfactant, limiting the ability of healthcare facilities to provide neonatal intensive care. However, the risks of expectant management are also likely to be greater as there is limited ability to provide adequate antenatal surveillance in many settings. Overwhelmed antenatal clinics may lack staffing and key resources such as blood pressure monitors and urine dipsticks, potentially delaying diagnosis of pre-eclampsia. Many women will not be admitted to hospital for monitoring even once a diagnosis is made, and this may be

due to limited bed capacity or an unwillingness on the woman's behalf due to financial concerns or family commitments. Lack of resources such as laboratory reagents and obstetric ultrasound means it is difficult to identify women and infants at high risk of complications and stillbirth. Thus, watching and waiting in this scenario risks missing early signs of clinical deterioration and losing the window of opportunity to act. This highlights the need to evaluate planned delivery for women with late preterm pre-eclampsia in low and lower-middle income countries, in order to generate evidence to guide clinical practice in these settings. In Chapters 5 to 7 of this thesis, I focus on how to design and deliver a clinical trial in these settings, assessing the feasibility and acceptability of planned delivery at proposed trial sites in India and Zambia, and describing the development of a clinical trial protocol adapted to suit the local healthcare system and community.

Chapter 6 explores the issues related to translating recruitment materials for informed consent in global health studies, with a particular focus on translating documents that are designed and written in high income, English-speaking countries, into Zambian languages. This highlights some of the ethical and methodological challenges faced when designing clinical trials for low and middle income countries, based upon research principles that are designed in high income countries and often based upon European mindsets and values; there is a clear power imbalance between researchers based in high income countries and their collaborators in low or lower-middle income countries. Much of the funding and technical capacity required for delivering a clinical trial comes from institutions based in high income countries, whereas the research itself, including participant enrolment, takes place in a low or lower-middle income country.(Horton, 2013; Park et al., 2021) In order to address this, collaborators based in these countries should be fully involved and engaged from the very initial stages of trial conception and design, facilitating a genuine process of co-creation that is driven by local needs, not those of the high income partner. Longer-term projects, with appropriate funding to support their duration, should focus on building local

research capacity in order to minimise these inequalities and establish more equal partnerships.

1.4. Rationale and context of trial sites

India and Zambia were selected as host countries for trial sites due to their geographical location (South Asia and Sub-Saharan Africa) and World Bank income classification (low and lower-middle income). Pre-existing research collaborations with healthcare facilities in both these countries demonstrated, during the CRADLE-3 trial, functional healthcare systems that, whilst vulnerable, had sufficient capacity to deliver high quality research programmes with high levels of staff engagement and motivation to optimise care and outcomes.(Vousden et al., 2019)

The tables below outline key indicators which provide a contextual overview of both countries, with the UK listed as a high income comparator.(The World Bank, 2022) Zambia has a total population of 18,383,956 of whom 50.5% are women. Whilst India's total population is significantly higher at 1,380,004,385, similar proportions of the population in both countries are rural (55.4% and 65.1% respectively) with approximately only half the population in both countries having access to universal healthcare (Table 1-2).

Table 1-2 Population indicators (The World Bank, 2022)

Indicator	**Zambia**	**India**	**United Kingdom**
Total population	18, 383, 956 (2020)	1, 380, 004, 385 (2020)	67, 215, 293 (2020)
Current health expenditure (% of GDP)	5.3 (2019)	3.0 (2019)	10.2 (2018)
Population growth (annual %)	2.9 (2020)	1.0 (2020)	0.4 (2020)
Population, female (% of total population)	50.5 (2020)	48.0 (2020)	50.6 (2020)
Urban population (% of total population)	44.6 (2020)	34.9 (2020)	83.9 (2020)
Rural population (% of total population)	55.4 (2020)	65.1 (2020)	16.1 (2020)
Universal healthcare service coverage index*	55.0 (2019)	61.0 (2019)	88.0 (2019)

(Year) indicates most recent data available (up to and including 2020)

*Coverage index for essential health services (based on tracer interventions that include reproductive, maternal, newborn and child health, infectious diseases, noncommunicable diseases and service capacity and access). It is presented on a scale of 0 to 100.

There is a stark disparity in maternal mortality ratio and lifetime risk of maternal death between both countries and the UK, with Zambia having the highest maternal mortality ratio (213 per 100,000 live births) of the three countries presented here (Table 1-3). The figures for infant and neonatal mortality show a similar pattern; the neonatal mortality rate in Zambia is 24.0 per 1,000 births (20.3 per 1,000 births in India) compared to 2.7 in the United Kingdom (Table 1-3). Further indicators allude to some of the wider determinants of such high mortality rates. For example, the proportion of women who were first married by the age of 18 is substantially higher in Zambia (29%) and India (25.3%) compared to the UK (0.1%); however, the proportion of married women with demand for family planning satisfied by modern methods is sub-optimal (68.5% in Zambia, 71.9% in India). Whilst coverage of antenatal care is good (96.9% of women in Zambia receive antenatal care), the proportion of women who receive at least four antenatal visits is substantially lower (63.5% of women in Zambia, 51.2% of women in India).

Table 1-3 Maternal and child health indicators (The World Bank, 2022)

Indicator	**Zambia**	**India**	**United Kingdom**
Maternal mortality ratio (modelled estimate, per 100,000 live births)	213 (2017)	145 (2017)	7 (2017)
Lifetime risk of maternal death (1 in: rate varies by country)	93 (2017)	290 (2017)	8,400 (2017)
Birth rate, crude (per 1,000 people)	35.4 (2020)	17.4 (2020)	10.2 (2020)
Fertility rate, total (births per woman)	4.5 (2020)	2.2 (2020)	1.6 (2020)
Adolescent fertility rate (births per 1,000 women ages 15-19)	114.7 (2020)	9.9 (2020)	11.2 (2020)
Teenage mothers (% of women ages 15-19 who have had children or are currently pregnant)	29.2 (2018)	7.9 (2016)	Data not available
Women who were first married by age 15 (% of women ages 20-24)	5.2 (2018)	5.4 (2016)	Data not available
Women who were first married by age 18 (% of women ages 20-24)	29.0 (2018)	25.3 (2016)	0.1 (2020)
Demand for family planning satisfied by modern methods (% of married women with demand for family planning)	68.5 (2018)	71.9 (2016)	Data not available
Completeness of birth registration (%)	14.0 (2018)	79.7 (2016)	100.0 (2017)
Pregnant women receiving prenatal care (%)	96.9 (2019)	79.3 (2016)	Data not available
Pregnant women receiving prenatal care of at least four visits (% of pregnant women)	63.5 (2019)	51.2 (2016)	Data not available
Prevalence of anaemia among pregnant women (%)	39.3 (2019)	50.1 (2019)	16.5 (2019)
Births attended by skilled health staff (% of total)	80.4 (2018)	81.4 (2016)	Data not available
Postnatal care coverage (% mothers)	69.7 (2018)	65.3 (2016)	Data not available
Intermittent preventive treatment (IPT) of malaria in pregnancy (% of pregnant women)	58.7 (2018)	Data not available	Data not available
Antiretroviral therapy coverage for PMTCT (% of pregnant women living with HIV)	98.0 (2020)	52.0 (2020)	Data not available

Low-birthweight babies (% of births)	11.6 (2015)	Data not available	7.0 (2015)
Exclusive breastfeeding (% of children under 6 months)	69.9 (2018)	54.9 (2016)	Data not available
Neonatal mortality rate (per 1,000 births)	24.0 (2020)	20.3 (2020)	2.7 (2020)
Infant mortality rate, infant (per 1,000 live births)	41.7 (2020)	27.0 (2020)	3.6 (2020)
Mortality rate, under-5 (per 1,000)	61.4 (2020)	32.6 (2020)	4.2 (2020)

(Year) indicates most recent data available (up to and including 2020)

PMTCT: Prevention of Mother to Child Transmission

Table 1-3 highlights some of the barriers to safe obstetric care. For example, in India and Zambia, approximately 20% of births are not attended by skilled health staff. Table 1-4 presents further indicators of universal healthcare coverage, including the ratio of specialist surgical workforce (1.5 per 100,000 population in Zambia compared to 133.3 per 100,000 population in the UK) which is relevant when considering access to emergency operative birth. The high proportion of the population at risk of impoverishing or catastrophic health expenditure for surgical care in India (data not available for Zambia) highlights some of the economic barriers women may face when deciding where and when to seek care in labour.

Table 1-4 Universal healthcare coverage indicators (The World Bank, 2022)

Indicator	**Zambia**	**India**	**United Kingdom**
Community health workers, per 1,000 people	Data not available	0.6 (2016)	Data not available
Hospital beds (per 1,000 people)	Data not available	0.5 (2017)	2.5 (2019)
Physicians (per 1,000 people)	0.1 (2016)	0.9 (2019)	5.8 (2019)
Specialist surgical workforce (per 100,000 population)	1.5 (2016)	6.8 (2014)	133.3 (2015)
Risk of impoverishing expenditure for surgical care (% of people at risk)	Data not available	24.1 (2020)	0.0 (2020)
Risk of catastrophic expenditure for surgical care (% of people at risk)	Data not available	31.1 (2020)	0.1 (2020)

(Year) indicates most recent data available (up to and including 2020)

Baseline health status is an important factor, and maternal undernutrition is a known contributor to adverse pregnancy outcomes.(Bhutta et al., 2013) The high level of childhood stunting in both India and Zambia (35% of children under five) illustrated by Table 1-5, highlights the poor nutritional status of these populations, which may be further compounded by infectious diseases such as malaria (incidence in 2020 for Zambia: 187 per 1,000 population at risk), an important cause of severe maternal anaemia, low birthweight and perinatal mortality.(Desai et al., 2007)

Table 1-5 Health and nutrition indicators (The World Bank, 2022)

Indicator	**Zambia**	**India**	**United Kingdom**
Completeness of death registration with cause-of-death information (%)	Data not available	10.0 (2011)	100.0 (2016)
Life expectancy at birth, total (years)	64.2 (2020)	69.9 (2020)	80.9 (2020)
People using at least basic drinking water services (% of population)	65.4 (2020)	90.5 (2020)	100.0 (2020)
People using at least basic sanitation services (% of population)	31.9 (2020)	71.3 (2020)	99.1 (2020)
People with basic handwashing facilities including soap and water (% of population)	17.9 (2020)	67.8 (2020)	Data not available
Prevalence of HIV, total (% of population ages 15-49)	11.2 (2020)	0.2 (2020)	Data not available
Prevalence of HIV, female (% ages 15-24)	5.4 (2020)	Data not available	Data not available
Women's share of population ages 15+ living with HIV (%)	61.7 (2020)	44.7 (2020)	30.6 (2020)
Antiretroviral therapy coverage (% of people living with HIV)	90.0 (2020)	62.0 (2020)	Data not available
Prevalence of overweight (% of adults)	27.8 (2016)	19.7 (2016)	63.7 (2016)
Prevalence of severe wasting (% of children under 5)	1.5 (2018)	4.9 (2017)	Data not available

Prevalence of stunting, height for age (% of children under 5)	34.6 (2018)	34.7 (2017)	Data not available
Prevalence of undernourishment (% of population)	Data not available	16.3 (2020)	2.5 (2020)
Cause of death, by communicable disease and maternal, prenatal and nutrition conditions (% of total)	56.5 (2019)	24.2 (2019)	8.2 (2019)
Cause of death, by non-communicable diseases (% of total)	34.8 (2019)	65.9 (2019)	88.2 (2019)
Diabetes prevalence (% of population ages 20 to 79)	4.5 (2019)	10.4 (2019)	3.9 (2019)
Incidence of HIV, all (per 1,000 uninfected population)	2.5 (2020)	0.1 (2020)	Data not available
Incidence of malaria (per 1,000 population at risk)	186.9 (2020)	3.2 (2020)	Data not available
Incidence of tuberculosis (per 100,000 people)	319.0 (2020)	188.0 (2020)	6.9 (2020)
Mortality rate attributed to household and ambient air pollution (per 100,000 population)	127.2 (2016)	184.3 (2016)	13.8 (2016)
Mortality rate attributed to unsafe water, unsafe sanitation and lack of hygiene (per 100,000 population)	34. 9 (2016)	18.6 (2016)	0.2 (2016)

(Year) indicates most recent data available (up to and including 2020)

Table 1-6 illustrates some of the wider social determinants of health, such a low levels of literacy and high unemployment, which contribute further to the cultural and economic barriers in accessing and receiving care. Whilst these figures are often collected via household surveys or self-reported data, with obvious limitations in the ability to collect in-depth and accurate data, they nevertheless provide an important overview and insight into the status of each country. Where data are missing, it serves to further highlight the difficulty in gaining complete data in some regions where comprehensive record-keeping and data management systems remains an ongoing challenge, although it is important to acknowledge that this may apply to high income countries as well.

Table 1-6 Social development indicators (The World Bank, 2022)

Indicator	Zambia	India	United Kingdom
Comprehensive correct knowledge of HIV/AIDS, ages 15-49, female (2 prevent ways and reject 3 misconceptions)	45.6 (2018)	20.9 (2016)	Data not available
Literacy rate, adult total (% of people ages 15 and above)	86.7 (2018)	74.4 (2018)	Data not available
Literacy rate, adult female (% of females ages 15 and above)	83.1 (2018)	65.8 (2018)	Data not available
Maternal leave benefits (% of wages paid in covered period)	100.0 (2017)	100.0 (2017)	90.0 (2017)
Poverty headcount ratio at national poverty line (% of population)	54.4 (2015)	21.9 (2011)	18.6 (2017)
Public spending on education, total (% of GDP)	3.7 (2020)	4.5 (2020)	5.4 (2018)
Primary completion rate, female (% of relevant age group)*	78.6 (2013)	96.1 (2020)	101.5 (2019)
School enrolment, secondary, female (% gross)	Data not available	75.3 (2020)	120.1 (2019)
School enrolment, tertiary, female (% gross)	3.5 (2012)	31.3 (2020)	76.3 (2019)
Ratio of young literate females to males (% ages 15-24)	1.0 (2018)	1.0 (2018)	Data not available
Unemployment, total (% of total labour force)	12.8 (2020)	8.0 (2020)	4.5 (2020)

(Year) indicates most recent data available (up to and including 2020)

*Primary completion rate is calculated by dividing the number of new entrants (enrolment minus repeaters) in the last grade of primary education, regardless of age, by the population at the entrance age for the last grade of primary education and multiplying by 100. There are many reasons why the primary completion rate can exceed 100 percent. The numerator may include late entrants and overage children who have repeated one or more grades of primary education as well as children who entered school early, while the denominator is the number of children at the entrance age for the last grade of primary education.

1.5. Summary

Pre-eclampsia is a leading cause of maternal death globally, with women living in low and lower-middle income countries facing the highest risk of adverse outcomes. The impact of pre-eclampsia extends beyond the immediate peri-partum and postpartum period with long-term sequelae contributing to the global burden of

non-communicable disease. Accurate detection and monitoring of women with pregnancies complicated by pre-eclampsia is challenging in settings where lack of funding, skilled staff, and equipment, limits the delivery of high-quality care during pregnancy, labour, and birth. This is further compounded by the many social and economic barriers that women experience when deciding to seek and access care. Evidence from high income countries has shown that planned delivery from 34 weeks' gestation onwards reduces maternal morbidity, however the short and long-term infant outcomes remain unclear, and it has been difficult to demonstrate a significant reduction in serious, but rare, outcomes such as maternal death and stillbirth. The overarching research question that will be addressed in this thesis is whether planned delivery between 34 and 37 weeks' gestation in a low and lower-middle income setting, can reduce adverse pregnancy outcomes, compared to expectant management. Throughout this thesis I will explore the contextual factors influencing implementation of a randomised controlled trial in a low-resource environment, and the varying risks and benefits, particularly for the infant, associated with planned delivery in this setting.

Chapter 2 Aims and objectives

2.1. Aim

The overall aim of this thesis was to evaluate the impact of planned early delivery in late preterm pre-eclampsia on pregnancy outcomes in low and lower-middle income countries.

To achieve this, I reviewed the current available evidence on this topic (Chapter 3) and analysed data on longer-term infant outcomes from a timing of delivery trial based in the UK (Chapter 4). I assessed the feasibility and acceptability of implementing planned early delivery in India and Zambia (Chapter 5) and explored the language barriers to informed consent in Zambia (Chapter 6). I designed a trial protocol for a randomised controlled trial comparing planned early delivery to expectant management for women with pre-eclampsia between 34^{+0} and 36^{+6} weeks' gestation in India and Zambia (Chapter 7), and compared short-term maternal and perinatal outcomes between the two management groups (Chapter 8).

Each chapter is presented in individual manuscript form (Abstract, Introduction, Methods, Results, and Discussion) and matches the submitted manuscript or published paper. An overarching discussion pulling out themes across the whole thesis (but not duplicating the Discussion section within each chapter) is presented in Chapter 9.

The figures, terminology, and references used in each chapter are consistent with the published paper (or submitted manuscript). However, some of these have been superseded by more recent updates; where this is the case, the most contemporaneous figures are used in Chapter 1 (Introduction). Important examples of this include the number of maternal deaths attributable to pre-eclampsia and the proportion of pregnancies affected by pre-eclampsia, with estimates of these figures varying over time.

The specific objectives and research questions addressed by each chapter are described in more detail below.

2.1.1. Systematic review and individual participant data meta-analysis to assess the impact of planned early delivery from 34 weeks' gestation in women who have pre-eclampsia without severe features, compared to expectant management (Chapter 3).

The objective of this chapter was to review, synthesise, and analyse all available evidence from randomised controlled trials evaluating planned early delivery in women with pre-eclampsia, using individual participant data meta-analysis, to answer the following **research questions**:

- What is the impact of planned early delivery from 34 weeks' gestation onwards in women with pre-eclampsia on maternal mortality and morbidity?
- What is the impact of planned early delivery from 34 weeks' gestation onwards in women with pre-eclampsia on perinatal mortality and morbidity, including respiratory disease and the risk of being born small for gestational age?

2.1.2. Two-year follow-up of infant and maternal outcomes after a randomised controlled trial of planned early delivery or expectant management for late preterm pre-eclampsia (Chapter 4).

The objective of this chapter was to evaluate infant neurodevelopmental outcomes at two years of age, and maternal physical and mental health at six months and two years post birth, following either planned early delivery or expectant management for late preterm pre-eclampsia, to answer the following **research questions**:

- What is the longer-term impact of planned early delivery on infant neurodevelopment compared to expectant management?
- Is there any difference in the self-reported quality of maternal health following planned early delivery or expectant management?

2.1.3. Feasibility study of planned early delivery for late preterm pre-eclampsia in a low and lower-middle income setting (Chapter 5).

The objective of this chapter was to understand the current disease burden associated with pre-eclampsia, and the current clinical management offered to women who have pre-eclampsia, in India and Zambia. Additionally, I wanted to understand the perceived risks and benefits of planned early delivery amongst pregnant women, their families, and healthcare providers across the proposed trial sites. I used mixed methods, to address the following **research questions:**

- What proportion of women with pre-eclampsia experience an adverse pregnancy outcome after 34 weeks at the proposed trial sites?
- What are the gestation-specific perinatal outcomes of infants born to women with pre-eclampsia at the proposed trial sites?
- What care pathways are utilised, and what resources are available, to diagnose and manage pre-eclampsia at the proposed trial sites?
- What is the lived experience of healthcare providers, women, and their families of pre-eclampsia or high blood pressure in pregnancy?
- What do healthcare providers, women, and their families understand about the causes and management of pre-eclampsia or high blood pressure in pregnancy?
- What are the attitudes and beliefs of healthcare providers, women, and their families towards planned early delivery, induction of labour, and the implications of preterm birth?

2.1.4. Qualitative evaluation of the language barriers to informed consent in Zambia (Chapter 6).

The objective of this chapter was to understand the factors which promote or undermine participant comprehension of recruitment materials used in maternal health research studies conducted in Zambia, using qualitative methodology, to explore the following **research questions:**

- What is the lived experience of researchers and translators working in Zambia of designing, translating, and using recruitment materials?

- How does language, and the difference between English and Zambian languages, impact upon the translation process?
- How does the translation process and the design of recruitment materials influence the ability of potential research participants to understand the information provided to them?

2.1.5. Clinical trial protocol evaluating planned early delivery compared to expectant management for women with pre-eclampsia between 34^{+0} and 36^{+6} weeks' gestation, in low and lower-middle income settings (Chapter 7).

The objective of this chapter was to utilise the findings generated from the feasibility study to design a trial protocol suited to the local context, including consideration of the following topics:

- What is the estimated event rate in the expectant management (control) group and therefore what should the target sample size be?
- How should the eligibility criteria be designed to suit the local context?
- How should clinical outcomes be defined to suit the local context?

2.1.6. A randomised controlled trial of planned early delivery or expectant management for late preterm pre-eclampsia in a low income country and a lower-middle income country (Chapter 8).

The objective of this chapter was to undertake a randomised controlled trial across sites in India and Zambia to compare planned early delivery to expectant management for women with pre-eclampsia, without severe features, between 34^{+0} and 36^{+6} weeks' gestation, with the following **research questions:**

- Can planned early delivery for women with pre-eclampsia between 34^{+0} and 36^{+6} weeks reduce maternal mortality and morbidity without increasing short-term neonatal complications?
- How does planned early delivery influence other important short-term maternal and perinatal outcomes?

Chapter 3 Planned delivery or expectant management in pre-eclampsia: an individual participant data meta-analysis

This chapter matches the published paper, incorporating all relevant supplementary material, except when specified as an appendix.

3.1. Abstract

Objective

Pregnancy hypertension is a leading cause of maternal and perinatal mortality and morbidity. Between 34^{+0} and 36^{+6} weeks' gestation, it is uncertain whether planned delivery could reduce maternal complications without serious neonatal consequences. In this individual participant data (IPD) meta-analysis, we aim to compare planned delivery to expectant management, focusing specifically on women with pre-eclampsia.

Data sources

We performed an electronic database search using a pre-specified search strategy, including trials published between 1st January 2000 and 18th December 2021. We sought individual participant-level data from all eligible trials.

Study eligibility criteria

We included women with singleton or multifetal pregnancies with pre-eclampsia from 34 weeks' gestation onwards.

Study appraisal and synthesis methods

The primary maternal outcome was a composite of maternal mortality or morbidity. The primary perinatal outcome was a composite of perinatal mortality or morbidity. We analysed all available data for each pre-specified outcome on an intention-to-treat basis. For primary IPD meta-analyses, we used a one-stage fixed effects model.

Results

We included 1,790 participants from six trials in our analysis. Planned delivery from 34 weeks' gestation onwards significantly reduced the risk of maternal morbidity

(2.6% versus 4.4%; aRR 0.59, 95% CI 0.36-0.98), compared to expectant management. The primary composite perinatal outcome was increased by planned delivery (20.9% versus 17.1%; aRR 1.22, 95% CI 1.01-1.47), driven by short-term neonatal respiratory morbidity. However, infants in the expectant management group were more likely to be born small for gestational age (7.8% versus 10.6%; RR 0.74, 95% CI 0.55- 0.99).

Conclusions

Planned early delivery in women with late preterm pre-eclampsia provides clear maternal benefit and may reduce the risk of being born small for gestational age in the infant, with a possible increase in short-term neonatal respiratory morbidity. The potential benefits and risks of prolonging the pregnancy complicated by pre-eclampsia should be discussed with women as part of a shared decision-making process.

3.2. Introduction

Pregnancy hypertension is responsible for at least 27,800 maternal deaths (Wang et al., 2021) worldwide every year, as well as 500,000 infant deaths (Poon et al., 2019) including approximately 200,000 stillbirths.(Lawn et al., 2016) Whilst the prevalence of pre-eclampsia varies throughout the world, it complicates between 2-3% of pregnancies in a high income setting.(Roberts et al., 2011) Estimates for low and middle income countries are higher, with up to 12% of pregnancies affected in these settings.(Poon et al., 2019) Delivery is the only definitive management for this progressive and unpredictable condition and is routinely recommended for all women with pre-eclampsia from 37 weeks' gestation onwards.(World Health Organization, 2011) At gestations up to 34 weeks, if there are no immediate indications for delivery, expectant management is preferable due to the neonatal risks associated with early preterm birth.(World Health Organization, 2011)

It is less clear whether a policy of expectant management in the late preterm period (34 to 37 weeks) should be pursued, although if severe features of pre-eclampsia develop or the woman reaches 37 weeks, delivery is indicated. However, there is

uncertainty as to whether a policy of routine immediate delivery at this gestational window (34 to 37 weeks) could reduce maternal complications without serious neonatal consequences. Several studies have compared these two strategies in women with hypertensive disorders of pregnancy (including pre-eclampsia) from 34 weeks.(Boers et al., 2010; Broekhuijsen et al., 2015; Chappell, Brocklehurst, et al., 2019; Koopmans et al., 2009; Owens et al., 2014; The GRIT Study Group., 2003; Thornton et al., 2004) However, it has not been possible to draw firm conclusions from individual studies alone. Recent meta-analyses (Cluver et al., 2017; Wang et al., 2017) and individual participant data meta-analyses (Bernardes et al., 2019) of women with hypertensive disorders of pregnancy have shown that planned early delivery from 34 weeks' gestation reduces maternal complications, but the neonatal impact remains unclear. These previous reviews generally grouped all hypertensive disorders of pregnancy together, combining women with chronic hypertension, gestational hypertension, and pre-eclampsia. However, the underlying pathophysiology of pre-eclampsia is distinct, with maternal endothelial dysfunction leading to multi-organ complications and potentially severe maternal and fetal outcomes. Optimal timing of delivery in pre-eclampsia may therefore differ compared to other hypertensive disorders of pregnancy, and the balance of risks and benefits for the infant should also be considered within the context of this rapidly progressive and unpredictable disease. A limited subgroup analysis conducted as part of the previous IPD meta-analysis (Bernardes et al., 2019) in women with all types of pregnancy hypertension, identified women with pre-eclampsia as a population in whom planned delivery may confer significant benefit. The authors therefore highlighted a need to evaluate the impact of this intervention in women with pre-eclampsia specifically. Since this meta-analysis was published, a new trial has been reported, enrolling more women with pre-eclampsia than all previously included trials combined.(Chappell, Brocklehurst, et al., 2019) This enabled us to conduct an IPD meta-analysis evaluating timing of delivery on a wider set of maternal and perinatal outcomes in this high-risk group of women with pre-eclampsia. A meta-analysis evaluating early delivery or expectant management for late preterm pre-eclampsia was recently published.(Chatzakis et al., 2021) However,

this study was limited by its inclusion of just three randomised controlled trials, only two of which were used to evaluate the co-primary outcome of neonatal intensive care unit admission. Our IPD meta-analysis is strengthened by its ability to harmonise data to overcome inconsistencies in outcome definitions between trials, and to evaluate key outcomes such as neonatal morbidity in more detail.

3.3. Objective

The objective of this study was to undertake an IPD meta-analysis, focusing on women with pre-eclampsia alone. In women with pre-eclampsia from 34 weeks' gestation onwards, we aimed to evaluate the effect of planned early delivery on maternal mortality or morbidity and perinatal mortality or morbidity, compared to expectant management, using individual participant data from randomised controlled trials. The use of individual participant data enabled us to target our review to women with late preterm pre-eclampsia, and to perform subgroup analyses and adjustments that would not be possible with the use of aggregate data, for example using blood pressure values to reflect severity of disease. This is clinically relevant since the presence of additional risk factors in women with pre-eclampsia may alter management options.

3.4. Methods

3.4.1. Search strategy and study selection

We followed a protocol and statistical analysis plan published on the PROSPERO registry, in accordance with PRISMA-IPD guidance.(Stewart et al., 2015) We included studies that were randomised controlled trials comparing planned early delivery to expectant management in women presenting with pre-eclampsia from 34 weeks' gestation onwards. Cluster randomised trials or studies with a quasi-randomised design were excluded. To identify eligible studies, we electronically searched the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, MEDLINE, and ClinicalTrials.gov, using the search terms ('pre-eclampsia' OR 'preeclampsia') AND ('delivery' OR 'birth') with the limits 'human' and 'randomised controlled trial'. The final search date was 18 December 2021. We did not restrict

our search by language. We excluded trials published prior to the year 2000. This was due to changes in clinical practice and care of women with pre-eclampsia, as well as neonatal care, over time, such that findings from earlier trials may be difficult to interpret. To ensure that the search was comprehensive, we also hand-searched the reference lists of retrieved studies and any relevant reviews identified. Two independent review authors (Alice Beardmore-Gray and Jessica Fleminger) assessed all studies identified by the search strategy against study-level inclusion criteria. Any disagreement was resolved through discussion, or, if necessary, with a third review author (not required).

3.4.2. Eligibility criteria

We included women with singleton or multifetal pregnancies presenting with pre-eclampsia or superimposed pre-eclampsia from 34 weeks' gestation onward. The definition of pre-eclampsia or superimposed pre-eclampsia was that used by the study at the time. All definitions used would now be encompassed by the current ISSHP 2018 diagnostic criteria.(Brown et al., 2018)

3.4.3. Data extraction

We sought participant-level data from authors of all eligible trials. Available data were extracted from trial databases (provided via a data-sharing agreement) according to pre-specified variables by two of the review authors (Alice Beardmore-Gray and Paul Seed). Data were re-coded into a common format and definitions of key characteristics, diagnoses (e.g. pre-eclampsia), and outcomes were harmonised. A final dataset was then produced and rechecked for accuracy and completeness.

3.4.4. Assessment of risk of Bias

Two review authors (Alice Beardmore-Gray and Jessica Fleminger) independently assessed included trials for risk of bias using the Cochrane risk-of-bias tool.(Sterne et al., 2019)

3.4.5. Outcomes

The primary maternal outcome was a composite of maternal mortality and severe maternal morbidity (adapted from a previously published composite derived by

Delphi consensus).(von Dadelszen et al., 2011) Presence of severe maternal morbidity was defined as one or more of the following individual components: maternal death, eclampsia, stroke, pulmonary oedema, HELLP (haemolysis, elevated liver enzymes, low platelet count) syndrome, acute renal insufficiency, and placental abruption. The primary perinatal outcome was a composite of perinatal mortality or morbidity. This was defined as any one of perinatal death, neonatal death, or neonatal morbidity. The selection of components was guided by recent recommendations for core outcome sets in pre-eclampsia.(Duffy et al., 2020) Neonatal morbidity was defined as one or more of respiratory disease (any one of respiratory distress syndrome, need for respiratory support, neonatal unit admission for respiratory disease, or bronchopulmonary dysplasia), central nervous system complications (any one of intraventricular haemorrhage, intracerebral haemorrhage, periventricular leukomalacia, hypoxic ischemic encephalopathy, cerebral infarction, or convulsions), culture proven sepsis, necrotising enterocolitis, hypoglycaemia requiring intravenous glucose or neonatal unit admission, and jaundice requiring neonatal unit admission. For both composite outcomes, if data were missing (i.e. not collected for a particular component) we treated it as absent. Secondary maternal outcomes included severe postpartum haemorrhage, progression to severe hypertension, thromboembolic disease, hepatic dysfunction, onset of delivery, and admission to maternal intensive care unit. Secondary perinatal outcomes were gestational age at delivery, mode of delivery, birthweight, birthweight centile, baby sex, small for gestational age (<3rd centile, <10th centile), admission to neonatal unit, admission to neonatal intensive care unit, 5-minute Apgar score <7, and arterial pH <7.05.

3.4.6. Data synthesis

We analysed all available data for baseline maternal characteristics at enrolment, related process outcomes (such as time from randomisation to delivery), and for each pre-specified outcome, on an intention-to-treat basis. In each study, all outcomes of interest were either reported completely with less than 5% missingness, or not reported at all. Under these circumstances, multiple imputation is not feasible or recommended and we therefore analysed all outcomes without

imputation. For primary IPD meta-analyses, we used a one-stage fixed effects model. Standard errors, confidence intervals, and p values were adjusted for clustering within studies. In addition to this, we used robust standard errors to correct for clustering of twin pregnancies by mother for the perinatal outcomes.(Williams, 2000) We set out to calculate odds ratios using multilevel models as originally outlined in the statistical analysis plan. However, this multilevel model structure did not converge as there were not sufficient datapoints at each of the levels. We therefore performed a multivariate analysis, calculating risk ratios for binary outcomes and mean differences for continuous outcomes using a simpler, fixed effects model. We also calculated unadjusted risk differences. A fixed effects one-stage analysis such as this is appropriate where there are small studies with rare event numbers. We gave a separate intercept for each trial, but assuming the same treatment effect (i.e. we used fixed effects for each trial).

Numbers needed to treat or harm with 95% confidence intervals were calculated for outcomes where a significant difference between management groups was found. The analysis was adjusted for study, gestational age at randomisation (34^{+0} to 34^{+6} weeks, 35^{+0} to 35^{+6} weeks, 36^{+0} to 36^{+6} weeks, 37^{+0} to 37^{+6} weeks, 38^{+0} to 38^{+6} weeks, 39^{+0} to 39^{+6} weeks, 40^{+0} weeks and above), severity of systolic hypertension at study entry (<150 vs. ≥ 150 mmHg), parity (primiparous vs multiparous), and number of fetuses (singleton vs. all other). Severity of systolic hypertension at study entry was chosen because it is an objective marker of disease severity consistently available across studies and there is a known dose-response relationship between increasing blood pressure and adverse pregnancy outcomes.(Bone et al., 2021; Magee et al., 2016; Reddy et al., 2020) Where these pre-specified adjustment variables were missing, we calculated the average value (or proportion for categorical variables) across all studies and used this. We did not use multiple imputation methods as this is not recommended in this scenario. Subgroup analysis was conducted if there were at least 10 events in each subgroup, also using a one-stage fixed effects model. Pre-specified subgroups were study, gestational age at randomisation, parity, singleton vs. multifetal pregnancy,

previous caesarean section, pre-randomisation diabetes of any type, superimposed pre-eclampsia, and suspected fetal growth restriction at enrolment. Since many of the subgroups concerned the same adjustment variables used for our main analysis (including some additional subgroups of clinical relevance), our subgroup analysis was unadjusted, to better delineate the effect of these variables. Heterogeneity was assessed using I^2 (the proportion of the total variance of the outcome that is between studies, rather than between subjects within studies) as part of the subgroup analysis. We have also presented values for tau^2. No additional analyses were undertaken. This IPD meta-analysis was prospectively registered with PROSPERO: (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020206425).

3.5. Results

3.5.1. Study selection

We identified 1,617 references after duplicates were removed (Figure 3-1).

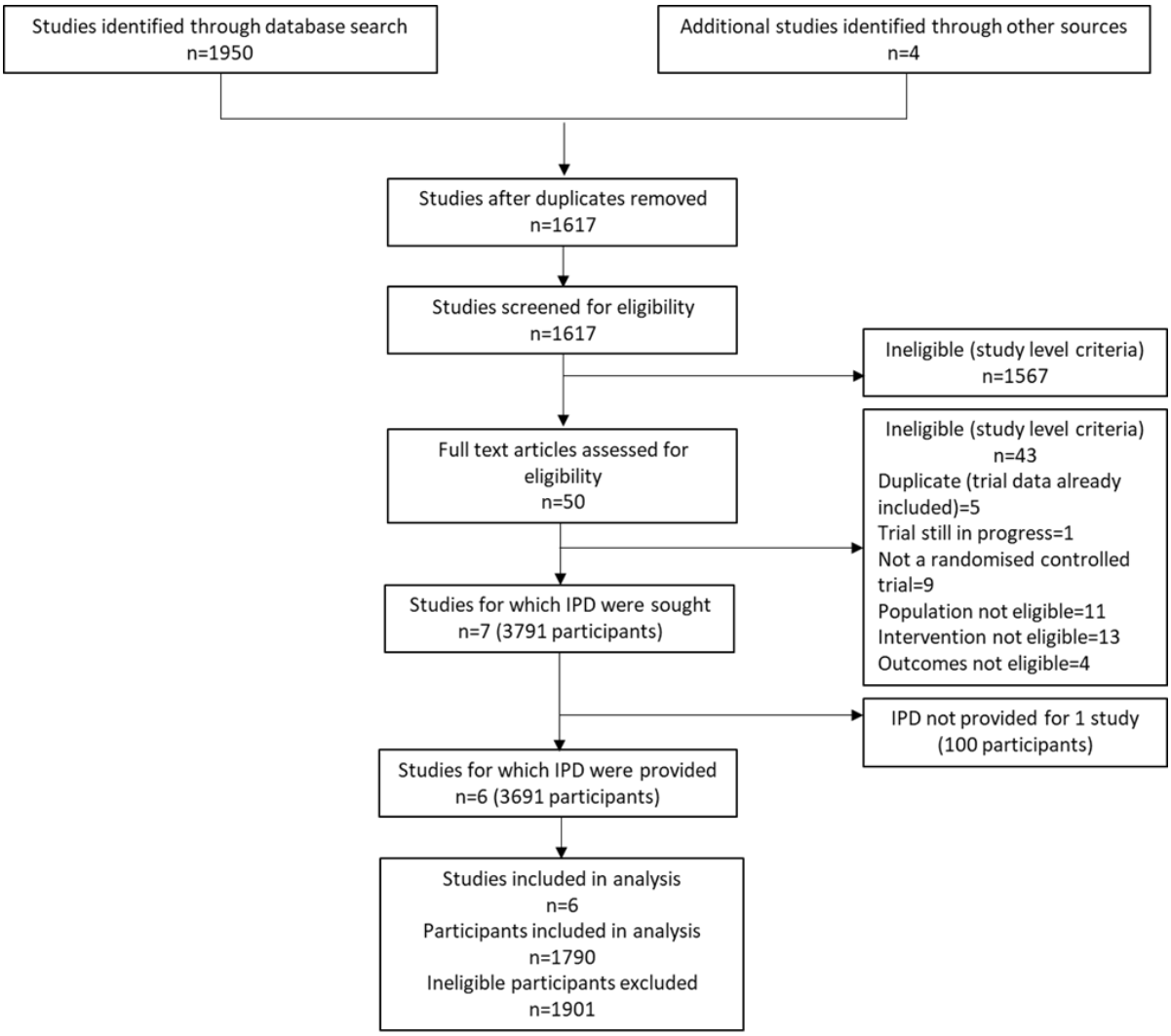


Figure 3-1 Flowchart summarising search results

1,567 references were excluded after title screening and 43 were excluded after abstract and full text screening. Seven trials (3791 participants) were considered eligible for inclusion at study-level. One trial (100 participants) was subsequently excluded as the trial authors did not respond to our request for participant-level data despite several attempts.(Majeed, 2014) The only published data available from this trial was a conference abstract and therefore we were not able to include any aggregate data for this trial. Six trials (Boers et al., 2010; Broekhuijsen et al., 2015; Chappell, Brocklehurst, et al., 2019; Koopmans et al., 2009; Owens et al., 2014; The GRIT Study Group., 2003) with participant-level data were available. Following data extraction and review by two of the authors, 1,901 participants were deemed ineligible for inclusion in this IPD meta-analysis, principally because of

women being enrolled with conditions other than pre-eclampsia, or prior to 34 weeks' gestation, with reasons given for exclusion in Table 3-1. The remaining 1,790 participants from six trials were therefore included in our analysis.

Table 3-1 Characteristics of included studies

Study	Setting	Total participants enrolled (n)	Trial participants (inclusion criteria)			Eligible for IPD (n)	Non-eligible for IPD (n)
			Gestational age (weeks)	Singleton or twin pregnancy	Diagnosis		
GRIT GRIT Study Group (2003)	69 hospitals in 13 European countries	548 Planned delivery n=296, Expectant management=292	24^{+0} to 36^{+0}	Singleton or twin	Fetal compromise with an umbilical artery Doppler waveform recorded (including pregnancies complicated by pre-eclampsia)	15 Planned delivery n=10, Expectant management n=5	493 randomised before 34 weeks; 40 no pre-eclampsia at study entry
HYPITAT Koopmans (2009)	38 hospitals in The Netherlands	756 Planned delivery n=377, Expectant management=379	36^{+0} to 41^{+0}	Singleton	Gestational hypertension or pre-eclampsia without severe features[a]	246 Planned delivery n=123, Expectant management n=123	510 no pre-eclampsia at study entry
DIGITAT *Boers* (2010)	52 hospitals in The Netherlands	650 Planned delivery n=321, Expectant management n=329	36^{+0} to 41^{+0}	Singleton	Suspected intra-uterine growth restriction (including pregnancies complicated by pre-eclampsia)	45 Planned delivery n=18, Expectant management n=27	605 no pre-eclampsia at study entry
Deliver or Deliberate *Owens* (2014)	1 hospital in the USA	169 Planned delivery n=97, Expectant management n=86	34^{+0} to 36^{+6}	Singleton or twin	Pre-eclampsia (ACOG 2002 criteria) without any other maternal-fetal complications	165 Planned delivery n=93, Expectant management n=72	4 randomised before 34 weeks

HYPITAT II Broekhuijsen (2015)	51 hospitals in The Netherlands	703 Planned delivery n=352, Expectant management=351	34^{+0} to 36^{+6}	Singleton or twin	Any hypertensive disorder of pregnancy without severe features[a]	420 Planned delivery n=209, Expectant management n=211	4 randomised before 34 weeks; 283 no pre-eclampsia at study entry
PHOENIX Chappell (2019)	46 hospitals in England and Wales	901 Planned delivery n=450, Expectant management n=451	34^{+0} to 36^{+6}	Singleton or twin	Pre-eclampsia (ISSHP 2014 criteria), not requiring immediate delivery	899 Planned delivery n=448, Expectant management n=451	2 withdrew from trial

ACOG: American College of Obstetricians and Gynecologists; ISSHP: International Society for the Study of Hypertension in Pregnancy.

[a]Pre-eclampsia defined as a diastolic BP of 90mmHg or higher measured on two occasions at least 6h apart, combined with proteinuria.

3.5.2. Study characteristics

A summary of characteristics of included studies, including details of the interventions, can be found in Tables 3-1, 3-2, and 3-3. Two trials (GRIT and DIGITAT) enrolled women with suspected fetal growth restriction on ultrasound, including pregnancies complicated by pre-eclampsia, over a wide gestational age range. HYPITAT and HYPITAT II trials enrolled women with any hypertensive disorder of pregnancy, from 36^{+0} and 34^{+0} weeks' gestation onwards, respectively. The PHOENIX Trial and Deliver or Deliberate trial focused specifically on women with pre-eclampsia (without severe features) between 34^{+0} and 36^{+6} weeks' gestation. None of the trials enrolled women with severe features of pre-eclampsia, or any other indications for immediate delivery. This was stated in each of their inclusion criteria (Table 3-1), with severe features defined in accordance with the relevant guidelines at the time (primarily ACOG or ISSHP criteria). These are consistent with current definitions.(The American College of Obstetricians and Gynecologists, 2020) For the purposes of this IPD meta-analysis we selected only those participants that met our eligibility criteria, described in the section above (3.4.2. Eligibility criteria).

Table 3-2 Additional study characteristics

Study	Funding source	Conflict of interest	Study design	Enrolment dates	Intervention	Antenatal corticosteroid (ACS) use
GRIT *GRIT Study Group* (2003)	MRC, European Union Concerted Action, Princess Beatrix Foundation	Nil	Randomised controlled trial	November 1993-March 2001	Delivery initiated within 48h of randomisation	Pre-randomisation ACS given in 70% of immediate delivery group and 69% of expectant management group. Post-randomisation ACS use not reported
HYPITAT *Koopmans* (2009)	ZonMw	Nil	Randomised controlled trial	October 2005-March 2008	Delivery initiated within 24h of randomisation	Not reported
DIGITAT *Boers* (2010)	ZonMw	Nil	Randomised controlled trial	November 2004-November 2008	Delivery initiated within 48h of randomisation	Not reported
Deliver or Deliberate *Owens* (2014)	Division of Maternal-Fetal Medicine in the Dept. of OBGYN at the University of Mississippi Medical Center	Nil	Randomised controlled trial	March 2002-June 2008	Delivery initiated within 12h of randomisation	Not reported
HYPITAT II *Broekhuijsen* (2015)	ZonMw	Nil	Randomised controlled trial	March 1st 2009-Feb 21st 2013	Delivery initiated within 24h of randomisation	Pre-randomisation ACS given in 7.5% of immediate delivery group and 8% of expectant management group. Post-randomisation ACS use 1% across both groups
PHOENIX *Chappell* (2019)	NIHR Health technology assessment programme	Nil	Randomised controlled trial	Sept 29th 2014-Dec 10th 2018	Delivery initiated within 48h of randomisation	Post- randomisation ACS given in 65% of immediate delivery group and 55% of expectant management group

Table 3-3 Additional study characteristics

Study	Short-term primary outcome	Short-term secondary outcomes
GRIT *GRIT Study Group* (2003)	Infant survival up to hospital discharge	Mode of delivery, surrogate outcomes for fetal morbidity: birthweight, sex, Apgar score <7 at 5 minutes, cord pH <7.0, ventilation >24hs, necrotising enterocolitis, neonatal convulsions, GMH/IVH, PVL/VM, stillbirth, neonatal death, death >28 days
HYPITAT *Koopmans* (2009)	Composite measure of poor maternal outcomes defined as: maternal mortality, maternal morbidity (eclampsia, HELLP syndrome, pulmonary oedema, thromboembolic disease, or placental abruption), progression to severe disease and major PPH up to maternal hospital discharge and 6 weeks after birth	Mode of delivery, neonatal mortality, and neonatal morbidity (composite outcome consisting of a 5 minute Apgar score <7, umbilical artery pH <7.05 or admission to a neonatal intensive care unit)
DIGITAT *Boers* (2010)	Composite measure of adverse neonatal outcome (defined as death before hospital discharge, 5 minute Apgar score <7, umbilical artery pH <7.05, or admission to the neonatal intensive care unit)	Operative delivery (vaginal instrumental delivery or caesarean section), neonatal length of stay in the NICU or neonatal ward, length of stay in the maternal hospital and maternal morbidity (PPH >1,000ml, gestational hypertension or pre-eclampsia, pulmonary oedema, thromboembolism, or any other serious event)
Deliver or Deliberate *Owens* (2014)	Maternal mortality, maternal morbidity, and progression of pre-eclampsia with the appearance of severe features as defined by the American College of Obstetricians and Gynecologists (ACOG)	Onset of labour, progression to severe pre-eclampsia, postpartum complications (HELLP syndrome, eclampsia), total hospital length of stay (LOS) post-delivery (days), total hospital LOS (days). Additional neonatal outcomes: birthweight, small for gestational age, arterial umbilical cord pH, NICU admission, asphyxia, respiratory distress syndrome, transient tachypnoea of the new-born, apnoea, NICU LOS (days)
HYPITAT II *Broekhuijsen* (2015)	*Maternal:* composite of adverse maternal outcomes (thromboembolic disease, pulmonary oedema, eclampsia, HELLP syndrome, placental abruption, or maternal death) up to maternal final discharge from hospital and 6 weeks after birth.	Instrumental vaginal delivery, caesarean section, 5-minute Apgar score of less than 7, umbilical artery pH of less than 7.05, admission to a NICU, death before discharge, suspected or confirmed neonatal infection or sepsis, hypoglycaemia necessitating intravenous glucose, transient

	Neonatal: Respiratory distress syndrome (RDS), defined as need for supplementary oxygen for more than 24h combined with radiographic findings typical for RDS up to infant final discharge from hospital	tachypnoea of the new-born, meconium aspiration syndrome, pneumothorax or pneumomediastinum, necrotising enterocolitis, IVH, PVL and convulsions
PHOENIX *Chappell* (2019)	*Maternal:* composite of maternal morbidity of fullPIERS (von Dadelszen et al., 2011) outcomes, with the addition of recorded systolic BP of at least 160mmHg post randomisation, up to primary maternal hospital discharge *Perinatal:* composite of neonatal deaths within 7 days of delivery and perinatal deaths or neonatal unit admissions before infant primary hospital discharge	Individual components of the composite primary outcome, use of antihypertensive drugs, progression to severe pre-eclampsia (systolic BP of at least 160mmHg, platelet count <100, abnormal liver function enzymes - ALT or AST >70), time and mode of onset of labour, confirmed thromboembolic disease, confirmed sepsis, primary and additional indications for delivery; and placental abruption. Stillbirth, NND within 7 days of delivery, NND before hospital discharge, admissions to NNU, number of nights in each category of care, total number of nights in hospital, BW, BW centile, BW less than 10th or 3rd centile, GA at delivery, Apgar score at 5 min after birth, umbilical arterial and venous pH at birth, need for supplementary oxygen before discharge, number of days required, need for respiratory support, other indications and main diagnoses resulting in NNU admission and health resource use outcomes

GMH: Germinal matrix hemorrhage; IVH: intraventricular hemorrhage; PVL: Periventricular leukomalacia; VM: ventriculomegaly; HELLP syndrome: Hemolysis, elevated liver enzymes, low platelet count syndrome; PPH: post-partum hemorrhage; NICU: neonatal intensive care unit; NNU: neonatal unit; NND: neonatal death; BW: birthweight; GA: gestational age; ALT: alanine aminotransferase; AST: aspartate transaminase.

3.5.3. Risk of bias of included studies

The results of our risk of bias assessment using the Cochrane Risk of Bias 2 tool can be found in Figures 3-2 and 3-3. The PHOENIX and HYPITAT trials were prospectively registered in a clinical trials registry (prior to enrolment of first participants). The GRIT, DIGITAT, Deliver or Deliberate, and HYPITAT II trials were retrospectively registered. Four of the included trials were assessed as being at low risk of bias. The HYPITAT II trial had some concerns due to minor discrepancies between the published protocol and final paper. The Deliver or Deliberate trial was judged to be at high risk of bias. This was primarily due to limited reporting regarding the randomisation process and an imbalance in the final analysis population suggesting post-randomisation exclusions. Tables 3-4 and 3-5 describe the missing data for each maternal and perinatal variable by study. Where data were missing, this was usually due to the outcome not being collected, with very few cases of data missing due to incomplete reporting or exclusions.

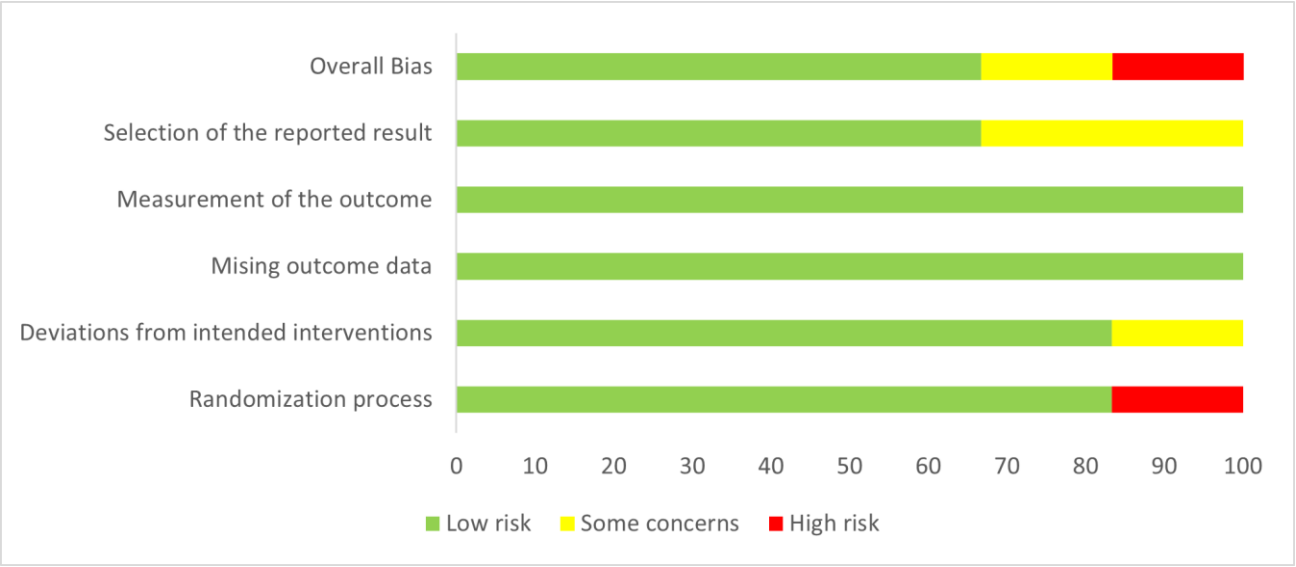


Figure 3-2 Risk of bias (using Cochrane RoB2 tool) presented as percentage across all included studies

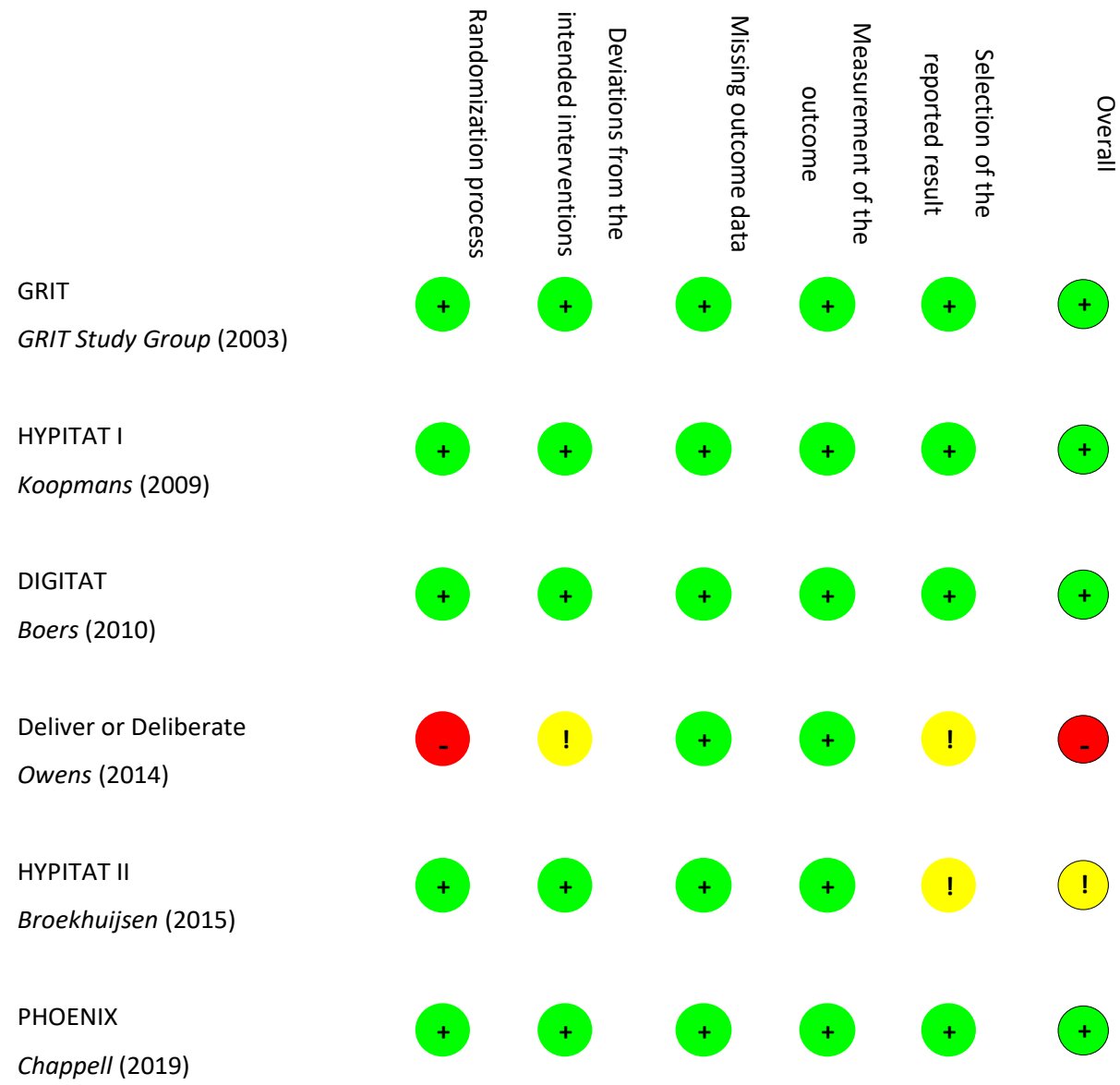


Figure 3-3 Risk of bias summary (using Cochrane RoB 2 tool) about each risk of bias domain for each included study

Table 3-4 Missing maternal variables

	HYPITAT n=246	**HYPITAT II n=420**	**DIGITAT n=45**	**Deliver or Deliberate n=165**	**GRIT n=15**	**PHOENIX n=899**
Maternal death	0	0	0	0	15	0
Eclampsia	0	0	0	0	15	0
Stroke	246	420	0	0	15	0
Pulmonary oedema	0	0	0	165	15	0
HELLP syndrome	0	0	0	0	15	0
Renal insufficiency	246	0	0	0	15	0
Placental abruption	0	0	0	165	15	0
Post-randomisation severe hypertension	0	0	45	165	15	0
Hepatic dysfunction	0	0	0	0	15	0
Thromboembolic disease	0	0	0	165	15	0
Severe postpartum haemorrhage	0	0	0	0	15	0
Pre-labour caesarean section	0	0	0	165	15	2[a]
Intensive care unit admission	0	420	0	165	15	0

HELLP syndrome: Hemolysis, elevated liver enzymes, low platelet count syndrome.

[a]Data missing/excluded. All other missing variables were not collected.

Table 3-5 Missing perinatal variables

	HYPITAT n=246	**HYPITAT II n=454**	**DIGITAT n=45**	**Deliver or Deliberate n=165**	**GRIT n=15**	**PHOENIX n=946**
Stillbirth	0	0	0	0	0	0
Neonatal death	0	0	0	0	0	0
Respiratory distress syndrome	0	0	0	0	15	946
Need for respiratory support	0	454	0	0	0	0
Neonatal unit admission for respiratory disease	246	454	45	165	15	0
Bronchopulmonary dysplasia	246	454	45	0	15	946
Cerebral infarction	246	454	45	165	15	946
Hypoxic ischemic encephalopathy	246	0	45	165	15	0
Intra-cerebral haemorrhage	246	454	45	165	15	946
Intra-ventricular haemorrhage	0	0	0	0	0	0
Convulsions	0	0	0	165	0	0
Peri-ventricular leukomalacia	0	0	0	165	15	0
Neonatal sepsis	246	454	0	165	15	0
Necrotising enterocolitis	0	0	0	0	0	0
Jaundice	0	454	0	165	15	0
Hypoglycaemia	246	0	45	165	15	0
Gestational age at delivery	1[a]	0	0	0	0	2[a]
Mode of delivery	0	454	0	0	0	2[a]
Birthweight	0	1[a]	0	0	0	2[a]
Sex	0	0	0	0	0	2[a]
Neonatal unit admission	0	0	0	165	15	2[a]
Neonatal intensive care unit admission	0	0	0	0	15	0
5 -minute Apgar score less than 7	0	0	0	0	0	0
Arterial pH less than 7.05	0	0	0	0	15	0

[a]Data missing/excluded. All other missing variables were not collected.

3.5.4. Synthesis of results

Baseline maternal characteristics at enrolment were similar across planned delivery and expectant management groups (Table 3-6). Importantly, the proportion of women with suspected fetal growth restriction and severe hypertension at enrolment (Table 3-6) was balanced between the two management groups, as expected with randomisation.

Table 3-6 Baseline maternal characteristics at enrolment

Characteristic	**n**	**Planned delivery n=901**		**n**	**Expectant management n=889**
Maternal age (years; mean (SD))	901	29.56 (6.32)		889	29.97 (6.12)
White European ethnicity	891	618 (69.4%)		884	624 (70.6%)
No previous births	891	564 (63.3%)		884	555 (62.8%)
Singleton pregnancy	901	866 (96.1%)		889	843 (94.8%)
Previous caesarean section	780	99 (12.7%)		785	101 (12.9%)
Pre-randomisation diabetes	780	94 (12.1%)		785	88 (11.2%)
Suspected fetal growth restriction	808	124 (15.3%)		817	132 (16.2%)
Systolic blood pressure ≥ 160mmHg	810	227 (28.0%)		818	221 (27.0%)
Systolic blood pressure ≥ 150mmHg	810	442 (54.6%)		818	433 (52.9%)
Diagnosis of superimposed pre-eclampsia	675	100 (14.8%)		689	113 (16.4%)

None of the trials enrolled women with severe features of pre-eclampsia, however we acknowledge some participants may have had transiently high blood pressure readings prior to enrolment. This alone would not be an indication for delivery.(Brown et al., 2018) The difference in median time from randomisation to delivery between the two groups was 4.0 (95% CI 3.0 to 4.0) days. One-stage meta-analysis found that planned delivery from 34 weeks' gestation onwards significantly reduced the risk of major maternal morbidity (2.6% versus 4.4%; adjusted risk ratio [aRR] 0.59, 95% CI 0.36 to 0.98; p=0.041), compared to expectant management (Table 3-7). This direction of effect was also consistent across secondary maternal outcomes (Table 3-8), with a significant reduction in post-randomisation severe hypertension (risk ratio [RR] 0.80, 95% CI 0.73-0.87).

Table 3-7 Primary maternal outcome

	Planned delivery n=891	**Expectant management n=884**	**Effect size[a]**
Primary composite maternal outcome n (%)	23 (2.6%)	39 (4.4%)	aRR[b] 0.59 (0.36 to 0.98) p value=0.041
			Unadjusted Risk Difference (%) -1.8% (-3.5 to -0.1)
Individual components:			
Maternal death	0/891 (0.0%)	1/884 (0.1%)[c]	-
Eclampsia	3/891 (0.3%)	6/884 (0.7%)	RR 0.50 (0.12 to 1.98)
Stroke	0/559 (0.0%)	0/550 (0.0%)	-
Pulmonary oedema	1/798 (0.1%)	4/812 (0.5%)	RR 0.25 (0.03 to 2.27)
HELLP syndrome	12/891 (1.3%)	23/884 (2.6%)	RR 0.52 (0.26 to 1.03)
Renal insufficiency	4/768 (0.5%)	6/761 (0.8%)	RR 0.66 (0.19 to 2.33)
Placental abruption	4/768 (0.5%)	4/812 (0.5%)	RR 1.02 (0.26 to 4.05)

HELLP syndrome: Haemolysis, elevated liver enzymes, low platelet count syndrome.

[a]Effect sizes are risk ratios (95% confidence intervals) unless stated otherwise.

[b]Risk ratio adjusted (aRR) for study, gestational age at randomisation, singleton pregnancy, parity, and severity of hypertension at study entry. Presented as unadjusted (RR) where model failed to converge.

[c]This death was considered unrelated to trial allocation by the original study authors.

Table 3-8 Secondary maternal outcomes

Secondary maternal outcome	**Planned delivery n=891**	**Expectant management n=884**	**Effect size[a]**
Post-randomisation severe hypertension	396/780 (50.8%)	498/785 (63.4%)	RR[b] 0.80 (0.73 – 0.87)
Hepatic dysfunction	72/891 (8.1%)	96/884 (10.9%)	aRR 0.76 (0.57 to 1.01)
Thromboembolic disease	1/798 (0.1%)	1/812 (0.1%)	-
Severe postpartum haemorrhage	87/891 (9.8%)	98/884 (11.1%)	aRR 0.88 (0.68 to 1.15)
Pre-labour caesarean section	156/797 (19.6%)	180/811 (22.2%)	RR 0.88 (0.73 to 1.07)
Intensive care unit admission	9/589 (1.5%)	19/601 (3.2%)	aRR 0.48 (0.22 to 1.07)
Time from randomisation to delivery (days), Median (IQR)	2.0 (1.0 to 3.0) n=890[c]	6.0 (3.0 to 10.0) n=883[c]	Median difference (95% CI) 4.0 (3.0 to 4.0)

[a]Effect sizes are risk ratios (95% confidence intervals) unless stated otherwise. [b]Risk ratio adjusted (aRR) for study, gestational age at randomisation, singleton pregnancy, parity, and severity of hypertension at study entry. Presented as unadjusted risk ratios (RR) where model failed to converge. [c]One woman (from each group) excluded due to missing gestational age at delivery.

The primary composite perinatal outcome of perinatal mortality (stillbirth or early neonatal death) or morbidity was increased by planned delivery (20.9% versus 17.1%; aRR 1.22, 95% CI 1.01 to 1.47; p=0.040). This result was driven by a significant increase in neonatal respiratory disease (risk ratio [RR] 1.41, 95% CI 1.05-1.90) (Table 3-9). Neonatal unit admission was also increased amongst infants born to mothers in the planned delivery group (risk ratio [RR] 1.21, 95% CI 1.08-1.36) (Table 3-10). However, infants in the planned delivery group were less likely to be born small for gestational age, both <3rd centile (risk ratio [RR] 0.74, 95% CI 0.55-0.99) and <10th centile (risk ratio [RR] 0.82, 95% CI 0.70-0.97).

Table 3-9 Primary perinatal outcome

	Planned delivery n=936	**Expectant management n=935**	**Effect size[a]**
Composite primary perinatal outcome	196 (20.9%)	160 (17.1%)	aRR[b] 1.22 (1.01 to 1.47) p=0.040
			Unadjusted Risk difference (%) 3.83 (0.17 to 7.48)
Individual components:	**Planned delivery**	**Expectant management**	**RR**
Stillbirth	0/936 (0.0%)	0/935 (0.0%)	-
Neonatal death	1/936 (0.1%)	0/935 (0.0%)	RR 1.00 (1.00 to 1.00)
Respiratory disease	95/936 (10.1%)	66/935 (7.1%)	RR 1.41 (1.05 to 1.90)
Central nervous system complications	11/936 (1.2%)	4/935 (0.4%)	RR 2.65 (0.90 to 7.83)
Neonatal sepsis	3/489 (0.6%)	2/502 (0.4%)	RR 1.54 (0.26 to 9.20)
Necrotising enterocolitis	3/936 (0.3%)	0/935 (0.0%)	RR 1.00 (1.00 to 1.00)
Hypoglycaemia	86/692 (12.4%)	86/708 (12.1%)	RR 1.03 (0.77 to 1.37)
Jaundice	19/612 (3.1%)	13/625 (2.1%)	RR 1.56 (0.78 to 3.11)

[a]Effect sizes are risk ratios (95% confidence intervals) unless stated otherwise. [b]Risk ratio adjusted (aRR) for study, gestational age at randomisation, singleton pregnancy, parity, and severity of hypertension at study entry. Presented as unadjusted risk ratio (RR) where model failed to converge.

As expected, given the nature of the intervention, there was an adjusted mean difference of -0.61 weeks in gestational age at delivery between infants in the planned delivery and expectant management groups and an adjusted mean difference of -127.28 g in birthweight between the two groups (Table 3-10). There was no significant difference in vaginal delivery between planned delivery and expectant management groups. The observed difference in the primary perinatal outcome between allocated groups was largely driven by a difference in respiratory distress syndrome, seen mainly in infants from trials conducted earlier in the time period (the HYPITAT II trial between 2009 and 2013, and the Deliver or Deliberate trial between 2002 and 2008).

Table 3-10 Secondary perinatal outcomes

Secondary perinatal outcome	**Planned delivery n=936**	**Expectant management n=935**	**Adjusted mean difference (CI)**
Gestational age at delivery (weeks; mean (SD))	36.2 (1.4) n=934	36.9 (1.5) n=934	-0.61 (-0.67 to -0.55
Birthweight (grams; mean (SD))	2561 (563.7) n=934	2681 (615.0) n=934	-127.28 (-171.0 to -83.5)
Birthweight centile (mean (SD))	41.0 (30.8) n=934	40.4 (33.2) n=933	-0.42 (-3.14 to 2.29)
			Effect size[a]
Small for gestational age (<10th centile)	198/934 (21.2%)	241/933 (25.8%)	RR[b] 0.82 (0.70 to 0.97)
Small for gestational age (<3rd centile)	73/934 (7.8%)	99/993 (10.6%)	RR 0.74 (0.55 to 0.99)
Neonatal unit admission	395/831 (47.5%)	336/858 (39.2%)	RR 1.21 (1.08 to 1.36)
Neonatal intensive care unit admission	56/926 (6.0%)	43/930 (4.6%)	aRR 1.20 (0.83 to 1.74)
5-minute Apgar score <7	30/936 (3.2%)	25/935 (2.7%)	aRR 1.20 (0.71 to 2.01)
Umbilical artery pH <7.05	17/926 (1.8%)	19/930 (2.0%)	aRR 0.85 (0.45 to 1.61)
Vaginal delivery	377/713 (52.9%)	349/702 (49.7%)	RR 1.06 (0.96 to 1.18)

[a]Effect sizes are risk ratios (95% confidence intervals) unless stated otherwise. [b]Risk ratio adjusted (aRR) for study, gestational age at randomisation, singleton pregnancy, parity, and severity of hypertension at study entry. Presented as unadjusted risk ratio (RR) where model failed to converge.

Individual components of the respiratory disease composite outcome by study are shown in Table 3-11. Overall, there were small numbers of central nervous system complications (individual components of this composite outcome by study are shown in Table 3-12), with babies from the earlier HYPITAT II and GRIT trials (conducted between 1993 and 2001) contributing the majority of cases.

Table 3-11 Perinatal respiratory disease

	HYPITAT n=246		HYPITAT II n=454		DIGITAT n=45		Deliver or Deliberate n=165		GRIT n=15		PHOENIX n=946	
	PD[a] n=123	EM[a] n=123	PD n=221	EM n=223	PD n=18	EM n=27	PD n=93	EM n=72	PD n=10	EM n=5	PD n=471	EM n=475
Respiratory disease (composite)	**1**	**1**	**14**	**3**	**1**	**0**	**18**	**10**	**1**	**0**	**60**	**52**
Individual components:												
Respiratory distress syndrome	0	1	14	3	0	0	10	6	-	-	-	-
Need for respiratory support	1	0	-	-	1	0	12	6	1	0	40	41
Bronchopulmonary dysplasia	-	-	-	-	-	-	0	0	-	-	-	-
Neonatal unit admission for respiratory disease	-	-	-	-	-	-	-	-	-	-	47	39

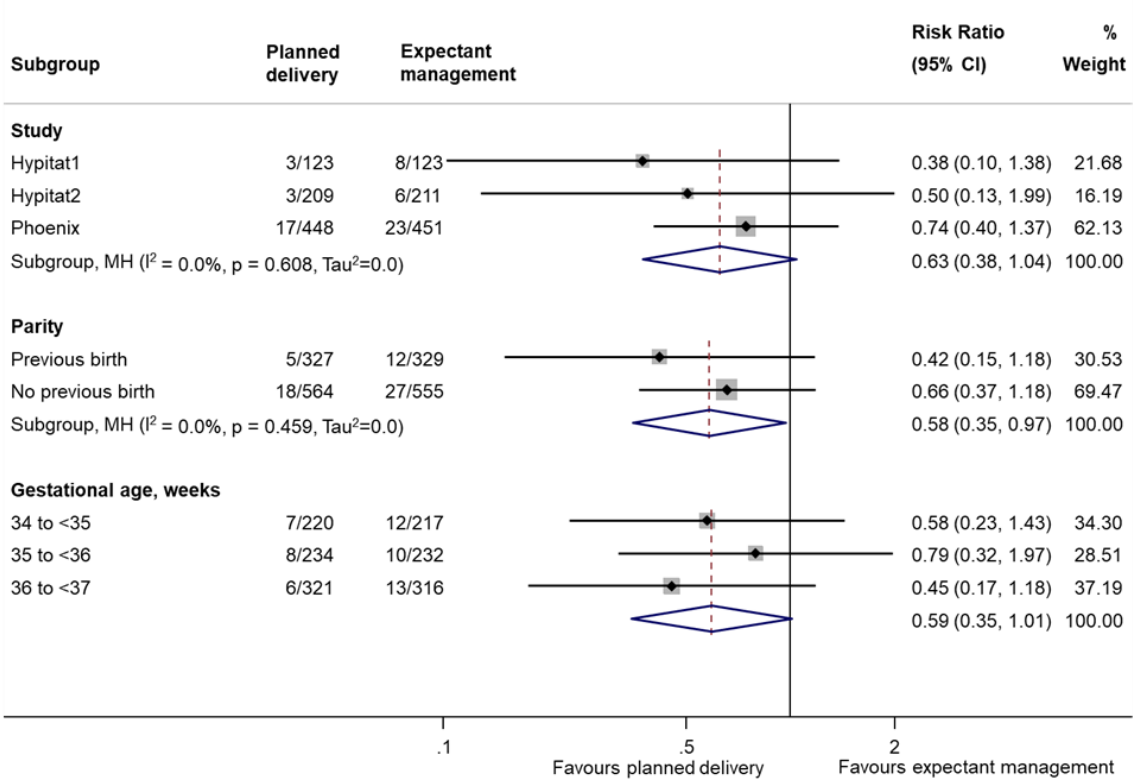
[a]PD denotes planned delivery group; EM denotes expectant management group. Dash (-) indicates outcome not collected by study.

Table 3-12 Perinatal central nervous system complications

	HYPITAT n=246		HYPITAT II n=454		DIGITAT n=45		Deliver or Deliberate n=165		GRIT n=15		PHOENIX n=946	
	PD[a] n=123	EM[a] n=123	PD n=221	EM n=223	PD n=18	EM n=27	PD n=93	EM n=72	PD n=10	EM n=5	PD n=471	EM n=475
Central nervous system complications (composite)	**0**	**1**	**6**	**3**	**0**	**0**	**0**	**0**	**3**	**0**	**2**	**0**
Individual components:												
Cerebral infarction	-	-	-	-	-	-	-	-	-	-	-	-
Hypoxic ischaemic encephalopathy	-	-	0	0	-	-	-	-	-	-	0	0
Intracerebral haemorrhage	-	-	-	-	-	-	-	-	-	-	-	-
Intraventricular haemorrhage	0	0	2	0	0	0	0	0	3	0	2	0
Convulsions	0	1	2	1	0	0	-	-	0	0	0	0
Periventricular leukomalacia	0	0	4	2	0	0	-	-	-	-	0	0

[a]PD denotes planned delivery group; EM denotes expectant management group. Dash (-) indicates outcome not collected by study.

Subgroup analyses (Figures 3-4 and 3-5) were consistent with the main results. Higher degrees of heterogeneity were seen when analysed by study, and by twin or singleton pregnancy. Subgroup analysis was only undertaken if there were 10 or more events in each subgroup which meant that the overall effect by study was different to that reported for the overall IPD meta-analysis, due to exclusion of certain trials from the subgroup analysis.

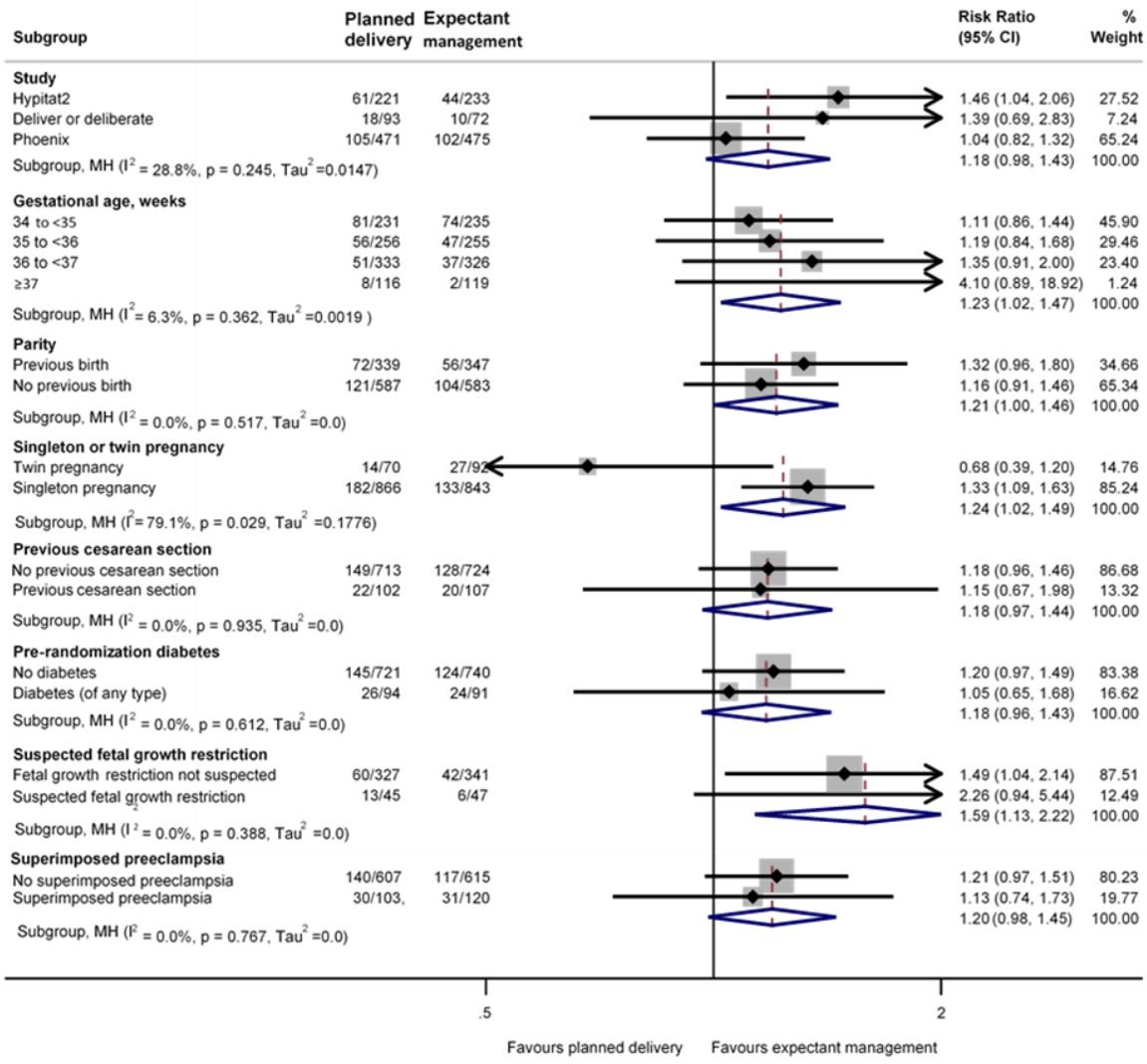


Weights and between subgroup heterogeneity tests are from the Mantel-Haenszel model. Pre-specified subgroup analysis was only performed if ≥10 events in each subgroup, and sub-groups without analysis for this reason are shown in Table 3-13.

Figure 3-4 Primary maternal outcome - subgroup analysis

Table 3-13 Primary maternal outcome in excluded subgroups (descriptive only)

Subgroup	Planned delivery	Expectant management
Study		
DIGITAT	0/18	1/27
Deliver or deliberate	0/93	1/72
GRIT	No maternal data	No maternal data
Gestational age at randomisation		
Gestational age ≥ 37 weeks	2/119	4/119
Singleton or twin pregnancy		
Twin pregnancy	1/35	1/46
Singleton pregnancy	22/856	38/838
Previous caesarean section		
No previous caesarean section	22/681	35/684
Previous caesarean section	1/99	2/101
Pre-randomisation diabetes		
No diabetes	22/686	33/697
Diabetes (of any type)	1/94	4/88
Suspected fetal growth restriction		
Fetal growth restriction not suspected	20/683	37/685
Suspected fetal growth restriction	3/115	1/127
Superimposed pre-eclampsia		
No superimposed pre-eclampsia	18/575	29/576
Superimposed pre-eclampsia	2/100	1/113



Weights and between subgroup heterogeneity tests are from the Mantel-Haenszel model. Pre-specified subgroup analysis was only performed if ≥10 events in each subgroup, and sub-groups without analysis for this reason are shown in Table 3-14.

Figure 3-5 Primary perinatal outcome - subgroup analysis (unadjusted)

Table 3-14 Primary perinatal outcome in excluded subgroups (descriptive only)

Subgroup	Planned delivery	Expectant management
Study		
HYPITAT	5/123	2/123
DIGITAT	4/18	2/27
GRIT	3/10	0/5

A summary of findings table and numbers need to treat and harm are presented in Tables 3-15 and 3-16.

3.5.4.1. Summary of findings

Planned delivery compared with expectant management for women with late preterm pre-eclampsia without severe features

Population: Pregnant women with a confirmed diagnosis of pre-eclampsia from 34 weeks' gestation onwards, not requiring immediate delivery

Setting: Multicentre trials across different high income countries in Europe and USA.

Intervention: Planned delivery within 48 hours of randomisation

Comparison: Usual care – expectant management

Table 3-15 Summary of findings

Outcomes		Relative effect (95% CI)	Number of participants (studies)
Maternal[a]			
Eclampsia		RR 0.50 (0.12 to 1.98)	1,775 (5 studies)
HELLP syndrome		RR 0.52 (0.26 to 1.03)	1,775 (5 studies)
Renal insufficiency		RR 0.66 (0.19 to 2.33)	1,529 (4 studies)
Placental abruption		RR 1.02 (0.26 to 4.05)	1,610 (4 studies)
Perinatal[a]			
Respiratory disease		RR 1.41 (1.05 to 1.90)	1,871 (6 studies)
Hypoglycaemia		RR 1.03 (0.77 to 1.37)	1,400 (2 studies)
Jaundice		RR 1.56 (0.78 to 3.11)	1,237 (3 studies)

HELLP syndrome: Hemolysis, elevated liver enzymes, low platelet count syndrome.

[a]Outcomes selected as most prevalent

Table 3-16 Numbers needed to treat and harm

Outcome	Number needed to treat/harm (95% CI)
Primary maternal	NNT 54.6 (28.3 to 816)
Primary perinatal	NNH 26.1 (13.5 to 363.5)

3.6. Comment

3.6.1. Principal findings

In this IPD meta-analysis, we show that planned early delivery from 34 weeks' gestation in women with pre-eclampsia significantly reduces adverse maternal outcomes, and the number of infants born small for gestational age. This was balanced against an increase in the composite perinatal outcome driven by short-term neonatal respiratory morbidity; there was no significant impact of gestational age on this primary outcome. These results indicate a clinically important maternal benefit, and in particular a reduction in severe hypertension and HELLP syndrome, among women allocated to planned delivery. Importantly the intervention did not increase the risk of caesarean section. Information on medical co-morbidities was not consistently available across all studies. However, other than singleton/twin pregnancy subgroup analysis for the primary perinatal outcome, there was no significant test of interaction for any pre-enrolment characteristics, such that we could not pre-define a particular group of pregnant women in whom the impact of the intervention might be different. The majority of participants included in this analysis were classified as White European, which should be taken into account when considering the generalisability of these findings to other populations.

The difference in incidence of respiratory disease between management groups was mainly seen amongst infants born to women from two trials, namely HYPITAT II (Broekhuijsen et al., 2015) and Deliver or Deliberate,(Owens et al., 2014) conducted earlier in the time period considered for this meta-analysis. In HYPITAT II, only 8.6% of women randomised to planned delivery received antenatal corticosteroids. Steroid use was not reported in the Deliver or Deliberate trial, though planned delivery took place within 12 hours of randomisation leaving little time for optimal steroid administration. By comparison, 65% of women in the PHOENIX Trial (Chappell, Brocklehurst, et al., 2019) allocated to planned delivery received antenatal corticosteroids; this likely influences the much lower incidence of adverse respiratory outcomes among infants in this trial, with no difference between the two management groups. Although we acknowledge that our analysis was not

specifically powered to address this question, it is likely that the difference in administration of steroids observed between different time epochs and trial settings explains our perinatal findings. This suggests that appropriately timed antenatal corticosteroid administration mitigates the short-term risk of respiratory complications for infants of women with pre-eclampsia, as previously demonstrated by a large systematic review.(McGoldrick et al., 2020) Antenatal corticosteroids have also been shown to reduce infant intraventricular haemorrhage,(McGoldrick et al., 2020) a rare outcome in infants at this late preterm gestation, providing further potential benefit in ameliorating the risk of central nervous system complications at this gestational age. Although some authors have raised concerns over the association between maternal antenatal corticosteroid treatment and childhood behavioural disorders in term-born children (based on a population-based study (Raikkonen et al., 2020)), the most recent Cochrane systematic review of randomised controlled trials reported that antenatal corticosteroids probably lead to a reduction in developmental delay in childhood (RR 0.51, 95% CI 0.27 to 0.97).(McGoldrick et al., 2020)

The rates of other serious neonatal complications, such as sepsis and necrotising enterocolitis, were low, as expected in this population. The relatively high rates of neonatal admission across both groups highlights the additional care this high-risk population of infants may require, irrespective of timing of delivery. In addition, infants born to mothers in the expectant management group were significantly more likely to be born small for gestational age. As low birthweight is a risk factor for long-term neurodevelopmental delay,(Figueras et al., 2008; van Wyk et al., 2012) and has been shown to be a more important predictor of long-term infant outcomes than gestational age at delivery,(Zwertbroek et al., 2020) avoidance of ongoing growth restriction may influence management choices. Use of ultrasound to accurately evaluate gestational age and presence of growth restriction should therefore be an integral part of assessment of a woman with pre-eclampsia. Whilst the average difference between the two groups was four days, the third quartile was ten days. It remains difficult to identify which women (and infants) are most

likely to require delivery within the following seven days, using clinical risk factor or biomarker prognostication,(Duhig et al., 2021) but for a progressive and unpredictable condition such as pre-eclampsia, this degree of pregnancy prolongation could be associated with a biologically plausible and clinically relevant difference in fetal growth restriction and neonatal outcomes. An increased awareness that expectant management increases the risk of a small for gestational age infant, most likely by perpetuating growth restriction within an adverse intrauterine environment, may lower the threshold for considering planned delivery from 34 weeks onwards. These findings raise interesting questions regarding the influence of expectant management on fetal growth restriction and the impact this may have on the infant, which should be addressed by future research.

3.6.2. Comparison with existing literature

In the USA, current guidelines recommend planned early delivery in women with late preterm pre-eclampsia with severe features,(The American College of Obstetricians and Gynecologists, 2019) but advise expectant management in women without severe features up to 37 weeks' gestation. The guidelines acknowledge that this latter recommendation is based on limited and inconsistent evidence.(The American College of Obstetricians and Gynecologists, 2020) Current UK (National Institute for Health and Care Excellence, 2019) and international (Brown et al., 2018) guidelines provide similar recommendations, but again note the uncertainty in clinical practice around thresholds for intervention and the limited evidence base. Many reviews, including a recent Cochrane review, have therefore called for evidence focusing on optimal timing of delivery in different types of pregnancy hypertensive disease. Our findings confirm clear maternal benefit associated with planned early delivery in women with pre-eclampsia from 34 weeks' gestation onwards, and provide greater understanding of perinatal benefits and risks, including factors (such as antenatal steroid use) that mitigate these. Our analysis extends the current evidence base and quantifies the benefit-risk balance specific to women with pre-eclampsia in the late preterm period. The important lack of increased risk in operative delivery is in keeping with other recent clinical studies comparing induction of labour with expectant management;(Grobman et

al., 2018; Mishanina et al., 2014; Roland et al., 2017) women and clinicians may perceive similar rates of vaginal delivery in both groups as important to their decision-making. The perinatal results are consistent with the interpretation by a systematic review evaluating planned early delivery for suspected fetal compromise which highlighted an increased short-term risk of respiratory complications and neonatal unit admission.(Stock et al., 2016) However, the varying use of antenatal corticosteroids across the different trials included in our analysis should be considered when interpreting these results. Planned sub-group analysis showed that there was no difference in the primary perinatal outcome in the most recent trial,(Chappell, Brocklehurst, et al., 2019) where the majority of women allocated to planned delivery received antenatal corticosteroids. Given that the universal administration of antenatal corticosteroids is not routinely recommended for women considered at risk of late preterm birth,(Norman et al., 2021) demonstrating benefit in certain clinical scenarios, such as planned delivery for pre-eclampsia, may guide clinical practice. Furthermore, we have demonstrated an increased risk of being born small for gestational age associated with expectant management, a finding consistent with similar studies, which is known to be associated with longer-term impaired neurodevelopmental outcomes.(Figueras et al., 2008; van Wyk et al., 2012) In addition to this, based on the largest and most recent trial in this population,(Chappell, Brocklehurst, et al., 2019) clinicians and women should be aware that with expectant management, there is an average prolongation of pregnancy of around three days only, with 74% progressing to severe pre-eclampsia (compared to 64% with planned delivery) and 55% requiring expedited delivery before 37 weeks' gestation. The high proportion of women who were delivered early is in keeping with an expectant management strategy and highlights the rapidly progressive nature of pre-eclampsia, often resulting in a constellation of maternal and fetal complications.

Data from this IPD meta-analysis (which included the trial discussed above) supported this finding with a difference in median time from randomisation to delivery of only 4 days between the two management groups. This study therefore

strengthens current evidence supporting a policy of considering planned early delivery for maternal benefit in late preterm pre-eclampsia. Planned delivery has been shown to be cost saving in the UK National Health Service setting compared to expectant management (£1,478 per woman), when total maternal and infant costs were considered, but the decision-making should reflect clinical and health economic factors together.

3.6.3. Strengths and Limitations

Following guidance on the use of IPD meta-analysis,(Tierney et al., 2015) we did not adopt an overly restrictive approach when selecting trials for inclusion, and this study is therefore strengthened by the inclusion of several large, well-conducted randomised clinical trials, the majority of which were assessed as being at low risk of bias. For most outcomes, heterogeneity between studies was low, although some important differences have been highlighted above. Furthermore, the use of a one-stage IPD meta-analysis approach allows the relative influence of multiple trial and participant characteristics on any intervention effect to be considered simultaneously.(Tierney et al., 2015) We had full access to trial data and were able to include all eligible participants for the large majority of studies. We were able to include complete data for most of our outcomes of interest, but we were limited by differences in outcome reporting between trials such that data were not available for every variable. This low missingness for the majority of variables and broad consistency between trials means that we have confidence in our results.
Limitations include changes in clinical practice during the time period of the trials included such that external factors (such as uptake of antenatal corticosteroid use) may impact directly on the main outcomes. Certain perinatal outcomes, such as bronchopulmonary dysplasia, cerebral infarction, and intra-cerebral haemorrhage were not collected across a large proportion of included studies, likely due to the rarity of these outcomes and the availability of more objective measures. Ideally, all trials should include longer-term follow-up of the women and infants, but retention within a study can be challenging, and expensive to undertake. We were not able to report indications for delivery as this information was not consistently available across the included trials. However, given the randomised nature of the data we

would not expect significant differences between the two management groups at baseline. The PHOENIX Trial reported indications for delivery for both management groups. In the planned delivery group, 99% of women had allocation to planned delivery arm as their recorded indication for delivery, consistent with trial procedures. By comparison, women in the expectant management group were delivered more frequently for both maternal and fetal indications, with over 50% requiring expedited delivery.

3.6.4. Clinical implications

Delivery is already known to improve maternal outcomes in pre-eclampsia. However, this review quantifies the effect, specific to gestation, on outcomes, and addresses the balance between maternal and fetal effects. We also address the question specifically in women who have pre-eclampsia without severe features. By synthesising and presenting the available data on this topic, we aim to provide as much information as possible on the balance of risks and benefits associated with each management strategy, so that women and their caregivers can make fully informed decisions. For clinicians who already have a low threshold for planned delivery in women with late preterm pre-eclampsia, this meta-analysis provides new evidence that could support this approach. Other clinicians may consider that although maternal benefit of planned delivery is clear, there is a trade-off with short-term perinatal morbidity. However, this may be ameliorated by judicial use of antenatal corticosteroids.

3.7. Conclusions

This meta-analysis of individual participant data from six randomised controlled trials synthesises the available evidence pertaining to timing of delivery in late preterm pre-eclampsia. We have clearly demonstrated that planned delivery in women with pre-eclampsia from 34 weeks onwards provides maternal benefit with no increased risk of operative delivery, compared to expectant management. Planned delivery reduces the likelihood of infants being born small for gestational age but increases short-term respiratory morbidity. The administration of antenatal corticosteroids reduces this risk, such that perinatal morbidity was no different

between the groups in the most recent trial; the potential benefits of antenatal corticosteroids should be discussed with women undergoing late preterm delivery. Further research is needed to identify optimal methods of determining which women and infants are at greatest risk of adverse outcomes, enabling stratification of surveillance and targeted intervention. A similar need for accurate prognostic strategies has been identified for planning delivery in pregnancies with suspected fetal compromise (Stock et al., 2016) and preterm prelabour rupture of membranes (Bond et al., 2017) as the challenges are common across these scenarios. Longer-term infant outcome data (including infants born with and without growth restriction) from large randomised controlled trials are also needed, as outcomes cannot be extrapolated from population-level databases comparing delivery at preterm gestations with term gestations in healthy pregnancies. There is also a need to establish the most clinically meaningful neonatal outcomes to measure when conducting pre-eclampsia trials, particularly those focused on timing of delivery. The impact of the intervention is likely to be very different in low-resource settings, where the majority of maternal and perinatal disease burden associated with pre-eclampsia lies.(Duley, 2009) As antenatal stillbirth is much more common in these settings,(Blencowe et al., 2016; Nathan, Seed, Hezelgrave, De Greeff, Lawley, Anthony, et al., 2018) it is possible that early delivery in women with pre-eclampsia in low and middle income countries may reduce not just adverse maternal outcomes, but fetal and perinatal deaths associated with severe maternal disease. However, this must also be balanced against the resource constraints in these environments. A multi-centre randomised controlled trial evaluating this is currently underway,(Beardmore-Gray et al., 2020) and may shed further light on this clinical dilemma in a different context. Our findings provide further information to guide women and clinicians in a high income setting, who must consider the balance of benefits and risks associated with planned delivery for women and their infants with late preterm pre-eclampsia. In line with recent recommendations,(National Institute for Health Research, 2022) we recommend that clinicians discuss the trade-off associated with earlier delivery (better for maternal outcomes but with increased admissions to the neonatal unit) with

women, fully supporting them to understand their options and consider both management strategies.

Chapter 4 Two-year follow-up of infant and maternal outcomes after planned early delivery or expectant management for late preterm pre-eclampsia (PHOENIX): a randomised controlled trial

This chapter matches the published paper, incorporating all relevant supplementary material, except when specified as an appendix.

4.1. Abstract

Objective

We evaluated the best time to initiate delivery in late preterm pre-eclampsia in order to optimise long-term infant and maternal outcomes.

Design

Parallel-group, non-masked, randomised controlled trial.

Setting

46 UK maternity units.

Population

Women with pre-eclampsia between 34^{+0} and 36^{+6} weeks' gestation, without severe disease, were randomised to planned delivery or expectant management.

Primary long-term outcome

Infant neurodevelopmental outcome at two years of age, using the PARCA-R (Parent Report of Children's Abilities-Revised) composite score.

Results

Between 29 Sept 2014, and 10 Dec 2018, 901 women were enrolled in the trial, with 450 allocated to planned delivery and 451 to expectant management. At two-year follow-up, the intention-to-treat analysis population included 276 women (290 infants) allocated to planned delivery and 251 women (256 infants) to expectant management. The mean composite standardised PARCA-R scores were 89.5

(standard deviation (SD) 18.2) in the planned delivery group and 91.9 (SD 18.4) in the expectant management group, with an adjusted mean difference of -2.4 (95% CI -5.4 to 0.5) points.

Conclusion

In infants of women with late preterm pre-eclampsia, average neurodevelopmental assessment at two years lies within the normal range, regardless of whether planned delivery or expectant management is pursued. Because of lower than anticipated follow-up, there was limited power to demonstrate these scores were not different, but the small between-group difference in PARCA-R scores is unlikely to be clinically important.

4.2. Introduction

Pre-eclampsia complicates 2–3% of pregnancies in high income settings (Roberts et al., 2011) and is a leading cause of iatrogenic preterm birth.(Duley, 2009) It is a multisystem disorder characterised by placental and maternal vascular dysfunction and associated with severe complications for both mother and infant.(Chappell et al., 2021) Potential adverse consequences include maternal and perinatal death, maternal stroke, renal and hepatic injury, and fetal growth restriction. Current management of pre-eclampsia in most high income settings involves close monitoring of the maternal and fetal condition with delivery recommended at 37 weeks or sooner, if there is evidence of severe maternal or fetal compromise.(Brown et al., 2018; National Institute for Health and Care Excellence, 2019) At 37 weeks' gestation, previous trials have shown that initiation of delivery benefits the woman without any additional perinatal risk.(Cluver et al., 2017)

In women with pre-eclampsia between 34^{+0} to 36^{+6} weeks, without severe features of the disease necessitating delivery, there is less evidence to guide optimal timing of birth.(Cluver et al., 2017) At this gestation, any maternal or perinatal benefit offered by early delivery must be balanced against the potential short- and long-term impacts of late prematurity to the infant. The PHOENIX Trial showed that a policy of routine planned early delivery between 34^{+0} to 36^{+6} weeks significantly

reduces short-term adverse maternal outcomes.(Chappell, Brocklehurst, et al., 2019) This was accompanied by an increase in neonatal unit admissions, but indicators of short-term neonatal morbidity were similar between groups. Before making firm recommendations to guide clinical practice based upon these findings, it is important to fully evaluate the impact of planned delivery in this group on longer-term infant outcomes. Planned delivery may improve neurodevelopmental outcomes as the disease process itself will be stopped, limiting ongoing placental dysfunction associated with fetal growth restriction and other morbidities. However, the consequences of the intervention (planned delivery resulting in an earlier gestational age by three to five days compared to expectant management) could also adversely impact neurodevelopmental outcomes. Thus, there remains a clinical dilemma about the best time to plan delivery, in order to optimise short- and long-term infant outcomes.

The aim of this follow-up study was to evaluate the primary infant outcomes of the PHOENIX Trial at two years, comparing neurodevelopmental outcomes for infants of women with late preterm pre-eclampsia randomised to planned early delivery or expectant management. Additionally, we evaluated the impact of the intervention on secondary maternal outcomes (health-related quality of life) and are separately reporting the health economic evaluation.

4.3. Methods

4.3.1. Study design and participants

The PHOENIX Trial was a parallel-group, non-masked, multicentre randomised controlled trial, across 46 UK maternity units. The published trial protocol (Chappell, Green, et al., 2019) and short-term co-primary outcomes (Chappell, Brocklehurst, et al., 2019) have described the detailed trial methodology, and therefore a brief summary is provided here. There were no substantial changes to the published study design, methods, or outcomes after the start of the trial. The trial was approved by the South Central-Hampshire B Research Ethics Committee (no13/SC/0645). We compared planned delivery to expectant management (usual

care) in pregnant women presenting with pre-eclampsia between 34^{+0} and 36^{+6} weeks' gestation, without severe features of the disease (which would necessitate immediate delivery), aged 18 years or older, with a singleton or dichorionic diamniotic twin pregnancy and at least one viable fetus; women with any other comorbidity or with a previous caesarean section or any fetal position were eligible. The only exclusion criterion to participation was clinician decision to initiate delivery within the subsequent 48 hours. After providing written informed consent, women were randomly assigned to planned delivery or expectant management via a secure web-based randomisation programme provided by MedSciNet. A (non-deterministic) minimisation algorithm including study centre, singleton or twin pregnancy, severity of hypertension in 48 hours before enrolment, parity, previous caesarean section, and gestational age at randomisation was used to ensure balance between groups. The intervention could not be masked from women, clinicians, or data collectors due to the nature of the intervention.

4.3.2. Interventions

Planned early delivery consisted of initiation of delivery within 48 hours of randomisation, to allow for administration of antenatal corticosteroids if deemed necessary by clinicians. Induction of labour was commenced according to local protocol, with caesarean section undertaken only if an additional obstetric indication was present. Expectant management consisted of usual care, with close monitoring of the maternal and fetal condition until either 37 completed weeks of pregnancy, or the development of severe features necessitating delivery.

4.3.3. Data collection

Baseline and short-term clinical outcome data were collected up until maternal and infant discharge from hospital and recorded on the web-based trial database. Long-term outcomes were assessed at six months post-delivery and again when the infant was two years of age. Questionnaires were posted to all woman at these time points (or a link sent electronically) and participants completed a paper copy, or an online version captured by the MedSciNet study database. Health resource use and

quality of life outcomes including the EQ-5D-5L questionnaire were also collected and are reported separately.

4.3.4. Outcomes

4.3.4.1. Infant

The primary long-term infant outcome was neurodevelopmental assessment at two years of age, using the PARCA-R (Parent Report of Children's Abilities-Revised) composite score.(Johnson, Bountziouka, Linsell, et al., 2019) Secondary long-term infant outcomes were the non-verbal and language PARCA-R subscale scores. The PARCA-R is a parent (or caregiver) completed questionnaire, taking 15 minutes to complete, which assesses non-verbal and language development. It is recommended by NICE (National Institute for Health and Care Excellence) as a practical and cost-effective method of identifying cognitive and language delay at 24 months in children born preterm.(National Institute for Health and Care Excellence, 2017) Raw scores from the non-verbal subscale (range 0-34) and language subscale (0-124) are summed to produce an overall composite score. Non-verbal PARCA-R scores were prorated if up to four subscale questions were missing. During the trial, the methodology to convert the overall composite score to an age- and sex-adjusted standard score and percentile rank relative to the norm was published,(Johnson, Bountziouka, Brocklehurst, et al., 2019) requiring the questionnaire to have been completed at two years corrected age (between 23 months and 16 days to 27 months and 15 days). A standardised score between 85 and 114 would indicate development in the normal range, with scores between 70 and 84 indicating mild delay, scores between 55 and 69 indicating moderate delay, and a score of 54 or less indicating severe delay.

4.3.4.2. Maternal

Secondary long-term maternal outcomes included quality of maternal physical and mental health using the validated SF-12v2 Health Survey, a short-form generic measure of health status with eight health-related domains.(Ware et al., 1996) Scores from each of the eight health concepts can be used to generate a physical

component summary scale score (PCS-12) and mental component summary scale score (MCS-12), both with a mean of 50 and a standard deviation of 10, with a higher score indicating better health. It has been validated in diverse populations, including women who are postpartum.(Emmanuel et al., 2012; Morrell et al., 2009; Norhayati et al., 2016; Vinturache et al., 2015)

For those participants who completed the long-term follow-up, we have additionally reported the co-primary short-term outcome (a composite of maternal morbidity of fullPIERS outcomes,(von Dadelszen et al., 2011) and recorded systolic blood pressure of at least 160mmHg post-randomisation) and the co-primary short-term perinatal outcome (a composite of neonatal deaths within seven days of delivery and perinatal deaths or neonatal unit admissions). Outcomes were selected before the development of a core outcome set for pre-eclampsia, which does not currently propose any long-term outcomes.(Duffy et al., 2020)

4.3.5. Sample size

An initial loss to follow-up rate of 20% assumed that long-term outcomes would be available for approximately 690 infants.(Chappell, Green, et al., 2019) This calculation was revised before follow-up was completed and analysis was undertaken, to take into account a higher than expected loss to follow-up rate of 40%. Based on this, it was anticipated that long-term outcomes would be available for approximately 568 infants in total (284 per group, assuming no difference in the loss to follow-up between groups). With a one-sided significance level of 2.5%, under a non-inferiority hypothesis, a sample size of 284 in each group achieves 88% power to detect a non-inferiority margin of difference in the mean PARCA-R score of no less than 4 points (one quarter of a standard deviation). A higher response rate would have enabled narrower confidence intervals and more certainty in our conclusions.

4.3.6. Statistical analysis

Demographics and clinical characteristics at baseline and short-term infant and maternal outcomes are reported using descriptive statistics. The primary inferences

for the two-year infant outcomes were based on a non-inferiority hypothesis testing framework in both the intention-to-treat (ITT) and the per-protocol (PP) analysis populations. The primary inferences for the six-month and two-year maternal outcomes were based on a superiority hypothesis testing framework in the intention-to-treat analysis population. All analyses used the expectant management group as the reference group. There were no interim analyses planned.

4.3.6.1. Infant outcomes

Due to the statistical analysis plan based on standardised scores, but with infant questionnaires being sent out at two years chronological age, a lower proportion than anticipated of PARCA-R questionnaires were completed during the time window for standardising (<23.5 and >27.5 months of age corrected for prematurity). To correct for this, multiple imputation by chained equations was used to impute the PARCA-R standardised scores for those infants (approximately 74% of responders). Imputation models included the raw PARCA-R scores, age corrected for prematurity, sex, minimisation factors, and any auxilary variables associated with the outcome or the missingness of the outcome. Imputation models were developed separately for each outcome and each population. Pooled estimates were obtained from linear regression models adjusted for minimisation factors as fixed effects and the correlation between multifetal pregnancies. Centre was not fitted as a random effect as planned due to model non-convergence. Pooled adjusted means, adjusted mean differences, and 95% confidence intervals are reported. The p-values for the composite score are reported only and are for one-sided 2.5% significance non-inferiority tests based on a margin of 4 standardised score points.

4.3.6.2. Maternal outcomes

Mixed-effect linear regression models adjusted for minimisation factors were fitted for the maternal outcomes (PCS-12 and MCS-12) with centre fitted as a random effect. The adjusted means, adjusted mean differences, 95% confidence intervals, and corresponding p-values are reported. The means and standard deviations for subdomains are unadjusted.

4.3.6.3. Subgroup analyses

Pre-specified subgroup analyses for the two-year infant outcomes were performed on the multiply imputed datasets for the composite PARCA-R score. Pooled estimates were obtained from the same linear regression models used for the primary analysis, containing an interaction term between the subgroup and study arm. Pooled adjusted means and 95% confidence intervals are reported.

4.3.6.4. Sensitivity analyses

Sensitivity analyses were performed on the two-year infant outcome excluding infants outside of the time window for standardisation. Mixed-effect linear regression models were fitted, adjusting for correlation between twins, minimisation factors as fixed effects, and centre as a random effect. The adjusted means, adjusted mean differences, and 95% confidence intervals are reported.

4.3.7. Role of the funding source

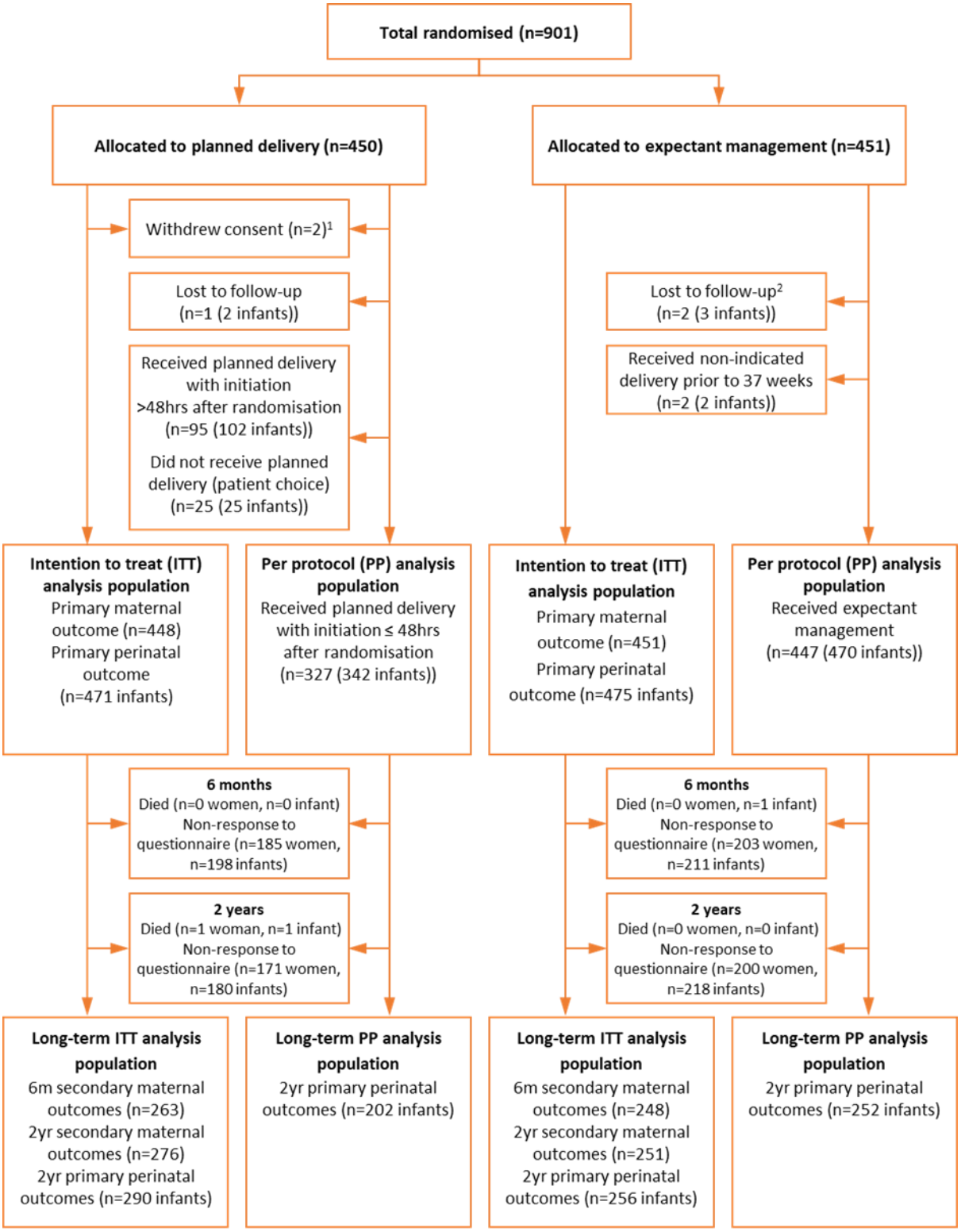
The study was funded by the NIHR Health Technology Assessment Programme (12/25/03) following external peer review, and with involvement of public representative panel members. The funder of the study had no role in study design, data collection, analysis, interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. The trial was prospectively registered with the ISRCTN registry ISRCTN01879376.

4.3.8. Patient and Public Involvement

We worked with representatives (including those with lived experience of pre-eclampsia) from Action on Pre-eclampsia (the patient support group) and Tommy's Charity (a national baby charity) to ensure that the voices of pregnant women (and their wider families) informed and influenced every stage of the research process. Full details on the methodology and outcomes of this are reported in the GRIPP2-SF checklist (Appendix 1) as part of the supplementary materials.

4.4. Results

Between 29 September 2014 and 10 December 2018, 901 women were enrolled in the trial, with 450 allocated to planned delivery and 451 allocated to expectant management (Figure 4-1). The intention-to-treat analysis population for short-term maternal and perinatal outcomes included 448 women (471 infants) allocated to planned delivery (as two of the allocated women withdrew consent) and 451 women (475 infants) allocated to expectant management. Follow-up for two-year assessment continued until 31 December 2020. At two-year follow-up, the long-term intention-to-treat analysis population included 290 infants (62%) and 276 women allocated to planned delivery and 256 infants (54%) and 251 women allocated to expectant management. There were no serious adverse events reported at long-term follow-up.



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. 1 woman in this group has documented delivery prior to 37 weeks (on electronic health records) but no further information available

Figure 4-1 CONSORT flow diagram of participants

4.4.1. Characteristics of women responding to follow-up

Baseline maternal and pregnancy characteristics of women responding at two years were broadly similar across the two randomised groups (Table 4-1). The median gestational age at randomisation in both groups was 36 weeks, and the prevalence of suspected growth restriction was similar (19.8% in planned delivery, 23.1% in expectant management). Study centre at randomisation of women responding at two years is shown in Appendix 2.

Table 4-1 Maternal demographic and pregnancy characteristics

Baseline characteristics	**Planned delivery (n=276)**	**Expectant management (n=251)**
Age at randomisation (years), mean (SD)	31.1 (5.7)	31.4 (6.1)
Ethnicity, n (%)		
White	200 (72.5)	189 (75.3)
Black	23 (8.3)	21 (8.4)
Asian	42 (15.2)	22 (8.8)
Other	11 (4.0)	19 (7.6)
Deprivation index quintile 5 (most deprived)*, n (%)	79 (30.6)	75 (31.0)
No previous pregnancies ≥24 weeks' gestation)**, n (%)	166 (60.1)	159 (63.3)
Previous caesarean section**, n (%)	40 (14.5)	43 (17.1)
History of pre-eclampsia, n (%)	50 (18.1)	47 (18.7)
Body mass index at booking (kg/m^2), mean (SD)	30 (7.6)	29.2 (6.7)
Smoking at booking, n (%)	16 (5.8)	16 (6.4)
Systolic BP at booking (mmHg), mean (SD)	119.0 (13.6)	119.5 (13.2)
Diastolic BP at booking (mmHg), mean (SD)	72.8 (10.0)	73.3 (10.21)
Pre-existing chronic hypersion, n (%)	29 (10.5)	33 (13.1)
Pre-existing chronic renal disease, n (%)	3 (1.1)	2 (0.8)
Pre-pregnancy diabetes, n (%)	15 (5.4)	14 (5.6)
Gestational diabetes, n (%)	36 (13.0)	21 (8.4)
Aspirin prescribed during pregnancy, n (%)	114 (41.3)	101 (40.2)
LMWH prescribed during pregnancy, n (%)	69 (25.0)	66 (26.3)
Characteristics at randomisation		
Gestational age at randomisation (weeks)**, median (IQR)	36 (35 to 36)	36 (35 to 36)
Singleton pregnancy**, n (%)	261 (94.6)	238 (94.8)
Highest systolic BP in previous 48hs (mmHg), mean (SD)	155 (14.8)	155.6 (16.1)

Highest diastolic BP in previous 48hs (mmHg), mean (SD)	95.8 (9.5)	95.8 (11.3)
Highest systolic BP in previous 48hs (mmHg)**, n (%)		
≤149	100 (36.2)	88 (35.1)
150-159	69 (25.0)	65 (25.9)
≥160	107 (38.8)	98 (39.0)
Urinary protein-creatinine ratio ≥30 (mg/mmol), n (%)	253 (91.7)	228 (90.8)
Urinary protein-creatinine ratio (mg/mmol), median (IQR)	88 (43 to 185)	87 (43 to 197)
Fetal growth restriction ultrasound in previous 2 weeks, n (%)	222 (80.4)	212 (84.5)
Suspected fetal growth restriction on ultrasound, n (%)	44 (19.8)	49 (23.1)
Inpatient at time of randomisation, n (%)	217 (78.6)	210 (83.7)

BP: blood pressure. LMWH: Low molecular weight heparin. *Deprivation quintiles calculated for participants in England only (not available for participants in Wales). **Minimisation factors used to ensure balance at randomisation.

In women who completed the two-year assessment, a higher proportion of infants in the planned delivery group had been delivered at 34 weeks' gestational age (17.2% vs. 11.7%), as expected with the trial intervention (Table 4-2) and had been admitted to the neonatal unit (40.3% vs. 35.5%), driven by admissions where the primary indication was listed as prematurity. However, a higher proportion of infants in the expectant management group were born small for gestational age (21.5% vs. 14.1% <10th centile; 5.1% vs. 2.8% <3rd centile), compared to those in the planned delivery group. Maternal mortality and morbidity were lower for responding women allocated to planned delivery, compared to those allocated to expectant management (65.2% vs. 75.5%) (Table 4-3).

Table 4-2 Short-term infant outcomes prior to hospital discharge home of responders at two-year assessment and non-responders

	Planned delivery	**Expectant mangement**		**Planned delivery**	**Expectant mangement**
	Responders (n=290)	**Responders (n=256)**		**Non-responders (n=181)**	**Non-responders (n=219)**
Gestational age at delivery (days), median (IQR)	253 (247, 257)	258 (251, 260)		251 (245, 257)	257 (252, 260)
34 weeks	50 (17.2)	30 (11.7)		39 (21.8)	17 (7.8)
35 weeks	88 (30.3)	42 (16.4)		51 (28.5)	34 (15.5)
36 weeks	96 (33.1)	70 (27.3)		63 (35.2)	68 (31.1)
≥37 weeks	56 (19.3)	114 (44.5)		26 (14.5)	100 (45.7)
Missing	0	0		2	0
Mode of birth					
Spontaneous vaginal	101 (34.8)	71 (27.7)		68 (38.0)	68 (31.1)
Assisted vaginal	28 (9.7)	24 (9.4)		12 (6.7)	23 (10.5)
Caesarean section	161 (55.5)	161 (62.9)		99 (55.3)	128 (58.4)
Missing	0	0		2	0
Birth weight (g), median (IQR)	2430 (2112 to 2775)	2438 (2150 to 2820)		2390 (2006 to 2753)	2510 (2160 to 3078)
Missing	0	0		2	0
Birthweight centile, median (IQR)*	37 (17 to 60)	30 (12 to 56)		34 (15 to 65)	32 (15 to 67)
<10th centile, n(%)	41 (14.1)	55 (21.5)		33 (18.4)	40 (18.3)
<3rd centile, n(%)	8 (2.8)	13 (5.1)		12 (6.7)	14 (6.4)
Missing	0	0		2	0
Apgar score at 5 minutes after birth, median (IQR)	10 (9 to 10)	10 (9 to 10)		9 (9 to 10)	10 (9 to 10)
Missing	0	0		2	0
Umbilical arterial pH collected	175 (60.3)	147 (57.4)		106 (58.6)	119 (54.3)
Median (IQR)	7 (7 to 7)	7 (7 to 7)		7 (7 to 7)	7 (7 to 7)
Missing	0	2		2	1
Admission to neonatal unit	117 (40.3)	91 (35.5)		79 (44.1)	68 (31.1)
Missing	0	0		2	0
Principal recorded indication for					

neonatal unit admission, n (%)					
Prematurity	50 (42.7)	25 (27.5)		33 (41.8)	15 (22.1)
Respiratory disease	31 (26.5)	18 (19.8)		16 (20.3)	23 (33.8)
Cardiovascular disease	0 (0.0)	1 (1.1)		0 (0.0)	0 (0.0)
Failed oximetry testing	0 (0.0)	1 (1.1)		0 (0.0)	0 (0.0)
Jaundice	6 (5.1)	7 (7.7)		6 (7.6)	4 (5.9)
Hypoglycaemia	8 (6.8)	20 (22.0)		13 (16.5)	11 (16.2)
Convulsions suspected/confirmed	0 (0.0)	0 (0.0)		1 (1.3)	0 (0.0)
Poor condition at birth	1 (0.9)	1 (1.1)		1 (1.3)	2 (2.9)
Infection suspected/confirmed	9 (7.7)	7 (7.7)		0 (0.0)	5 (7.4)
IUGR/ SGA	3 (2.6)	5 (5.5)		5 (6.3)	5 (7.4)
Poor feeding or weight loss	4 (3.4)	2 (2.2)		0 (0.0)	0 (0.0)
Congenital anomaly suspected/confirmed	2 (1.7)	0 (0.0)		0 (0.0)	0 (0.0)
Maternal admission/emergency	1 (0.9)	1 (1.1)		0 (0.0)	1 (1.5)
Monitoring	2 (1.7)	3 (3.3)		2 (2.5)	2 (2.9)
Continuing care	0 (0.0)	0 (0.0)		2 (2.5)	0 (0.0)
Need for respiratory support, n (%)	28 (9.7)	21 (8.2)		17 (9.5)	27 (12.3)
Missing	0	0		2	0
Need for supplementary oxygen prior to discharge, n (%)	40 (13.8)	22 (8.6)		20 (11.2)	27 (12.3)
Missing	0	0		2	0
Number of days supplemental oxygen required, median (IQR)	1 (1 to 2)	2 (1 to 3)		2 (1 to 3)	1 (1 to 4)
Range (min to max)	(0 to 7)	(1 to 11)		(1 to 12)	(0 to 31)
Missing	250	234		161	192
Total time in neonatal unit (days), median (IQR)	5 (3 to 8)	4 (3 to 8)		5 (3 to 8)	4 (2 to 7)

Number admitted for at least 1 day, n (%)	109 (37.6)	87 (34.0)		72 (39.8)	66 (30.1)
Category of care during neonatal unit stay (separation of baby from mother)					
Intensive care, n (%)	12 (4.1)	9 (3.6)		15 (8.4)	10 (4.6)
Days, median (IQR)	1 (1 to 2)	2 (1 to 2)		2 (1 to 3)	4 (3 to 5)
High dependency care, n (%)	33 (11.4)	24 (9.5)		18 (10.1)	9 (4.1)
Days, median (IQR)	1 (1 to 3)	2 (1 to 5)		2 (1 to 2)	2 (1 to 4)
Special care (carer not present), n (%)	101 (34.8)	80 (31.7)		67 (37.4)	63 (29.0)
Days, median (IQR)	5 (2 to 9)	7 (2 to 11)		6 (3 to 11)	5 (2 to 10)
Category of care during other postnatal stay (baby alongside mother)					
Transitional care (special care with carer present), n (%)	24 (8.3)	8 (3.2)		16 (8.9)	8 (3.7)
Days, median (IQR)	6 (2 to 9)	5 (4 to 6)		4 (2 to 6)	5 (4 to 6)
Postnatal care, n(%)	216 (74.5)	204 (81.0)		134 (74.9)	180 (82.9)
Days, median (IQR)	3 (2 to 5)	3 (2 to 4)		3 (2 to 4)	3 (2 to 5)

IUGR: intrauterine growth restriction. SGA: Small for gestational age. *Birthweight centile calculated using the Stata add-in function zanthro using the British 1990 Growth Reference (reanalysed 2009).

Table 4-3 Short-term maternal outcomes prior to hospital discharge home of responders at two-year assessment and non-responders

	Planned delivery	**Expectant mangement**		**Planned delivery**	**Expectant mangement**
	Responders (n=276)	**Responders (n=251)**		**Non-responders (n=172)**	**Non-responders (n=200)**
Maternal co-primary outcome (maternal morbidity composite outcome or systolic blood pressure ≥160 mmHg post-randomisation, n (%)	180 (65.2)	188 (75.5)		109 (63.7)	150 (75.0)
Missing	0	2		1	0
Maternal morbidity composite outcome, n (%)	42 (15.2)	47 (18.9)		26 (15.2)	43 (21.5)
Missing	0	2		1	0
Systolic blood pressure ≥160 mmHg post-randomisation, n (%)	165 (59.8)	178 (71.8)		102 (59.6)	135 (67.5)
Missing	0	3		1	0
Progression to severe pre-eclampsia, n (%)	180 (65.2)	185 (74.3)		107 (62.6)	149 (74.5)
Missing	0	2		1	0
Placental abruption, n (%)	3 (1.1)	3 (1.2)		1 (0.6)	1 (0.5)
Missing	0	2		1	0
Antihypertensive medication before delivery, n (%)	239 (86.6)	225 (89.6)		142 (83.0)	180 (90.0)
Missing	0	0		1	0
Onset of labour, n (%)					
Spontaneous	1 (0.4)	9 (3.6)		1 (0.6)	10 (5.0)
Induced	190 (68.8)	157 (62.8)		114 (66.7)	118 (59.0)
Pre-labour caesarean section	84 (30.4)	83 (33.2)		56 (32.7)	69 (34.5)
PROM and augmentation	1 (0.4)	1 (0.4)		0 (0.0)	3 (1.5)
Missing	0	1		1	0
Indication for delivery (non-exclusive)					
Spontaneous labour <37 weeks gestation	1 (0.4)	9 (3.6)		1 (0.6)	10 (5.0)
Trial allocation to planned delivery arm	275 (99.6)	0 (0.0)		170 (99.4)	0 (0.0)

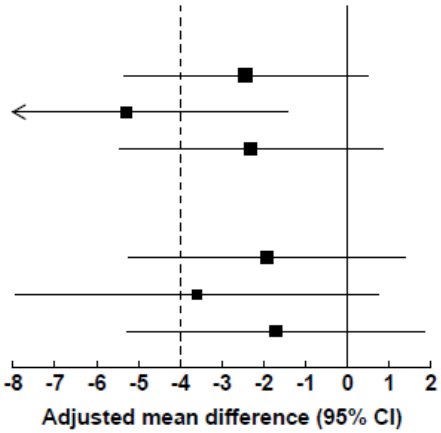
Reaching 37 weeks' gestation	5 (1.8)	115 (46.2)		3 (1.8)	73 (36.5)
Uncontrolled maternal hypertension	16 (5.8)	66 (26.5)		10 (5.8)	45 (22.5)
Maternal haematological abnormality	1 (0.4)	8 (3.2)		2 (1.2)	15 (7.5)
Maternal biochemical abnormality	10 (3.6)	28 (11.2)		9 (5.3)	29 (14.5)
Fetal compromise on ultrasound scan	8 (2.9)	20 (8.0)		8 (4.7)	30 (15.0)
Fetal compromise on cardiotocography	18 (6.5)	37 (14.9)		15 (8.8)	27 (13.5)
Severe maternal symptoms	5 (1.8)	27 (10.8)		4 (2.3)	21 (10.5)
Other (with none of the above)	0 (0.0)	2 (0.8)		0 (0.0)	0 (0.0)
Missing	0	2		1	0
Maternal complications between randomisation and discharge					
Confirmed thromboembolic disease, n (%)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)
Confirmed sepsis (positive blood or urine cultures), n (%)	0 (0.0)	4 (1.6)		2 (1.2)	2 (1.0)

PROM: Pre-labour rupture of membranes

4.4.2. Primary infant outcomes

Of the 546 infant questionnaires returned, and using imputed standardised scores for those who had a raw PARCA-R score outside of the age window for standardisation, the adjusted mean difference comparing planned delivery to expectant management for the composite PARCA-R score at two-years follow-up was -2.4 (89.5 vs. 91.9, 95% confidence interval [CI]: -5.4 to 0.5, non-inferiority p=0.1) in the intention-to-treat population (Figure 4-2). The confidence interval encompassed the 4-point margin and so we could not conclude non-inferiority. Similar results were seen in the per-protocol population: -1.9 (90.2 vs. 92.1, 95% CI: -5.2 to 1.4, non-inferiority p=0.1) (Figure 4-2). The adjusted means for both groups and populations were within the range of 85–114 (indicating normal neurodevelopment), as were the adjusted means for the subscale scores (Figure 4-2).

Outcome	Adjusted means (SD) Planned delivery	Expectant Management	Adjusted mean difference (95% CI)	Non-inferiority p-value
Intention-to-treat population	n=290	n=256		
Composite	89.47 (18.18)	91.90 (18.42)	-2.43 (-5.36, 0.50)	0.147
Non-verbal subscale	95.99 (24.05)	101.27 (22.95)	-5.28 (-9.14,-1.42)	
Language subscale	88.39 (18.77)	90.70 (19.77)	-2.31 (-5.44, 0.83)	
Per-protocol population	n=202	n=252		
Composite	90.15 (18.30)	92.07 (18.67)	-1.92 (-5.23, 1.39)	0.109
Non-verbal subscale	97.67 (24.32)	101.28 (22.94)	-3.61 (-7.94, 0.73)	
Language subscale	89.15 (19.25)	90.87 (20.53)	-1.72 (-5.27, 1.83)	



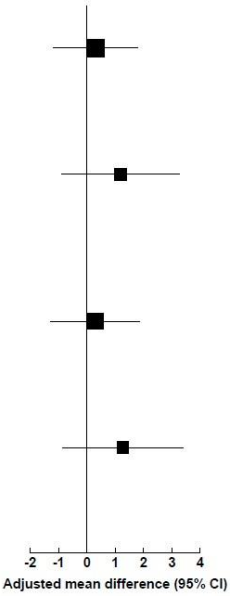
Standardised scores were imputed for responders who had raw PARCA-R scores outside of the time window for standardisation. The p-values are for one-sided 2.5% significance non-inferiority tests based on a margin of 4 standardised score points. The dashed line shows the non-inferiority margin. The solid line shows the line of no difference. SD: standard deviation; CI: confidence interval.

Figure 4-2 Primary infant long-term outcome non-inferiority comparison: Imputed Standardised Parent Report of Children's Abilities Revised (PARCA-R) at two years follow-up.

4.4.3. Maternal outcomes

For maternal outcomes, there were no significant differences in physical component summary scale score (PCS-12) and mental component summary scale score (MCS-12) between women allocated to planned delivery and expectant management arms at 2 years (PCS-12 mean difference 0.29 (CI -1.29 to 1.87), MCS-12 mean difference 1.27 (CI -0.86 to 3.40]) (Figure 4-3). Similar summary scores and subdomain scores were seen at six months and two years indicating no evidence of a change of health status during follow-up.

	Planned delivery		Expectant management		Adjusted mean difference (95% CI)	P-value
	N	Mean (SD)	N	Mean (SD)		
Six months	N=263		N=248			
PCS-12	246	51.4 (9.9)	236	51.1 (9.8)	0.31 (-1.17, 1.79)	0.682
Physical functioning	256	87.8 (23.3)	241	87.8 (24.2)		
Role-Physical	256	87.9 (22.0)	244	86.5 (21.6)		
Bodily Pain	259	87.1 (21.8)	245	88.0 (19.3)		
General Health	262	65.0 (21.5)	244	66.1 (21.8)		
MCS-12	246	48.0 (11.9)	236	46.8 (11.9)	1.19 (-0.89, 3.27)	0.263
Energy/fatigue	261	56.5 (23.5)	244	57.2 (24.8)		
Social Functioning	261	83.4 (24.4)	242	79.3 (25.1)		
Role-Emotional	255	84.9 (23.5)	244	83.8 (23.9)		
Mental Health	258	70.4 (20.1)	243	69.2 (21.4)		
Two years	N=276		N=251			
PCS-12	264	50.9 (10.6)	240	50.6 (10.6)	0.29 (-1.29, 1.87)	0.717
Physical functioning	266	86.5 (22.8)	243	85.7 (25.1)		
Role-Physical	268	84.4 (23.4)	244	84.5 (22.8)		
Bodily Pain	271	85.3 (23.2)	246	86.0 (23.3)		
General Health	271	63.3 (23.0)	246	62.2 (24.4)		
MCS-12	264	46.1 (13.0)	240	44.9 (13.0)	1.27 (-0.86, 3.40)	0.242
Energy/fatigue	271	55.4 (25.0)	243	53.2 (26.0)		
Social Functioning	271	80.6 (25.1)	245	78.7 (28.2)		
Role-Emotional	269	82.5 (23.2)	245	80.5 (25.1)		
Mental Health	269	66.4 (21.0)	243	64.3 (22.2)		



The solid line shows the line of no difference. PCS-12: Physical Component Summary Scale Score; MCS-12: Mental Component Summary Scale Score; SD: standard deviation; CI: confidence interval

Figure 4-3 Maternal secondary long-term outcomes: SF-12 Health Survey Summary Scale at six months and two years follow-up

4.4.4. Sensitivity analyses (infant outcomes)

Sensitivity analyses including infants assessed within 23.5 to 27.5 months corrected age only did not alter the findings (Tables 4-4 and 4-5).

Table 4-4 Ages and response times at two years for infants

	Planned delivery (n=290)	**Expectant management (n=256)**
Chronological age at two year assessment (days)		
Mean (SD)	734 (41.5)	734 (41.6)
Median (IQR)	723 (710 to 745)	721 (706 to 746)
Age corrected for prematurity at two year assessment (days)		
Mean (SD)	706 (42.2)	709 (42.8)
Median (IQR)	696 (680 to 716)	697 (684 to 723)
Age corrected for prematurity time window for completing two year assessment		
17 months 15 days - 18 months 14 days	1 (0.3)	0 (0.0)
20 months 15 days - 21 months 14 days	1 (0.3)	1 (0.4)
21 months 15 days - 22 months 14 days	90 (31.0)	72 (28.1)
22 months 15 days - 23 months 14 days	125 (43.1)	101 (39.5)
23 months 15 days - 24 months 14 days	**33 (11.4)**	**44 (17.2)**
24 months 15 days - 25 months 14 days	**17 (5.9)**	**18 (7.0)**
25 months 15 days - 26 months 14 days	**11 (3.8)**	**10 (3.9)**
26 months 15 days - 27 months 14 days	**7 (2.4)**	**7 (2.7)**
27 months 15 days - 28 months 14 days	3 (1.0)	0 (0.0)
28 months 15 days - 29 months 14 days	1 (0.3)	1 (0.4)
29 months 15 days - 30 months 14 days	1 (0.3)	2 (0.8)

Standardised PARCA-R scores are calculated within the 23.5 to 27.5 months' time window for an infant's age corrected for prematurity at two years.

Table 4-5 Sensitivity analysis of primary infant long-term outcome non-inferiority comparison excluding infants assessed outside 23.5 to 27.5 months corrected age: Standardised Parent Report of Children's Abilities Revised (PARCA-R) at two years follow-up

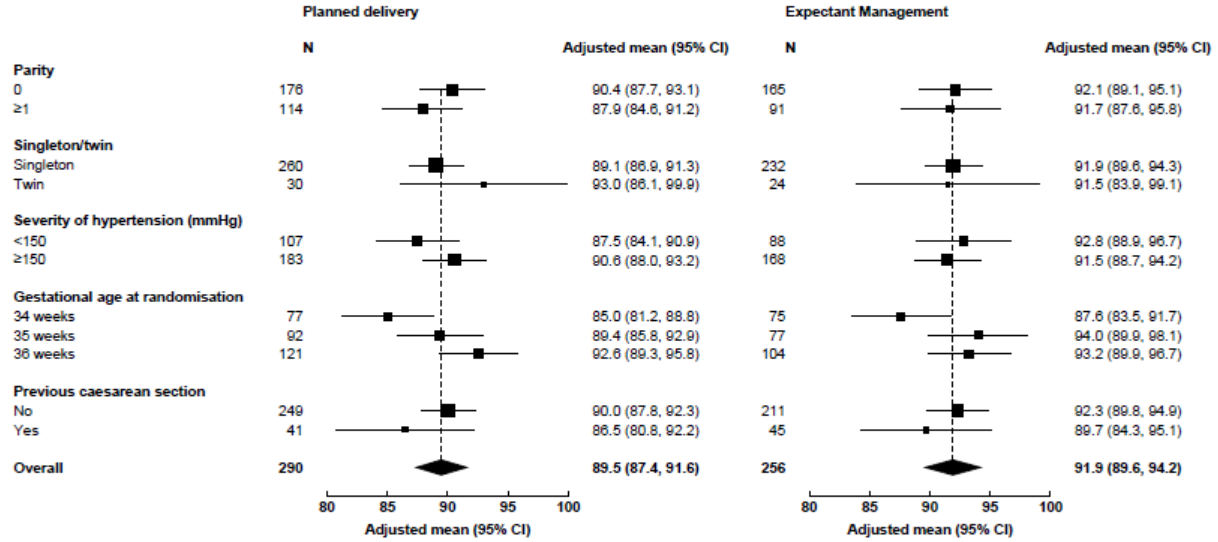
	Planned delivery		**Expectant management**		**Adjusted mean difference* (95% CI)**
	n	**Adjusted mean (SD)**	**n**	**Adjusted mean (SD)**	
Intention-to-treat	(n=68)		(n=79)		
Composite Score	66	90.9 (16.4)	72	95.2 (16.4)	-4.25 (-9.76,1.27)
Non-verbal subscale score	67	95.9 (19.1)	77	103.3 (19.1)	-7.39 (-13.69,-1.10)
Language subscale score	67	90.2 (17.1)	74	93.9 (17.1)	-3.63 (-9.32,2.05)
Per-protocol	(n=50)		(n=78)		
Composite Score	48	90.7 (16.0)	72	94.8 (16.0)	-4.05 (-9.92,1.83)
Non-verbal subscale score	49	96.8 (19.6)	76	103.2 (19.6)	-6.36 (-13.24,0.52)
Language subscale score	49	89.9 (16.8)	74	93.5 (16.7)	-3.57 (-9.66,2.52)

SD: standard deviation; CI: confidence interval

4.4.5. Sub-group analyses (infant outcomes)

Pre-specified analyses for the PARCA-R composite score did not suggest important clinical differences by sub-groups for both intention-to-treat and per-protocol populations (Figure 4-4).

A: Intention-to-treat analysis



B: Per-protocol analysis

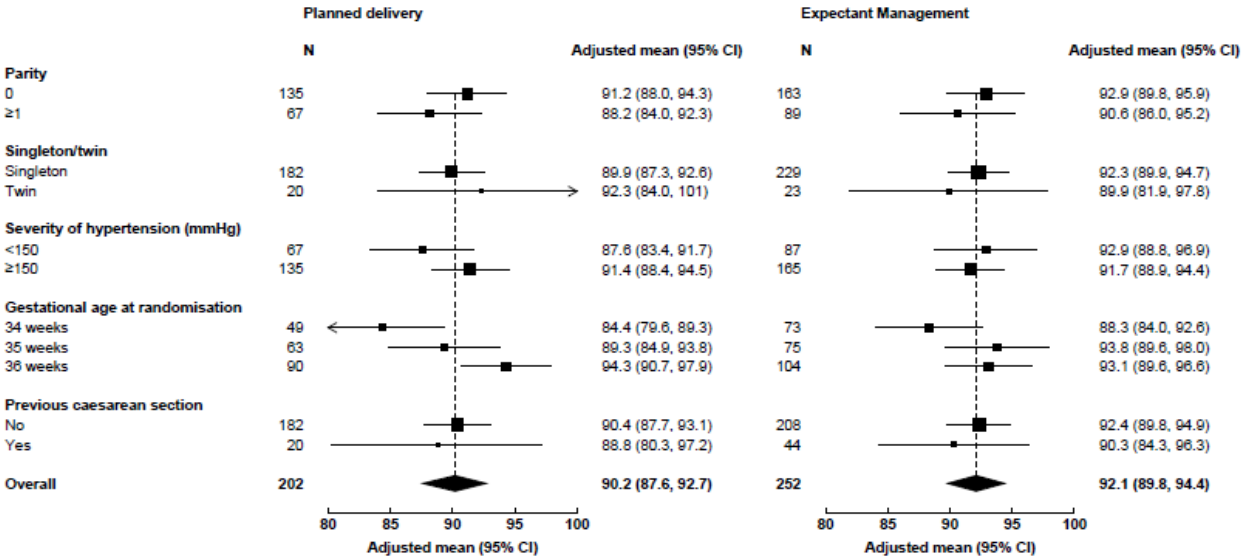


Figure 4-4 Subgroup analyses of the primary infant long-term outcome non-inferiority comparison: Imputed Standardised Parent Report of Children's Abilities Revised (PARCA-R) at two years

4.4.6. Women responding to follow-up

The baseline characteristics of responders and non-responders at two-year assessment are described in Tables 4-6 and 4-7. Maternal responders at two-year

follow-up were more likely to be white, have a low deprivation index score, and less likely to currently smoke at the time of initial antenatal visit compared to those who did not respond. Short-term infant outcomes between responders and non-responders at two-year follow-up were similar with regards to neonatal unit admission, birth of a small for gestational age (<10th centile) infant and short-term morbidity (Table 4-2).

Table 4-6 Maternal baseline characteristics of responders at two-year assessment and non-responders

	Planned delivery	**Expectant mangement**		**Planned delivery**	**Expectant mangement**
	Responders (n=276)	**Responders (n=251)**		**Non-responders (n=172)**	**Non-responders (n=200)**
Age at randomisation (years), mean (SD)	31.1 (5.74)	31.4 (6.10)		29.7 (7.25)	30.1 (6.50)
Ethnicity, n (%)					
White	200 (44.6)	189 (41.9)		113 (25.2)	122 (27.1)
Mixed	7 (1.6)	11 (2.4)		3 (0.7)	12 (2.7)
Asian	42 (9.4)	22 (4.9)		18 (4.0)	28 (6.2)
Chinese	0 (0.0)	1 (0.2)		0 (0.0)	0 (0.0)
Black	23 (5.1)	21 (4.7)		35 (7.8)	31 (6.9)
Other	3 (0.7)	6 (1.3)		2 (0.4)	7 (1.6)
Unknown	1 (0.2)	1 (0.2)		1 (0.2)	0 (0.0)
Deprivation Index quintile, n (%)*					
England					
1 (Least deprived)	35 (13.6)	20 (8.3)		6 (3.8)	5 (2.7)
2	37 (14.3)	33 (13.6)		16 (10.0)	20 (10.8)
3	45 (17.4)	48 (19.8)		19 (11.9)	24 (12.9)
4	64 (24.8)	63 (26.0)		42 (26.3)	55 (29.6)
5 (Most deprived)	79 (30.6)	75 (31.0)		82 (51.3)	85 (45.7)
Missing	0	1		0	0
Wales unavailable	16	11		7	11
Parity (previous pregnancies ≥24 weeks' gestation)*, n (%)					
0	166 (37.1)	159 (35.3)		88 (19.6)	101 (22.4)
1	66 (14.7)	52 (11.5)		38 (8.5)	51 (11.3)
2	30 (6.7)	28 (6.2)		19 (4.2)	24 (5.3)

>2	14 (3.1)	12 (2.7)		27 (6.0)	24 (5.3)
Previous caesarean section**, n (%)	40 (14.5)	43 (17.1)		38 (22.1)	35 (17.5)
History of pre-eclampsia, n (%)	50 (18.1)	47 (18.7)		36 (20.9)	45 (22.5)
Body mass index at booking (kg/m^2), mean (SD)	30 (7.59)	29.2 (6.70)		29.5 (6.84)	30.5 (7.79)
Smoking status at booking, n (%)					
Never smoked	214 (77.5)	179 (71.3)		113 (65.7)	130 (65.0)
Quit before booking	42 (15.2)	52 (20.7)		22 (12.8)	34 (17.0)
Smoking at booking	16 (5.8)	16 (6.4)		37 (21.5)	34 (17.0)
Unknown	4 (1.4)	4 (1.6)		0 (0.0)	2 (1.0)
Blood pressure at booking (mmHg)					
Systolic BP at booking (mmHg), mean (SD)	119.0 (13.6)	119.5 (13.2)		118.3 (15.6)	119.7 (14.3)
Diastolic BP at booking (mmHg), mean (SD)	72.8 (10.0)	73.3 (10.2)		72.6 (10.6)	73.6 (10.6)
Pre-existing chronic hypertension, n (%)	29 (10.5)	33 (13.1)		22 (12.8)	20 (10.0)
Pre-existing chronic renal disease, n (%)	3 (1.1)	2 (0.8)		3 (1.7)	2 (1.0)
Pre-pregnancy diabetes, n (%)	15 (5.4)	14 (5.6)		10 (5.8)	14 (7.0)
Gestational diabetes, n (%)	36 (13.0)	21 (8.4)		26 (15.1)	32 (16.0)
Aspirin prescribed during pregnancy, n (%)	114 (41.3)	101 (40.2)		56 (32.6)	88 (44.0)
LMWH prescribed during pregnancy, n (%)	69 (25.0)	66 (26.3)		56 (32.6)	51 (25.5)

BP: blood pressure. LMWH: Low molecular weight heparin. *Deprivation quintiles calculated for participants in England only (not available for participants in Wales).
**Minimisation factors used to ensure balance at randomisation.

Table 4-7 Maternal characteristics at randomisation of responders at two-year assessment and non-responders

	Planned delivery	**Expectant mangement**		**Planned delivery**	**Expectant mangement**
	Responders (n=276)	**Responders (n=251)**		**Non-responders (n=172)**	**Non-responders (n=200)**
Gestational age at randomisation* (weeks), median (IQR)	36 (35 to 36)	36 (35 to 36)		35 (35 to 36)	36 (35 to 36)
34^{+0} to 34^{+6}	73 (26.4)	72 (28.7)		58 (33.7)	63 (31.5)
35^{+0} to 35^{+6}	85 (30.8)	73 (29.1)		52 (30.2)	59 (29.5)
36^{+0} to 36^{+6}	118 (42.8)	106 (42.2)		62 (36.0)	78 (39.0)
Number of live fetuses at study entry*					
1	261 (94.6)	238 (94.8)		164 (95.3)	189 (94.5)
2	15 (5.4)	13 (5.2)		8 (4.7)	11 (5.5)
Highest systolic BP in previous 48hs (mmHg), mean (SD)	155 (14.8)	155.6 (16.1)		153.6 (13.9)	154.6 (14.5)
Highest systolic BP in previous 48hs (mmHg)**, n (%)					
≤149	100 (36.2)	88 (35.1)		63 (36.6)	75 (37.5)
150-159	69 (25.0)	65 (25.9)		52 (30.2)	58 (29.0)
≥160	107 (38.8)	98 (39.0)		57 (33.1)	67 (33.5)
Highest diastolic BP in previous 48hs (mmHg), mean (SD)	95.8 (9.5)	95.8 (11.3)		95.6 (9.7)	95.9 (8.4)
Urinary protein-creatinine ratio (after 20 weeks) ≥30 (mg/mol), n (%)	253 (91.7)	228 (90.8)		152 (88.4)	179 (89.5)
Most recent urinary protein-creatinine ratio (mg/mmol), median (IQR)	88 (43 to 185)	87 (43 to 197)		78 (42 to 188)	70 (40 to 152)
Missing	0	0		0	1
Fetal growth restriction ultrasound in previous two weeks, n (%)	222 (80.4)	212 (84.5)		144 (83.7)	163 (81.5)
Suspected fetal growth restriction	44 (19.8)	49 (23.1)		35 (24.3)	36 (22.1)
Bishop score at study entry					

<2	1 (0.4)	0 (0.0)		1 (0.6)	2 (1.0)
2 to 6	4 (1.4)	2 (0.8)		3 (1.7)	2 (1.0)
≥6	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)
Cervix not assessed	271 (98.2)	249 (99.2)		168 (97.7)	196 (98.0)
In-patient at time of trial entry	217 (78.6)	210 (83.7)		145 (84.3)	161 (80.5)

*Minimisation factors used to ensure balance at randomisation.

4.5. Discussion

4.5.1. Main findings

The mean standardised PARCA-R scores at two years for infants of mothers with late preterm pre-eclampsia randomised to planned early delivery or expectant management indicate that, on average, their neurodevelopment is within the normal range for both trial groups.(Johnson, Bountziouka, Linsell, et al., 2019) This provides reassuring data on the long-term outcomes of infants born late preterm, even when the additional complication of pre-eclampsia is present. Subgroup analysis by gestational age at randomisation showed that mean standardised scores remained within the normal range even at earlier gestations (34^{+0} to 34^{+6} weeks), where disease severity may also be worse. The confidence intervals for the adjusted mean difference of -2.4 points in the planned delivery arm compared to the expectant management arm were above the pre-specified threshold to be able to definitively conclude non-inferiority of planned delivery. However, a mean difference of two points is unlikely to be clinically important at two years of age. No evidence of a difference was found in quality of maternal mental or physical health at six months and two years between the two groups. Mean SF12-v2 scores were consistent with those previously reported in similar populations.(Norhayati et al., 2016; Vinturache et al., 2015)

4.5.2. Strengths and Limitations

This is the largest trial to date evaluating planned early delivery in late preterm pre-eclampsia and provides important information for clinicians and women faced with this clinical scenario. Long-term follow-up was identified as an important component of the research question and every possible strategy was employed to

maximise the number of respondents. Similar trials attempting long-term follow-up of women and their infants report response rates varying from 14% to 61%,(The INFANT Collaborative Group, 2017; Zwertbroek et al., 2019; Zwertbroek et al., 2020) demonstrating the challenge associated with this objective, particularly when the population of interest is generally healthy and not under routine clinical follow-up (in contrast to infants born very preterm). Thus, the inclusion of long-term outcome data is a strength of this study and is likely to be of interest to women with pre-eclampsia and their clinicians.

The trial was limited by higher loss to follow-up than expected, meaning that the extent and direction of bias in outcomes (between responders and non-responders) is uncertain. This was compounded by PARCA-R questionnaires being sent out at chronological rather than corrected age, meaning that imputation was needed to convert some raw scores into standardised scores. With a smaller sample size than expected for the long-term primary outcome, and the consequently reduced precision of our estimates, our ability to draw firm conclusions is limited. A longer follow-up period (e.g. up to five years) would have enabled us to provide further evidence on long-term infant outcomes using measures such as intelligence quotient (IQ), and to identify whether any of the differences observed between the two groups resulted in any clinical meaningful differences at school age, but this runs the risk of greater attrition and increased expense.

4.5.3. Interpretation

Infants born late preterm have been found to be at increased risk of neurodevelopmental delay and poor school performance in the long-term,(Johnson et al., 2015; Johnson et al., 2018; Moster et al., 2008; Murray et al., 2017; Petrini et al., 2009) but this is typically compared to healthy infants born at term.(Teune et al., 2011) Pre-eclampsia is a disease state associated with fetal growth restriction,(Burton et al., 2019) which itself is demonstrated to adversely impact childhood development.(Figueras et al., 2008; van Wyk et al., 2012) In this scenario, it is possible that earlier delivery might improve long-term neonatal outcomes, compared to expectant management which is associated with increased risk of

growth restriction.(Boers et al., 2010; Chappell, Brocklehurst, et al., 2019; Zwertbroek et al., 2019) In support of this, previous trials have shown that whilst infants of women with hypertensive disorders of pregnancy who underwent planned early delivery between 34^{+0} to 36^{+6} weeks had a small difference in neurodevelopmental outcomes at two years of age,(Zwertbroek et al., 2019) these differences did not persist at five-year follow-up.(Zwertbroek et al., 2020) At five years of age, other factors such as maternal education and birthweight appear to be more important predictors of long-term infant development than near-term gestational age at delivery.(Johnson et al., 2015; Zwertbroek et al., 2020)

This trial provides strong evidence that planned early delivery reduces immediate adverse maternal outcomes with no evidence of differences in self-reported quality of maternal physical and mental health at six months and two years between the intervention groups. However, the impact upon the infant remains unclear. Planned early delivery may increase the need for neonatal unit admission in the short-term, primarily for an indication of prematurity (i.e. a routine admission without objective morbidity) but there is no evidence that it increases short-term neonatal morbidity. At two years, mean PARCA-R scores for infants across both groups were within the normal range, which suggests no clinically important long-term harm to the infant, but as the confidence intervals for the mean difference between the groups crosses the pre-specified non-inferiority margin, uncertainty remains. Pre-eclampsia is an independent risk factor for adverse infant neurodevelopmental outcomes,(Ananth & Friedman, 2014; Habli et al., 2007; Johnson et al., 2015; Warshafsky et al., 2016) and mean PARCA-R scores in this trial were at the lower end of the normal range, consistent with previous studies. Infants in the planned early delivery group had lower PARCA-R scores compared to those in the expectant management group, but the mean difference of -2.4 points is unlikely to be clinically meaningful or to influence longer-term outcome such as school-performance, particularly once other important predictors such as socio-economic status are taken into account.(Johnson et al., 2015) In addition, the risks associated with late prematurity must be balanced against those with associated ongoing growth restriction.

Future research must focus on how best to communicate these findings to women and translate them into clinical practice. Choice of clinically meaningful neonatal outcomes, particularly for infants born to mothers with pre-eclampsia, remains a challenge and an area where further work and consensus building is needed.(Duffy et al., 2020) Furthermore, an intervention such as planned early delivery is likely to have a considerably different impact in different contexts where resources and disease burden are different. The majority of maternal and perinatal deaths associated with pre-eclampsia occur in low and middle income countries,(Say et al., 2014) which have markedly higher stillbirth rates (Nathan, Seed, Hezelgrave, De Greeff, Lawley, Conti-Ramsden, et al., 2018) than those reported in high income healthcare settings. A multi-centre randomised controlled trial evaluating the effect of planned delivery on adverse maternal outcomes and perinatal morbidity and mortality is currently underway.(Beardmore-Gray et al., 2020)

4.6. Conclusion

Our results show that in women with late preterm pre-eclampsia, average neurodevelopmental assessment of the infants at two years lies within the normal range, regardless of timing of delivery. The small between-group difference in PARCA-R scores is unlikely to be clinically important, but because of lower than anticipated follow-up, there was limited power to demonstrate these scores were not different. This follow-up provides further information for clinicians about the balance of risks of benefits of planned early delivery between 34^{+0} to 36^{+6} weeks to facilitate shared decision making.

Chapter 5 Planned early delivery for late preterm pre-eclampsia in a low and middle income setting: a feasibility study

This chapter matches the published paper, incorporating all relevant supplementary material, except when specified as an appendix.

5.1. Abstract

Background

Pre-eclampsia is a leading cause of maternal and perinatal mortality and morbidity globally. Planned delivery between 34^{+0} and 36^{+6} weeks may reduce adverse pregnancy outcomes but is yet to be evaluated in a low and middle income setting. Prior to designing a randomised controlled trial to evaluate this in India and Zambia, we carried out a six-month feasibility study in order to better understand the proposed trial environment and guide development of our intervention.

Methods

We used mixed methods to understand the disease burden and current management of pre-eclampsia at our proposed trial sites and explore the acceptability of the intervention. We undertook a case notes review of women with pre-eclampsia who delivered at the proposed trial sites over a 3-month period, alongside facilitating focus group discussions with women and partners, and conducting semi-structured interviews with healthcare providers. Descriptive statistics were used to analyse audit data. A thematic framework analysis was used for qualitative data.

Results

Case notes data (n=326) showed that in our settings, 19.5% (n=44) of women with pre-eclampsia delivering beyond 34 weeks experienced an adverse outcome. In women delivering between 34^{+0} and 36^{+6} weeks, there were similar proportions of antenatal stillbirths (n=3 [3.3%]) and neonatal deaths (n=3 [3.4%]); median infant birthweight was 2.2kg and 1.9kg in Zambia and India respectively. Lived experience of women and healthcare providers was an important facilitator to the proposed

intervention, highlighting the serious consequences of pre-eclampsia. A preference for spontaneous labour and limited neonatal resources were identified as potential barriers.

Conclusions

This study demonstrated a clear need to evaluate the intervention and highlighted several challenges relating to trial context that enabled us to adapt our protocol and design an acceptable intervention. Our study demonstrates the importance of assessing feasibility when developing complex interventions, particularly in a low-resource setting. Additionally, it provides a unique insight into the management of pre-eclampsia at our trial settings and an understanding of the knowledge, attitudes, and beliefs underpinning the acceptability of planned early delivery.

5.2. Background

The disproportionate burden of pre-eclampsia in low income (LIC) and lower-middle income countries (LMIC), particularly in Sub-Saharan Africa and South Asia, is well described.(Duley, 2009; Say et al., 2014; Shennan et al., 2017) Hypertensive disorders are the second biggest cause of maternal mortality worldwide,(Say et al., 2014) and pre-eclampsia itself is responsible for 76,000 maternal deaths and 500,000 perinatal deaths every year.(Poon et al., 2019) The vast majority of these (98%) occur in low and middle income countries.(Duley, 2009) Despite this, there is a lack of research into interventions which could be implemented in these regions in order to improve pregnancy outcomes. One such intervention, planned early delivery, has been shown to reduce adverse maternal outcomes in a high income setting,(Bernardes et al., 2019; Chappell, Brocklehurst, et al., 2019) but is yet to be evaluated in a LIC or LMIC. The proposed CRADLE-4 Trial aims to establish whether planned early delivery in women with late preterm pre-eclampsia (between 34^{+0} and 36^{+6} weeks' gestation) is effective in reducing adverse pregnancy outcomes in India and Zambia. To our knowledge, it will be the first trial to evaluate timing of delivery in late preterm pre-eclampsia in a LIC or LMIC. It is now widely recognised that conducting an assessment of feasibility is an essential step prior to the development and evaluation of a healthcare intervention as part of a larger-scale

clinical trial.(Bugge et al., 2013; Eldridge et al., 2016) We therefore designed this initial feasibility study in order to understand the contextual factors likely to influence trial implementation and assess the perceived barriers and facilitators to the intervention. The findings were used to directly inform the design of the main trial protocol. We anticipate that the results of this study would not just optimise delivery of the trial itself, but also improve the external validity of any significant trial findings such that they are generalisable to similar settings and practicable to implement in a real-world environment.

5.3. Methods

5.3.1. Aims and objectives

The overall aim of this study was to explore the feasibility of planned early delivery in women with pre-eclampsia (not requiring immediate delivery) between 34^{+0} and 36^{+6} weeks' gestation in order to inform the design of the intervention and the main trial protocol. By assessing feasibility, we aimed to explore areas of uncertainty surrounding the main trial design. Specific study objectives were to confirm the need for the proposed intervention, obtain estimates to help with sample size calculation, explore potential outcome measures, understand the resource limitations likely to impact upon overall study design, and to establish whether the proposed intervention would be acceptable to all stakeholders (pregnant women, their partners, and relevant healthcare providers). In order to meet these objectives, we set out to understand the disease burden associated with pre-eclampsia at the proposed trial sites, understand the current management of pregnancies complicated by pre-eclampsia at the proposed trial sites, and to explore the perceived risks and benefits of the intervention by women, their partners, and healthcare providers involved in the delivery of maternal and new-born healthcare.

Ethical approval was provided by King's College London Research Ethics Committee (LRS-18/19-8818), University of Zambia Research Ethics Committee (014-11-18),

and KLE Academy of Higher Education and Research Institutional Ethics Committee (KAHER/IEC/2019-20/D-2742).

5.3.2. Study design

CRADLE-4 Phase 1 study was designed as a mixed-methods (Pluye & Hong, 2014) feasibility study which took place over a six-month period from 1st January 2019 to 30th June 2019. We chose to include qualitative research methods, which have gained increasing recognition for their important contribution to feasibility studies and may be the most effective way of exploring key areas of uncertainty such as acceptability and local context.(O'Cathain et al., 2015) They are also increasingly used to address important questions about health and healthcare, particularly relevant in fields such as women's health where, for example, understanding women's experiences of childbirth is critical to the delivery of respectful maternity care.(Pope & Campbell, 2001) In this study, we used a parallel approach,(Creswell & Clark, 2017) whereby quantitative and qualitative data collection and analysis were conducted separately and simultaneously and brought together at the interpretation stage.(Ostlund et al., 2011) This is a pragmatic approach to integration for such datasets and allowed for qualitative data to complement and explain interesting findings from the quantitative data analysis.(Onwuegbuzie & Leech, 2005) Analysis and interpretation of these integrated data was therefore exploratory, reflecting guidance for mixed methods feasibility studies.(O'Cathain et al., 2015)

5.3.3. Study settings

The study was conducted across four of the proposed sites for the interventional phase of the trial in India and Zambia. These are tertiary level hospitals (providing Comprehensive Emergency Obstetric and Newborn Care) situated in urban environments:

- University Teaching Hospital, Lusaka, Zambia
- Ndola Teaching Hospital, Ndola, Zambia
- KLE Academy of Higher Education and Research's, J N Medical College Hospital, Belgaum, Karnataka, India

- S Nijalingappa Medical College and Hanagal Shri Kumareshwar Hospital and Research Centre, Bagalkot, Karnataka, India

An additional site, Chipata first level hospital, was also used to facilitate two of the focus group discussions in Lusaka, Zambia.

5.3.4. Case notes review

We undertook a retrospective case notes review of all women with pre-eclampsia who delivered at the study sites between January and March 2019. Following discussion with local site teams and initial site visits, and noting the high prevalence of pre-eclampsia and maternal morbidity in these settings, a three month period was deemed adequate to provide a reliable estimate of the number of women who would be potentially eligible for the main trial. A retrospective assessment of pre-eclampsia cases at these facilities over the preceding year did not indicate any meaningful seasonal variation that might influence these results. We also collected key maternal and infant outcomes to inform selection of primary and secondary outcomes and undertake a power calculation for the main trial. Women's data were included if they had been diagnosed with pre-eclampsia and delivered at one of the participating sites. Relevant clinical notes were identified using ward registers with a record of diagnosis (e.g. pre-eclampsia) at discharge. The corresponding neonatal files were then located in order to record neonatal outcomes. Data were collected directly from case records by trained research assistants at each site. Study data were collected and managed using Research Electronic Data Capture Tools (REDCap). Whilst every effort was made to directly enter data onto REDCap, where internet connectivity made this impossible, data were entered onto paper case report forms (CRFs) and then inputted onto REDCap. Information was collected on baseline demographics, current pregnancy details, methods of gestational age determination, use of pre-eclampsia diagnostic criteria, clinical management of pre-eclampsia, and gestation specific maternal and neonatal outcomes.

5.3.5. Focus group discussions

In order to assess acceptability of the intervention to women and their families, we facilitated separate focus group discussions for pregnant women and their male

partners (or closest supporting relative such as mother or mother-in-law). In both India and Zambia, women are generally considered to have low-decision making power in their households, particularly in relation to decisions on healthcare and how to use cash earnings.(International Institute for Population Sciences (IIPS) and ICF International., 2017; Zambia Statistics Agency. et al., 2019) We therefore identified male partners as being an important group to include in the feasibility study, recognising they may exert considerable influence over a woman's choice whether to participate in a research study or not. Participants were considered eligible if either they or their partner (or relative) were attending for routine antenatal care at any of the study sites. Individuals invited to take part were provided with written information detailing what their participation would involve (approximately one hour of audio-recorded focus group discussion) and written informed consent was obtained from all participants prior to initiation of the focus group discussion. Each focus group discussion was facilitated by a member of the local research team with previous experience in qualitative health research, using the local language preferred by participants (either Nyanja or Bemba in Zambia, or Kannada in India). Discussions took place in private spaces within the healthcare facility (e.g. seminar room). Refreshments were provided and transport costs were reimbursed. A focus group discussion guide (Appendix 3) was used to explore key questions relating to participants' knowledge of pre-eclampsia, attitudes and beliefs towards planned early delivery, and previous lived experience of hypertensive disorders of pregnancy. Each discussion was audio recorded, transcribed, translated, and subsequently analysed using NVivo qualitative data analysis software.

5.3.6. Key stakeholder interviews

Semi-structured interviews were used to explore the acceptability of the intervention to healthcare providers. A stratified, purposive, sampling strategy was used to identify key stakeholders,(Palinkas et al., 2015) with individuals selected based on their potential influence in the main trial, following discussion with each of the local site teams. We identified a cross-section of staff involved in the delivery of maternal and newborn care across study sites which included obstetricians,

paediatricians, midwives, maternity nurses, and neonatal nurses. These individuals were then invited (either by phone, e-mail, or in person) to take part in a semi-structured interview, lasting approximately 30 minutes. Following an invitation to participate, each individual was provided with written information about what their participation would involve, and if willing to take part, they were asked to provide written informed consent. Interviews were conducted at times convenient for the participant and private office spaces were used. A topic guide (Appendix 4) was used to explore participants' understanding of pre-eclampsia, their clinical experience of the condition, and the perceived risks and benefits of planned early delivery between 34^{+0} and 36^{+6} weeks' gestation in women with pre-eclampsia. The interviews were conducted in English (as this was the professional working language at each of the study sites), and discussions were audio recorded, transcribed, and subsequently analysed using NVivo qualitative data analysis software.

5.3.7. Data analysis

Descriptive analysis and summary statistics were used for the quantitative data generated from the case notes review. Qualitative data generated from the focus group discussions and stakeholder interviews were initially analysed separately and then combined. Triangulation of qualitative data (i.e. combining data from interviews and focus groups) in this way has been shown to enhance understanding of complex phenomena.(Onwuegbuzie & Leech, 2005; Ostlund et al., 2011) Data were analysed using a thematic framework analysis appropriate to cross-disciplinary health research.(Gale et al., 2013) This adopts a deductive approach which enabled themes to be developed based on a combination of *a priori* research questions.(Pope et al., 2000) Thematic framework analysis is used to show presence and absence of patterns amongst different groups and does not rely on data saturation. Nevertheless, we adopted a pragmatic approach to data collection, continuing until we were satisfied enough data had been collected covering all major themes in the framework.

The thematic framework (Figure 5-1) assessed three key domains, reflecting the study objectives: understanding disease burden of pre-eclampsia; current

management of pre-eclampsia; and the acceptability of planned early delivery. Each of these were evaluated from a maternal perspective, an infant perspective, and a health system perspective.

The domains of disease burden and current management were chosen in order to explore the need for the intervention and understand the contextual factors likely to impact trial implementation. They were also considered to be important determinants of acceptability as they may influence the perceived risks and benefits that women and healthcare providers attribute to the intervention as a result of their experiences. Understanding these perceptions at an early stage of trial development was seen as an important step, not just in assessing the feasibility of the trial itself, but also the long-term feasibility of the intervention, should the main trial prove it to be effective.

5.4. Results

Medical records for 326 women with pre-eclampsia (and 342 infants) who delivered at one of the study sites between January and March 2019 were included in the case notes review. A total of eight focus group discussions (n=59 participants) took place with the number of participants in each focus group ranging between six and ten. Five focus group discussions involved pregnant women attending for routine antenatal care (four in Zambia, n=29 participants; one in India, n=6 participants) and three separate focus groups were facilitated with their male partners (two in Zambia, n=17 participants; one in India, n=7 participants). A total of 29 healthcare providers were interviewed. This purposive sample included nine obstetricians (Zambia n=6, India n=3), six paediatricians (Zambia n=2, India n=4), six midwives (Zambia n=6), two maternity nurses (India n=2), five neonatal nurses (Zambia n=3, India n=2), and one healthcare assistant (India n=1). An integrated summary of key qualitative and quantitative findings, presented according to the thematic framework, is shown below in Figure 5-1. Key maternal data are shown in Table 5-1 and infant data in Table 5-2, grouped by gestational age (34^{+0}-36^{+6} and ≥37 weeks). Illustrative quotes drawn from qualitative data are found in Tables 5-3, 5-4 and 5-5.

Supplementary maternal and infant data, including deliveries before 34 weeks, are shown in Tables 5-6 and 5-7.

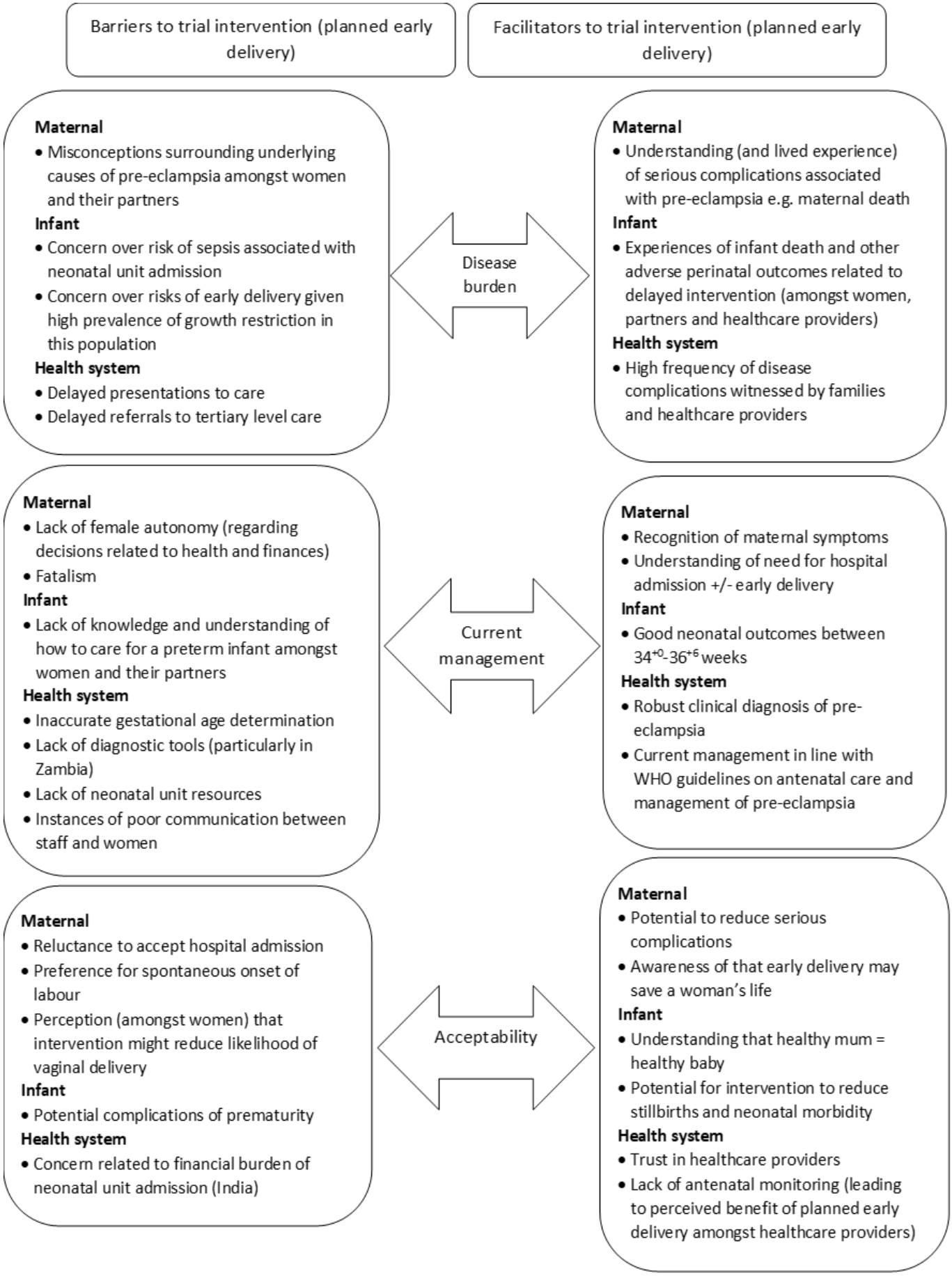


Figure 5-1 Integrated summary of key themes and findings

Table 5-1 Case notes review - maternal data

	34-36^{+6} weeks n (%)		**≥37 weeks n (%)**	
	Zambian sites	Indian sites	Zambian sites	Indian sites
Total number of women	n=69	n=15	n=98	n=44
Maternal characteristics				
Mean (SD) age (years)	26.5 (7.0)	24.5 (3.2)	25.8 (5.9)	24.4. (4.2)
Primiparous	28 (40.5)	10 (66.7)	57 (58.2)	31 (70.5)
Singleton pregnancy	64 (92.8)	14 (93.3)	94 (95.9)	44 (100)
Ultrasound scan during pregnancy	44 (63.8)	8 (53.3)*	63 (64.3)	33 (75.0)*
At pre-eclampsia diagnosis				
SBP ≥140 or DBP ≥90 mmHg	68 (98.6)	11 (73.3)*	93 (94.9)	30 (68.2)*
≥ 1 + protein on urine dipstick	62 (89.9)	8 (53.3)	83 (84.7)	21 (47.7)
Quantitative assessment of proteinuria	0	0	0	0
Creatinine tested	18 (26.1)	15 (100)	23 (23.5)	42 (95.5)
Liver enzymes tested	24 (34.8)	15 (100)	24 (24.5)	42 (95.5)
Platelets tested	49 (71.0)	15 (100)	60 (61.2)	41 (93.2)
Pre-eclampsia management				
Given antihypertensives	61 (88.4)	15 (100)	88 (89.8)	35 (79.5)
>1 antihypertensive agent	56 (81.6)	8 (53.3)	70 (71.4)	14 (31.8)
Received antenatal corticosteroids	42 (60.9)	4 (26.7)	9 (9.2)	1 (2.3)
Received magnesium sulfate	47 (68.1)	12 (80.0)	61 (62.2)	19 (43.2)
Admitted antenatally	66 (95.7)	15 (100)	90 (91.8)	44 (100)
Onset of labour:				
Spontaneous	22 (31.9)	3 (20.0)	43 (43.9)	24 (54.5)
Induced	25 (34.8)	4 (26.7)	28 (28.6)	5 (11.4)
Pre-labour caesarean section	22 (31.9)	8 (53.3)	27 (27.6)	15 (34.1)
Not documented	0	0	0	0
Composite of severe maternal mortality and morbidity, n (%)	12 (17.4)	6 (40.0)	17 (17.3)	9 (20.5)
Individual components (non-exclusive events):				
Death	0	0	0	0
Stroke	0	0	0	0
Eclampsia	9 (13.0)	3 (20.0)	9 (9.2)	5 (11.4)
Hysterectomy	0	0	0	0
Placental abruption	0	3 (20.0)	1 (1.0)	0
Pulmonary oedema	0	0	0	0
Blood transfusion	3 (4.3)	2 (13.3)	7 (7.1)	4 (9.1)
Severe hypertension	60 (87.0)	13 (86.7)	68 (69.4)	31 (70.5)
Other maternal complications:	7 (10.1)	4 (26.7)	6 (6.1)	4 (9.1)

Documented primary indication for delivery by clinician (n = induced plus pre-labour CS)	n=47	n=12	n=55	n=20
Severe pre-eclampsia	34 (72.3)	9 (75.0)	40 (72.7)	15 (75.0)
Eclampsia	6 (12.8)	3 (25.0)	6 (10.9)	5 (25.0)
Other	6 (12.8)	0	9 (16.4)	0
Hospital length of stay	n=69	n=15	n=98	n=44
Median (IQR) pre-delivery length of stay (days)	1 (1-3)	1 (1-1)	1 (1-2)	1 (1-1)
Median (IQR) postnatal length of stay (days)	3 (2-5)	8 (7-11)	3 (2-4)	7 (5-9)

*records of antenatal ultrasound or clinic visits not always available

Table 5-2 Case notes review - infant data

	34-36^{+6} weeks n (%)		**≥37 weeks n (%)**	
	Zambian sites	Indian sites	Zambian sites	Indian sites
Total number of infants (n)	n=74	n=16	n=102	n=44
Livebirths	72 (97.3)	15 (93.8)	99 (97.1)	41 (93.2)
Antepartum stillbirths	2 (2.7)	1 (6.3)	2 (2.0)	2 (4.5)
Intrapartum stillbirths	0	0	1 (1.0)	1 (2.3)
Neonatal deaths (% of livebirths)	2 (2.7)	1 (6.7)	2 (2.0)	1 (2.4)
No birth outcome reported	0	0	0	0
Mode of delivery:				
Spontaneous vaginal delivery	32 (43.2)	3 (18.75)	44 (43.1)	12 (27.2)
Assisted vaginal delivery	1 (1.4)	0	5 (4.0)	0
Caesarean section	41 (55.4)	13 (81.3)	52 (51.0)	32 (72.7)
Not documented	0	0	1 (1.0)	0
Median (IQR) gestation at delivery (days)	249 (243-252)	251 (245-255)	269 (266-280)	272 (266-282)
Median (IQR) birthweight (kg)	2.2 (1.9-2.7)	1.9 (1.8-2.3)	2.8 (2.3-3.3)	2.7 (2.5-3.0)
Median (IQR) birthweight centile*	16 (5-73)	5 (2-17)	18 (3-49)	11 (4-24)
Small for gestational age (birthweight <10th centile)	28 (38.3)	10 (62.5)	37 (36.3)	22 (50.0)
Admission to neonatal unit n (% livebirths)	37 (50.0)	13 (86.7)	32 (32.3)	17 (41.5)
Primary indication for neonatal unit admission n (% livebirths):	n=72	n=15	n=99	n=41
Prematurity	13 (18.1)	0	3 (3.0)	0
Low birthweight	3 (4.2)	3 (20.0)	1 (1.0)	1 (2.4)
Respiratory distress	3 (4.2)	5 (33.3)	1 (1.0)	4 (9.8)
Birth Asphyxia/Cyanosis	5 (6.9)	0	7 (7.1)	2 (4.9)
Jaundice	0	5 (33.3)	0	8 (19.5)
Other	0	0	1 (1.0)	2 (4.8)

No clinical indication (healthy lodger)	7 (9.7)	0	14 (14.1)	0
Not documented	6 (8.3)	0	5 (5.1)	0
Respiratory support required (and type):	**9 (12.5)**	**5 (33.3)**	**5 (5.1)**	**8 (19.5)**
Oxygen	4 (5.6)	2 (13.3)	4 (4.0)	5 (12.1)
Continuous positive airway pressure	5 (6.9)	2 (13.3)	1 (1.0)	1 (2.4)
Intubation and ventilation	0	1 (6.7)	0	2 (4.9)
Antibiotics given (and indication):	9 (12.5)	3 (20.0)	6 (6.1)	6 (14.6)
Presumed sepsis	8 (11.1)	1 (6.7)	5 (5.1)	5 (12.2)
Prematurity	1 (1.2)	0	0	0
Confirmed infection	0	2 (13.3.)	1 (1.0)	1 (2.4)
Additional clinical outcomes:				
Neonatal hypoglycaemia	0	2 (13.3)	2 (2.0)	3 (7.3)
Neonatal seizures	0	1 (6.7)	0	2 (4.9)
Nasogastric feeding required	4 (5.6)	6 (40.0)	1 (1.0)	13 (31.7)
Hypoxic ischaemic encephalopathy	0	5 (33.3)	1 (1.0)	6 (14.6)
Necrotising enterocolitis	0	0	0	0
Outcome of NICU admission n (% admissions)	n=37	n=13	n=32	n=17
Discharged alive	28 (75.7)	12 (92.3)	30 (93.8)	13 (76.5)
Died	2 (5.4)	1 (7.7)	2 (6.3)	1 (5.9)
No outcome recorded	7 (18.9)	0	0	1 (5.9)
Left against medical advice	0	0	0	2 (5.9)
Hospital length of stay				
Median (IQR) length of stay (days)	4 (2-7)	6 (1-7)	3 (2-5)	6 (4-8)

*Calculated using Intergrowth centiles (Villar et al., 2014)

Table 5-3 Disease burden

	Pregnant women	Partners	Healthcare providers
Maternal factors Facilitators	In my case, this condition started with high blood pressure and swelling of body parts. It affected me so much that I was admitted to intensive care unit (ICU). This condition is related to high blood pressure *(Zambia)*	Mother may have fits, haemorrhage (*India)*	I have seen eclampsia, I have seen HELLP syndrome, I have seen pulmonary oedema. I have seen stroke, I have seen a massive IC bleed three weeks back. Because of the severe pre-eclampsia we lost the mother *(Obstetrician, India)*
Barriers	Is pre-eclampsia connected to sexually transmitted diseases? *(Zambia)*	It could be, maybe you are giving her too much pressure at home that's why that blood pressure keeps on going up *(Zambia)*	We need to sensitise them. Because mostly, you would ask the woman if at all she has heard of that condition. And she will be so surprised, asking how come it's high, that condition, or where the BP has come from *(Midwife, Zambia)*
Baby factors Facilitators	I also know one woman who had high BP and got fits. Her baby died but she is fine *(India)*	I have not seen but heard about it. In fact, it happened with one of my relatives. That mother's BP was very high and baby died inside the womb *(India)*	They could have…the baby could die whilst in utero because of the raised BP, and they could have a baby with severe asphyxia because of their condition *(Neonatal nurse, Zambia)*
Barriers	Baby will not put weight if it is born early *(India)*	Mother may have fits and stroke. Baby's growth will be restricted because of adverse effect of high BP *(India)*	And also the risk of sepsis is also very high. Because in our set-up, if the baby is shifted to the mother's side, her handling is more by the attendants. Improper handling. So they won't do hand washing and things. So the risk of sepsis is very high *(Paediatrician, India)*

Health system factors **Facilitators**	This is what I can say about the dangers of high blood pressure, my sister in-law passed on due to this condition and they only managed to save the child….. So I think from this example, we can see how dangerous this condition is *(Zambia)*	I know one woman who got seizures in pregnancy due to high BP. She was admitted to hospital. Baby died but mother survived *(India)*	Quite frequently, exactly. Yeah. Almost every week we have most attention from complications from pre-eclampsia. There are those that go for severe form, they go for dialysis. They have some renal injury as well, you know (*Junior doctor, Zambia)*
Barriers	If woman has high BP then she may not understand what to do!!! (*India)*	They delayed in bringing this lady to the hospital and by the time she was brought in, the placenta had burst and the baby died in the womb as a result *(Zambia)*	Sometimes the challenge is that despite being told antenatally, these mothers who experience headaches, they remain at home until that headache is very persistent that they even fail to sleep or do anything. That's when they come to the hospital. Sometimes it's late, yes *(Midwife, Zambia)*

Table 5-4 Current management

	Pregnant women	Partners	Healthcare providers
Maternal factors Facilitators	And also maybe the swelling of the body, usually it is the legs, the hands….*(Zambia)*	I have an in-law who had high blood pressure and swelling of the body whilst she was pregnant with twins. She underwent forced labour and that's how she was saved *(Zambia)*	First thing, I hope, first thing when they come, we give an IEC. That is heath talk. We talk to our women every day. So the health talk includes danger signs in pregnancy, and what to prepare *(Midwife, Zambia)*
Barriers	Family member will decide whose life is important and who should be saved i.e. mother or baby *(India)*	Some children born early at 7th and 8th months will survive and some will not survive. My child did not survive. I feel it's the destiny which decides the fate of each child. (He laughs in pain) Life and death is in the hands of God *(India)*	They are told at home no; you don't have to agree to induction. You don't have to agree to this. So they follow that. And they would rather follow what their parents or their relatives tell them not do it *(Midwife, Zambia)*
Baby factors Facilitators	At 34 weeks the baby is strong and big enough to be delivered. Overall, this will save the lives of both the mother and child. I once gave birth at 36 weeks and the baby weighed 3.8 kilograms *(Zambia)*	Both mother and baby will survive. Even the baby is small we can take care of baby so that it can have normal development *(India)*	I mean, as I said, between 34 and 37 weeks, babies are normal with none of these co-morbidities. Outcome will be good with monitoring *(Paediatrician, India)*

Barriers	Baby was very small so kept in the incubator. The cost of treatment was very high so could afford to keep baby in NICU for 4 days and then took the baby home against medical advice. In home they tried to take care of baby. They used Hot water bottle to keep baby warm. Baby survived for 21 or 27 days and then died *(India*)	Baby may require more care and medication. Apart from this, I do not know much (*India)*	Okay. So there are some things that I think…of course we are professional, but you may know them when you are in the shoes of the patient. So for example I think it is easy as a doctor to say give the baby medicine three times a day, but you don't know the actual struggle that the mother goes through to make those babies swallow that medicine *(Junior doctor, Zambia)*
Health system factors **Facilitators**	So I think they want to deliver you before you get to the stage where you might start fitting and the like *(Zambia)*	I tell people who had high BP to go to hospital early and deliver early by caesarean section or else mother will die *(India)*	Gestational hypertension means only the high BP. Then pre-eclampsia means they'll have all the categories. They have proteinuria, pedal enema, it may have abdominal wall oedema. They have them *(Community healthcare worker, India)*
Barriers	Just to add a few words, sometimes when we pregnant women go for antenatal clinics, they tell us medical terms that we can't understand (*Zambia)*	If it is indicated to deliver it is better to deliver and if you delay in such condition people will scold you (*India)*	Because the few vents, we have like four vents on the unit. And if I have six babies, obviously two babies won't be put on the vent, and then they actually end up dying *(Paediatrician, Zambia)*

Table 5-5 Acceptability

	Pregnant women	Partners	Healthcare providers
Maternal factors Facilitators	We would be able to save the life of the mother and the baby (*Zambia)*	On my own behalf, rather than losing my spouse I would say anyway, just do false labour (*Zambia)*	Okay. First of all we are going to preserve the mother's life, we are going to prevent her from tipping into severe PE. Yeah *(Midwife, Zambia)*
Barriers	Urban people cannot tolerate labour pain, so they prefer to deliver by caesarean section *(India)*	Then on the disadvantages I think it's the actual forcing of labour before it's due. Like everything else that's forced, this in itself is a disadvantage. For example, in forced labour medicine is used to induce it, these medicines have side effects. God himself meant for pregnancy to last for 9 months before labour can start, but before that time you force it *(Zambia)*	So they tend not to understand the dangers of the condition that they have. So most of them request to go home, "sister, I want to be discharged" *(Midwife, Zambia)*
Baby factors Facilitators	Baby will have advantages. Baby will have less complications *(India)*	Delivering early is okay because by waiting, an expectant mother might die with the pregnancy, or the child might die. The risks are just too many, so it's better to deliver this person and save both lives (*Zambia)*	Actually I'm treating preterm, I am really comfortable. Rather than severe asphyxia. You can't do anything *(Paediatrician, India)*

Barriers	Maybe my worry is, I am not too sure if there are some conditions on developmental milestones that these children go through as a result of having been born too early *(Zambia)*	The baby might not have grown properly so it may have some problems *(India)*	So the thing is, when you deliver a baby at 34 weeks, obviously they are not yet mature. There are a few complications that the baby may suffer as a result of prematurity, for example physiological jaundice, their immunity's not yet as strong, they may have to undergo septic screenings *(Junior doctor, Zambia)*
Health system factors **Facilitators**	The Doctor has the authority to save you because they have been trained to do so. This is why in the first place we go to them (Doctors) because if you did not want to be saved, you would not have come *(Zambia)*	Doctors are god so whatever they suggest we will agree for that *(India)*	Because there are those who start antenatal from the clinics, and the follow-up is not that very good. There are times when the BPs are high at the clinic and they don't refer them, they refer them quite late at the hospital *(Midwife, Zambia)*
Barriers	If we have saving we will spend it if not we will ask any known person for help. If the patients are very poor they will sell their assets like Gold and bear the expenses of hospital in emergency to save mother and child (*India)*	We will borrow money from friends. If we have saved money, we can use that. There are no insurance schemes right now to pay for expenses of pregnant woman (*India)*	One more challenge I would… many times the parents are not willing to keep the baby for such a long time. Because they feel that, I mean, the time spent, the amount and the revenues spent on these babies is not good *(Paediatrician, India)*

5.4.1. Disease burden

5.4.1.1. Maternal factors

Case notes review data highlighted the serious maternal and perinatal morbidity associated with pre-eclampsia across sites in both countries (Tables 5-1 and 5-2). Notably, n=12 (14.3%) women who delivered between 34^{+0}-36^{+6} weeks experienced eclampsia, compared to n=14 (9.9%) delivering at term (≥37 weeks). Placental abruption, acute kidney injury, and HELLP syndrome were also frequently recorded clinical outcomes (Table 5-6). Between 34^{+0}-36^{+6} weeks, n=60 (87%) women in Zambia and n=13 (86.7%) women in India developed severe hypertension, which supports the finding that approximately three quarters of women at this gestation underwent clinician-initiated delivery for severe pre-eclampsia.

Complementing this quantitative data, women, partners, and healthcare providers all demonstrated a clear understanding of the complications linked to pre-eclampsia and were able to share examples of their own lived experience, either as healthcare providers managing these complications or as patients (or patient relatives) experiencing the disease itself (Table 5-3). Whilst healthcare providers were able to provide more detailed accounts using medical terms, women and their partners could identify links between raised blood pressure and serious complications such as death, stroke, and eclampsia ("fits"). However, potential barriers to understanding were also highlighted. For example, misconceptions surrounding the underlying cause of pre-eclampsia were identified, with women and partners sometimes making connections between raised blood pressure and emotional states, and healthcare providers identifying a need to improve awareness around the condition.

5.4.1.2. Infant factors

Overall, there were a low number of infant deaths occurring after 34 weeks' gestation in our sample. Between 34^{+0}-36^{+6} weeks, the proportion of antepartum stillbirths (n=3, [3.3%]) was similar to the proportion of neonatal deaths (n=3, [3.4%]). Importantly, the proportion of neonatal deaths that occurred in infants born late preterm (34^{+0}-36^{+6} weeks) and term (≥37 weeks) was low in both groups (n=3, [3.3%] and n=3, [2.1%] respectively). Furthermore, whilst respiratory distress was a more commonly documented indication for neonatal unit admission in infants born late preterm (n= 8, [16.0%] late preterm vs. n= 5 [10.2%] term),

birth asphyxia was more common in those born at term (n= 5[10.0%] late preterm vs. n=9, [18.4%] term). Additionally, women, partners, and healthcare providers in both countries frequently mentioned instances of infant death, with examples of the baby dying “inside the womb” the most commonly reported infant complication of pre-eclampsia. Whilst recognising this important risk associated with continuing pregnancy, healthcare providers also expressed concern regarding the risks of early delivery. Interview participants mentioned high rates of hospital-acquired infection within neonatal units. However, these concerns were not borne out by the case notes review data which demonstrated only small numbers of confirmed infection amongst infants born after 34 weeks (n=4, 4.0% of total neonatal unit admissions). There was also a perceived concern that higher rates of growth restriction amongst infants of women with pre-eclampsia would put these infants at greater risk of complications of prematurity. However, only n=6 (12.0%) late preterm neonatal unit admissions were due to low birthweight.

5.4.1.3. Health system factors

Case notes review data demonstrated that in Zambia, approximately 1 in 5 women experienced a composite outcome of severe maternal mortality or morbidity (in India, this proportion was even higher with 2 in 5 women experiencing the composite outcome, though our sample size was smaller). Healthcare providers reported witnessing complications of pre-eclampsia on a weekly if not daily basis, and women and partners were both able to recall examples of friends and family (including their own partners in the case of male participants) affected by pre-eclampsia, often with severe consequences. Thus, pre-eclampsia was perceived as an important and frequent problem by pregnant women and their partners, and healthcare providers highlighted a clear need to optimise current management. Nevertheless, potential barriers to implementing a facility-based intervention (such as planned early delivery) were identified. These centred around delayed presentations to care related in part to lack of understanding amongst the local community, as well as delayed referrals from peripheral healthcare facilities to tertiary level care.

5.4.2. Current management

5.4.2.1. Maternal factors

Case notes review data showed that the majority of women diagnosed with pre-eclampsia met the diagnostic criteria of hypertension and proteinuria, as outlined by international guidelines.(Brown et al., 2018; World Health Organization, 2011) There was widespread use of antihypertensives and magnesium sulfate, suggesting appropriate management of those with severe disease. In accordance with WHO guidelines on the management of pre-eclampsia, over 90% of women across both country sites were admitted to hospital once diagnosed and referred (although our predominantly urban sample based in tertiary healthcare facilities may not necessarily be generalisable to other settings). Amongst healthcare providers there was a good understanding of both diagnosis and management of pre-eclampsia and particularly the need for early delivery (Table 5-4). This was supported by responses from women and partners who were able to recall many of the common signs and symptoms of pre-eclampsia in addition to recognising that medical interventions (such as induction of labour) may be required in order to save a woman's life. However, important themes identified from the focus group discussions at both Indian and Zambian sites also included a sense of fatalism and the idea that the outcome of a pregnancy would be "decided by God", rather than medical intervention. A lack of female autonomy related to making decisions regarding healthcare was also apparent in both countries, with partners and extended family members often given the power to decide whether to proceed with an intervention such as induction of labour or caesarean section.

5.4.2.2. Infant factors

Neonatal outcome data collected as part of the case notes review demonstrated good neonatal outcomes between 34^{+0}-36^{+6} weeks. Median birthweight was above 1.8kg (the threshold for neonatal unit admission according to local protocols) in both Indian and Zambian settings. Whilst a high proportion of livebirths were admitted to the neonatal unit (n=37, [50.0%] in Zambia, n=13 [86.7%] in India), the majority of these infants were discharged alive (n=28 [75.7%] in Zambia, n=12 [92.3%] in India) and only three neonatal deaths were recorded following neonatal unit admission (n=2 [5.4%) in Zambia, n=1 [7.7%] in India). The same number (n=3 [3.4%]) of neonatal deaths were recorded for neonates born ≥37 weeks. Small numbers of neonates born between 34^{+0}-36^{+6} weeks required

respiratory support (n=9, [12.5%] of neonates in Zambia and n=5 [33.3%] of neonates in India), but serious morbidity (such as necrotising enterocolitis (n=0), or neonatal seizures (n=1 [2%])) was rare at this late preterm gestation. Qualitative data complemented these findings, particularly interviews with healthcare providers who expressed confidence that after 34 weeks' gestation, infants were likely to do well. Even amongst women and partners, there was recognition that hospitals and doctors were able to help small, premature babies, and several women reported personal experiences of delivering their babies early, with positive outcomes. Nevertheless, some gaps in knowledge and understanding regarding the care of a preterm infant were identified during the focus group discussions. There was limited understanding of what a neonatal unit admission might involve and the type of support that could be provided to preterm infants, as well as examples of individuals who had attempted (sometimes unsuccessfully) to care for a preterm infant at home in order to avoid the cost of a neonatal unit admission.

5.4.2.3. Health system factors

Whilst maternal case notes data demonstrated robust clinical diagnosis of pre-eclampsia across the proposed trial sites and good adherence to WHO guidelines on the management of pre-eclampsia, it was also clear that resource limitations present a significant challenge in these settings. For example, amongst women who delivered between 34^{+0} and 36^{+6} weeks' gestation, only n=5 [7.2%] women in Zambia and n=5 [33.3%] women in India (Table 5-6) had an obstetric ultrasound scan before 20 weeks' gestation, making accurate gestational age determination harder. There was a clear disparity in the availability of laboratory investigations between the two countries noted. Whilst creatinine and liver enzyme testing appeared to be routinely available at the two Indian sites, approximately only a quarter of women in Zambia had these tests performed after 34 weeks. No women in either country had a quantitative (e.g. protein: creatinine ratio or 24-hour urinary protein collection) assessment of proteinuria performed. Whilst neonatal outcomes were reassuring, interviews with healthcare providers also highlighted a number of concerns relating to a lack of neonatal resources, in particular ventilators and medications such as surfactant and anti-convulsants. A further challenge relating to women's willingness to accept care was identified during focus group discussions which revealed examples of poor communication between healthcare providers and women or families. These examples often related to a

lack of explanation, or at times a didactic and paternalistic approach to delivering care and thus a breakdown of rapport between clinical staff and women.

Table 5-6 Case notes review – supplementary maternal data including deliveries before 34 weeks' gestation

	<34 weeks n (%)		**34-36^{+6} weeks n (%)**		**≥37 weeks n (%)**	
	Zambian sites	Indian sites	Zambian sites	Indian sites	Zambian sites	Indian sites
Total number of women	n=87	n=13	n=69	n=15	n=98	n=44
Maternal characteristics						
Mean (SD) age (years)	28.8 (7.4)	24.2 (3.3)	26.5 (7.0)	24.5 (3.2)	25.8 (5.9)	24.4. (4.2)
Primiparous	30 (34.5)	8 (61.5)	28 (40.5)	10 (66.7)	57 (58.2)	31 (70.5)
Singleton pregnancy	81 (93.1)	13 (100)	64 (92.8)	14 (93.3)	94 (95.9)	44 (100)
Ultrasound scan during pregnancy	60 (69.0)	6 (46.1)	44 (63.8)	8 (53.3)	63 (64.3)	33 (75.0)
Ultrasound before 20 weeks' gestation	4 (4.6)	3 (23.1)	5 (7.2)	5 (33.3)	7 (7.1)	24 (54.5)
At pre-eclampsia diagnosis						
SBP ≥140 or DBP ≥90 mmHg	80 (92.0)	13 (100)	68 (98.6)	11 (73.3)	93 (94.9)	30 (68.2)
≥ 1 + protein on urine dipstick	77 (88.5)	8 (61.5)	62 (89.9)	8 (53.3)	83 (84.7)	21 (47.7)
Quantitative assessment of proteinuria	0	0	0	0	0	0
Creatinine tested	43 (49.4)	13 (100)	18 (26.1)	15 (100)	23 (23.5)	42 (95.5)
Median (IQR) creatinine value (µmol/L)	86 (69-105)	65 (53-80)	72 (63-83)	67 (55-80)	66 (57-97)	62 (53-80)
Liver enzymes tested	47 (54.0)	13 (100)	24 (34.8)	15 (100)	24 (24.5)	42 (95.5)
Median (IQR) alanine transaminase level (U/l)	27 (14-48)	15 (12-18)	12 (11-28)	18 (13-47)	17 (13-31)	15 (12-20)
Median (IQR) aspartate aminotransferase level (U/l)	42 (32-59)	20 (17-30)	30 (21-42)	22 (15-44)	33 (24-44)	25 (18-30)
Platelets tested	73 (83.9)	12 (92.3)	49 (71.0)	15 (100)	60 (61.2)	41 (93.2)
Median (IQR) platelets level (x10^9/l)	169 (98-231)	217 (167-217)	174 (146-242)	166 (122-262)	190 (142-260)	211 (181-266)
Pre-eclampsia management						
Given antihypertensives	78 (89.7)	13 (100)	61 (88.4)	15 (100)	88 (89.8)	35 (79.5)
>1 antihypertensive agent	72 (87.8)	10 (76.9)	56 (81.6)	8 (53.3)	70 (71.4)	14 (31.8)

Received antenatal corticosteroids	63 (72.4)	4 (30.8)	42 (60.9)	4 (26.7)	9 (9.2)	1 (2.3)
Received magnesium sulfate	77 (88.5)	10 (76.9)	47 (68.1)	12 (80.0)	61 (62.2)	19 (43.2)
Admitted antenatally	78 (89.7)	13 (100)	66 (95.7)	15 (100)	90 (91.8)	44 (100)
Onset of labour						
Spontaneous	14 (16.1)	2 (15.4)	22 (31.9)	3 (20.0)	43 (43.9)	24 (54.5)
Induced	46 (52.9)	5 (38.5)	25 (34.8)	4 (26.7)	28 (28.6)	5 (11.4)
Pre-labour caesarean section	25 (28.7)	6 (46.1)	22 (31.9)	8 (53.3)	27 (27.6)	15 (34.1)
Not documented	2 (2.3)	0	0	0	0	0
Composite of severe maternal mortality and morbidity (n women)	29 (33.3)	9 (69.2)	12 (17.4)	6 (40.0)	17 (17.3)	9 (20.5)
Individual components (non-exclusive events)						
Death	0	0	0	0	0	0
Stroke	0	0	0	0	0	0
Eclampsia	15 (17.2)	7 (53.8)	9 (13.0)	3 (20.0)	9 (9.2)	5 (11.4)
Hysterectomy	0	0	0	0	0	0
Placental abruption	2 (2.3)	0	0	3 (20.0)	1 (1.0)	0
Pulmonary oedema	1 (1.1)	0	0	0	0	0
Blood transfusion	11 (12.6)	2 (15.4)	3 (4.3)	2 (13.3)	7 (7.1)	4 (9.1)
Additional clinical outcomes:						
Severe hypertension	74 (85.0)	12 (92.3)	60 (87.0)	13 (86.7)	68 (69.4)	21 (47.7)
Post-partum haemorrhage	3 (3.4)	0	2 (2.9)	2 (13.3)	4 (4.1)	0
Acute Kidney Injury	2 (2.3)	1 (7.7)	0	0	0	0
Haemolysis, elevated liver enzymes and low platelet count (HELLP) Syndrome	8 (9.2)	1 (7.7)	3 (4.3)	1 (6.6)	1 (1.0)	3 (6.8)
Haemodialysis	1 (1.1)	0	0	0	0	0
Intensive care unit admission	2 (2.3)	0	1 (1.4)	0	1 (1.0)	1 (2.2)
Sepsis	2 (2.3)	0	1 (1.4)	1 (6.6)	0	0
Vaginal delivery n (% induced deliveries)	36 (78.3)	5 (100)	16 (64.0)	4 (100)	13 (46.4)	4 (80.0)

Documented primary indication for delivery by clinician (n = induced plus pre-labour CS)	n=71	n=11	n=47	n=12	n=55	n=20
Severe pre-eclampsia	40 (56.3)	3 (27.2)	34 (72.3)	9 (75.0)	40 (72.7)	15 (75.0)
Eclampsia	15 (21.1)	7 (63.6)	6 (12.8)	3 (25.0)	6 (10.9)	5 (25.0)
Other:						
Intra-uterine fetal death	13 (18.3)	1 (9.0)	2 (4.3)	0	0	0
Placental abruption	1 (1.4)	0	1 (2.1)	0	1 (1.8)	0
Severe hypertension	1 (1.4)	0	0	0	2 (3.6)	0
Fetal distress	0	0	3 (6.4)	0	4 (7.2)	0
Reached 37 weeks' gestation	0	0	0	0	1 (1.8)	0
Indication not documented	1	0	1	0	1 (1.8)	0
Hospital length of stay	n=87	n=13	n=69	n=15	n=98	n=44
Median (IQR) pre-delivery length of stay (days)	2 (1-4)	1 (1-2)	1 (1-3)	1 (1-1)	1 (1-2)	1 (1-1)
Median (IQR) postnatal length of stay (days)	4 (3-6)	12 (9-12)	3 (2-5)	8 (7-11)	3 (2-4)	7 (5-9)

Table 5-7 Case notes review – supplementary infant data including deliveries before 34 weeks' gestation

	<34 weeks n (%)		**34-36^{+6} weeks n (%)**		**≥37 weeks n (%)**	
	Zambian sites	Indian sites	Zambian sites	Indian sites	Zambian sites	Indian sites
Number of infants (n)	n=93	n=13	n=74	n=16	n=102	n=44
Livebirths	56 (60.2)	8 (61.5)	72 (97.3)	15 (93.8)	99 (97.1)	41 (93.2)
Antepartum stillbirths	31 (33.3)	3 (23.1)	2 (2.7)	1 (6.3)	2 (2.0)	2 (4.5)
Intrapartum stillbirths	4 (4.3)	2 (15.4)	0	0	1 (1.0)	1 (2.3)
Neonatal deaths (% of livebirths)	15 (26.8)	3 (37.5)	2 (2.7)	1 (6.7)	2 (2.0)	1 (2.4)
No birth outcome reported	2 (2.2)	0	0	0	0	0
Mode of delivery:						
Spontaneous vaginal delivery	47 (50.5)	5 (38.5)	32 (43.2)	3 (18.75)	44 (43.1)	12 (27.2)
Assisted vaginal delivery	0	0	1 (1.4)	0	5 (4.0)	0
Caesarean section	43 (46.2)	8 (61.5)	41 (55.4)	13 (81.3)	52 (51.0)	32 (72.7)
Not documented	3 (3.2)	0	0	0	1 (1.0)	0
Median (IQR) gestation at delivery (days)	212 (196-224)	206 (189-223)	249 (243-252)	251 (245-255)	269 (266-280)	272 (266-282)
Median (IQR) birthweight (kg)	1.4 (1-1.7)	1.2 (0.8-1.3)	2.2 (1.9-2.7)	1.9 (1.8-2.3)	2.8 (2.3-3.3)	2.7 (2.5-3.0)
Median (IQR) birthweight centile*	23 (3-76)	7 (3-42)	16 (5-73)	5 (2-17)	18 (3-49)	11 (4-24)
Small for gestational age (birthweight <10th centile)	28 (30.1)	7 (53.8)	28 (38.3)	10 (62.5)	37 (36.3)	22 (50.0)
Admission to neonatal unit n (% livebirths)	48 (85.7)	8 (100)	37 (50.0)	13 (86.7)	32 (32.3)	17 (41.5)
Primary indication for neonatal unit admission N (% livebirths):	n=56	n=8	n=72	n=15	n=99	n=41
Prematurity	37 (66.1)	3 (37.5)	13 (18.1)	0	3 (3.0)	0
Low birthweight	2 (3.6)	0	3 (4.2)	3 (20.0)	1 (1.0)	1 (2.4)
Respiratory distress	4 (7.1)	5 (62.5)	3 (4.2)	5 (33.3)	1 (1.0)	4 (9.8)

Birth Asphyxia/Cyanosis	2 (3.6)	0	5 (6.9)	0	7 (7.1)	2 (4.9)
Jaundice	0	0	0	5 (33.3)	0	8 (19.5)
Other	0	0	0	0	1 (1.0)	2 (4.8)
No clinical indication (healthy lodger)	1 (1.8)	0	7 (9.7)	0	14 (14.1)	0
Not documented	2 (3.6)	0	6 (8.3)	0	5 (5.1)	0
Respiratory support required (and type):	**16 (28.6)**	**7 (87.5)**	**9 (12.5)**	**5 (33.3)**	**5 (5.1)**	**8 (19.5)**
Oxygen	5 (8.9)	1 (12.5)	4 (5.6)	2 (13.3)	4 (4.0)	5 (12.1)
Continuous positive airway pressure	8 (14.3)	1 (12.5)	5 (6.9)	2 (13.3)	1 (1.0)	1 (2.4)
Intubation and ventilation	1 (1.8)	5 (62.5)	0	1 (6.7)	0	2 (4.9)
Antibiotics given (and indication):	13 (23.2)	7 (87.5)	9 (12.5)	3 (20.0)	6 (6.1)	6 (14.6)
Presumed sepsis	11 (19.6)	6 (75.0)	8 (11.1)	1 (6.7)	5 (5.1)	5 (12.2)
Prematurity	1 (1.8)	0	1 (1.2)	0	0	0
Confirmed infection	1 (1.8)	1 (12.5)	0	2 (13.3.)	1 (1.0)	1 (2.4)
Additional clinical outcomes:						
Neonatal hypoglycaemia	4 (7.1)	2 (25.0)	0	2 (13.3)	2 (2.0)	3 (7.3)
Neonatal seizures	0	1 (12.5)	0	1 (6.7)	0	2 (4.9)
Nasogastric feeding required	9 (16.1)	7 (87.5)	4 (5.6)	6 (40.0)	1 (1.0)	13 (31.7)
Hypoxic ischaemic encephalopathy	1 (1.8)	4 (50.0)	0	5 (33.3)	1 (1.0)	6 (14.6)
Necrotising enterocolitis	0	1 (12.5)	0	0	0	0
Outcome of NICU admission n (% admissions)	n=48	n=8	n=37	n=13	n=32	n=17
Discharged alive	27 (56.2)	3 (37.5)	28 (75.7)	12 (92.3)	30 (93.8)	13 (76.5)
Died	13 (27.1)	3 (37.5)	2 (5.4)	1 (7.7)	2 (6.3)	1 (5.9)
No outcome recorded	8 (16.7)	0	7 (18.9)	0	0	1 (5.9)
Left against medical advice	0	2 (25.0)	0	0	0	2 (5.9)
Hospital length of stay						
Median (IQR) length of stay (days)	5 (2-6)	17 (8-24)	4 (2-7)	6 (1-7)	3 (2-5)	6 (4-8)

*Calculated using Intergrowth centiles (Villar et al., 2014)

5.4.3. Acceptability

5.4.3.1. Maternal factors

When considering the perceived risks and benefits of planned early delivery from a maternal perspective, the most important perceived benefit amongst healthcare providers, women, and partners was the potential to save the woman's life and reduce the likelihood of life-threatening complications (Table 5-5). Whilst potential disadvantages were also identified (most notably there was a reluctance amongst women and their partners to accept early induction of labour), the benefit of preserving the woman's life was seen to outweigh any potential risks associated with a preterm delivery. Whilst some women and partners expressed concern that induced labour may increase the need for operative delivery, this fear was not supported by case notes review data which showed that between 34^{+0}-36^{+6} weeks, the majority of women who underwent induction of labour were able to deliver vaginally (Table 5-6). Whilst healthcare providers expressed concerns regarding women's willingness to accept hospital admission based on a lack of understanding of the seriousness of the condition, most women and their partners felt that they would accept medical intervention if it meant saving the life of both the woman and their baby.

5.4.3.2. Infant factors

The perceived risks of early delivery to the infant identified by healthcare providers, women, and partners was the impact of preterm delivery and the ways in which this may affect the infant's growth and development. However, overriding these concerns was a firm recognition of the mother-infant dyad and the idea that the best way to achieve a healthy infant was first to ensure the health of the mother. The consequences of waiting to deliver were clearly stated and included infant death due to stillbirth or severe birth asphyxia.

5.4.3.3. Health system factors

Considering the acceptability of planned early delivery from a health system perspective, the inherent challenges in delivering antenatal care and providing

follow-up for high-risk women in these settings acted as a facilitator towards the intervention, as healthcare providers perceived a benefit to earlier intervention, given these challenges. Furthermore, whilst household decision making was often deferred to other family members (particularly male members of the household), women and partners demonstrated a high level of trust placed in medical professionals and ultimate decision-making authority provided to doctors. Countering this, was the perceived financial risk of a neonatal unit admission, which was highlighted as a particular issue in India, whereas care in Zambia was provided largely free of charge.

5.4.4. Discussion

Assessing the disease burden due to pre-eclampsia across our study sites demonstrated the high prevalence of adverse pregnancy outcomes associated with the condition in these settings. Combining case notes data with the powerful lived experiences of healthcare providers, women, and their partners highlighted a strong desire for optimising current management and confirmed a need for evaluation of our proposed intervention (planned early delivery). Whilst it is not possible to draw firm conclusions based upon our relatively small sample, the infant data suggests there is no increased risk of neonatal mortality associated with late preterm delivery compared to term delivery in this high-risk population, and that prolonging pregnancy in this situation may be at least as risky to the infant as iatrogenic preterm delivery. In particular, there appears to be a higher risk of hypoxic brain injury secondary to severe maternal disease amongst infants born at term, compared to those born late preterm. Supporting this, a surprising finding was the positive attitude of paediatric doctors towards planned early delivery. Interview data showed that despite our concern that these individuals may perceive greater risk associated with the intervention, they felt more confident in managing late prematurity as compared to birth asphyxia following an emergency delivery for severe pre-eclampsia, and therefore attributed greater benefit to planned early delivery. Overall, neonatal outcome data provided reassuring evidence that the proposed trial sites have the facilities and skills to appropriately manage late prematurity. Data from the case notes review and stakeholder interviews identified

key resource limitations which influenced the design of the interventional trial protocol. In particular, we were able to modify the eligibility criteria and refine our selection of maternal and perinatal outcomes, developing pragmatic, clinical definitions that would enable these variables to be measured reliably. Important facilitators assessed as part of current management included a strong recognition of the signs and symptoms of pre-eclampsia and an understanding of the need for hospital admission and early delivery. This reflects the fact that in our study settings, there is positive engagement with antenatal care,(Gianetti et al., 2019; International Institute for Population Sciences (IIPS) and ICF International., 2017; Zambia Statistics Agency. et al., 2019) and good provision of the WHO recommended 'Information, Education, Communication' sessions to women during these visits.(World Health Organization, 2016) Whilst healthcare providers, women, and their partners did perceive some risk associated with planned early delivery (such as undergoing induction of labour or the costs of a preterm delivery), overall the intervention was found to be acceptable to the majority of stakeholders with clear perceived benefits identified (reducing the risk of death, serious complications, and stillbirth) that were felt to outweigh any potential disadvantages. Our findings therefore suggest that, with appropriate modifications to suit the local context, the interventional phase of the trial would be feasible to deliver and acceptable both to those delivering the intervention (healthcare providers) and those receiving it (pregnant women with pre-eclampsia).

The mixed-methods design of this study enabled the integration of data from multiple sources. Qualitative data were used to explore and explain quantitative findings, with case notes review data also validating (or in some cases dispelling) key themes identified in analyses of focus group discussions and interviews. Case notes review data provided important findings relating to current management of pre-eclampsia as well as the availability of specific resources and the incidence of severe morbidity. This enabled an objective assessment of feasibility, and rigorous case-finding and data collection provided a complete and realistic assessment over a three-month period. The acceptability of the intervention, and the perceived risks

and benefits of planned early delivery, were assessed qualitatively and this enabled a methodical and thorough understanding of knowledge, attitudes, and beliefs amongst local pregnant women and their partners. This sample of focus group participants was deliberately selected to be representative of the target study population for the main trial. Focus group data has therefore informed our recruitment strategy when designing the trial protocol and ensured engagement of local stakeholders from the outset. Our study was limited by challenges with documentation, for example, despite extensive efforts it was not always possible to locate antenatal and neonatal records and thus capture all outcomes. Additionally, further research may elucidate the role of sociodemographic influences on decision-making (e.g. around pregnancy interventions). The position of the research team facilitating focus group discussions as midwives and researchers was both a strength and a limitation. For example, as midwives they were able to build trust and rapport with colleagues and women; however, this role may also have created a power imbalance between facilitator and participants. Steps were taken to counter this, for example, acting as facilitators at healthcare facilities where they did not work clinically.

Our study findings enabled us to modify implementation of the main trial in order to suit the local context. For example, in order to address common misconceptions regarding the causes of pre-eclampsia and management of preterm birth, we developed brief educational videos to supplement trial recruitment materials. Recognising the involvement of male partners and learning from previous experiences of poor communication, discussions regarding trial participation would be encouraged to take place with both the woman and her partner present. Taking resource limitations into account, the CRADLE-4 Trial inclusion criteria will utilise a broad definition of pre-eclampsia based on simple clinical parameters (hypertension and dipstick proteinuria) and gestational age determination based upon known last menstrual period (LMP) rather than first trimester ultrasound. However, the use of early (prior to 20 weeks) and late ultrasound will be encouraged, particularly when reliable data on LMP is not available. This is a pragmatic approach that would be

transferable to similar settings. Furthermore, whilst it can be challenging to distinguish between growth restriction and early prematurity without accurate gestational age determination, we did not want to impose stringent criteria that could potentially exclude growth restricted fetuses (on the mistaken premise of prematurity before 34 weeks), who are in fact at the highest risk of intra-uterine death and potentially may benefit most from early delivery. Clinical outcomes were also adapted. The primary short-term maternal outcome used in the main trial will be based on the miniPIERS composite of adverse maternal outcomes,(Payne et al., 2014) with the addition of severe hypertension. The miniPIERS composite had previously been selected for use in a prospective study of women with any hypertensive disorder of pregnancy in a low and middle income setting.(Payne et al., 2014) We further modified the outcome definitions based upon our study findings. For example, we modified the definition of "blood transfusion" to include a request for transfusion even if blood products were unavailable at time of request or not received. Acknowledging the discrepancy in biochemistry testing between sites, we also plan to report a separate maternal mortality and morbidity composite of components detected by a clinical diagnosis only, as a secondary maternal outcome. Perinatal outcomes were also adapted via iterative discussion with site teams, building upon findings from stakeholder interviews with paediatric staff. For example, recognising that culture-proven sepsis is a difficult outcome to detect due to limited laboratory resources, a diagnosis of possible serious bacterial infection (based on WHO Integrated Management of Childhood Illness guidelines (Robinson, 1996)) was added as a secondary perinatal outcome.

Based upon the maternal and neonatal outcome data collected during the case notes review, we anticipate a maternal event rate (composite outcome of severe maternal mortality or morbidity with severe hypertension) of 80% and a neonatal event rate (stillbirth or neonatal death of neonatal unit admission for >48 hours with morbidity) of 23% in the expectant management (usual care) group of the main trial, in women with late preterm pre-eclampsia. This informed our sample

size calculation, which is detailed in the published trial protocol.(Beardmore-Gray et al., 2020)

The Medical Research Council guidelines on developing and evaluating complex interventions recognise that interventions are often undermined by problems of acceptability, compliance, delivery of the intervention, recruitment, and retention.(Craig et al., 2019) The guidelines therefore advocate that initial feasibility studies are undertaken in order to address these potential issues when designing the main study protocol. Considering an intervention such as planned early delivery in pre-eclampsia in India and Zambia, there are several behaviours required by those delivering the intervention (healthcare providers) and those receiving it (women) which are complex and need to be understood. Selecting meaningful maternal and perinatal outcomes, which can be reliably measured in a real-world setting, was also a potential challenge. Despite its importance, feasibility work is often poorly described and under-reported.(Bugge et al., 2013) The CRADLE-4 feasibility study therefore serves as an important example of how the Medical Research Council guidelines on developing and evaluating complex interventions can be put into practice and used to guide the development of a randomised trial design. Furthermore, there is currently inconsistent reporting of outcomes from randomised trials evaluating interventions for pre-eclampsia,(Dildy, 2017) leading to the potential omission of clinically important outcomes and difficulty in comparing and contrasting individual studies, thus limiting our ability to draw firm conclusions from the evidence available. Recent work has therefore focused on the development of a core outcome set for pre-eclampsia research.(Duffy et al., 2020) The CRADLE-4 Trial, informed by its feasibility phase, presents an opportunity to develop and validate these core outcomes, such that they may be shared and used in future pre-eclampsia trials taking place in similar settings.

5.4.5. Conclusion

Pre-eclampsia is a progressive and unpredictable disease and deciding when to recommend delivery presents a challenging scenario to clinicians around the world. The balance of risks and benefits must be carefully weighed depending on the

gestational age of the pregnancy and the severity of the condition. When considering the specific gestational window between 34^{+0} and 36^{+6} weeks, it is clear that planned early delivery is likely to reduce adverse maternal outcomes, but further clarity is needed regarding impact on neonatal outcomes and other key maternal considerations such as mode of delivery. Our preliminary findings from this study suggest that whilst planned early delivery may involve an increased risk of neonatal unit admission, with small numbers of babies requiring additional support with feeding and breathing, continuing with expectant management poses a significant risk of stillbirth and birth asphyxia. A larger scale randomised controlled trial is needed to fully evaluate which management strategy poses the least risk overall. This feasibility study has demonstrated that whilst contextual challenges related to the proposed trial environment need to be taken into consideration, such a trial is indeed feasible and the proposed intervention is acceptable to local stakeholders (healthcare providers, women, and their partners). These preliminary findings have directly influenced the design of the interventional phase protocol, specifically the selection of outcome measures, with a view to contributing towards core outcome sets for similar trials taking place in low or middle income settings. Staff training and participant recruitment materials will address the gaps in knowledge identified during focus group discussions and interviews as well as fears and fixed beliefs surrounding early delivery. Co-creating a trial protocol with local stakeholders at this stage and taking into account the feasibility and acceptability of the intervention will be key in ensuring that any evidence generated as part of this research can be successfully implemented and sustained within routine clinical practice.

Chapter 6 Lost in Translation: A qualitative evaluation of the barriers to informed consent in Zambia

6.1. Abstract

Introduction

The provision of comprehensible information is essential to the process of valid informed consent. Recruitment materials designed by sponsoring institutions in English-speaking, high income countries are commonly translated for use in global health studies in other countries; however, key concepts are often missed, misunderstood or "lost in translation".

Methods

We explored the barriers to informed consent, focusing on the challenges of translating recruitment materials for maternal health studies into Zambian languages, using a qualitative approach. This incorporated a multi-stakeholder workshop, in-depth interviews with researchers and translators, and two community-based focus groups with volunteers from community advisory boards.

Results

The workshop highlighted difficulties in translating research terms and pregnancy-specific terms, as well as widespread concern that current templates are too long, use overly formal language, and are designed with little input from local teams. Framework analysis of in-depth interviews identified barriers to participant understanding relating to design and development of recruitment materials, local context, and communication styles. Focus group participants confirmed these findings and suggested potential solutions to ensure the language and content of recruitment materials can be better understood.

Conclusion

Our findings demonstrate that the way in which recruitment materials are currently designed, translated, and disseminated does not enable potential participants to fully understand the information provided. Instead of using overly complex

institutional templates, recruitment materials should be created through an iterative and interactive process that provides truly comprehensible information in a format appropriate for its intended participants.

6.2. Introduction

6.2.1.1. Statement of the problem

Global health research typically involves partnerships between high income and low or middle income countries. These partnerships can sometimes perpetrate inherent structural inequalities or power dynamics,(Bhakuni & Abimbola, 2021; Hommes et al., 2021; Horton, 2013; Rasheed, 2021; Zarowsky, 2011) whereby research methodology and institutional processes designed in a high income country may be imposed on low income partners without considering the relevance or acceptability to the local population. The process of informed consent, and ethical review of consent documents, are two of the domains which may be affected by this imbalance. This study evaluates an example from Lusaka, Zambia, which specifically explores how language barriers, and issues surrounding translation of recruitment materials, may impact upon informed consent.

Informed consent is fundamental to any research involving human beings. For consent to be valid, participants must have the capacity to consent, act voluntarily, and be provided with sufficient comprehensible information. These principles are well described and upheld by international ethical and legal frameworks.(Council for International Organizations of Medical Sciences, 2016; World Medical Association, 2013) However, these frameworks are based upon knowledge systems generated and perpetuated by dominant groups in high income countries (Bhakuni & Abimbola, 2021) and often imposed upon other communities without considering local expertise. The participant information leaflets and consent forms (recruitment materials) used for enrolling participants in global health studies are often designed by sponsoring institutions based in high income countries (Bhutta, 2004) and therefore meet the needs of trial sponsors and ethical review boards, rather than those of the intended participants. There is a focus on written documentation,

complex medico-legal language, and lengthy forms providing excessive information. These forms are then translated via a process of forward and back translation, into the local language(s) of the country where the research is taking place. However, a 2014 review into participant comprehension found that the majority of trial participants across different African countries did not understand several key domains of informed consent such as voluntariness, confidentiality, and the difference between taking part in research and seeking medical care.(Afolabi et al., 2014) This is attributed to a lack of conceptual equivalence,(Gjersing et al., 2010; Marshall, 2008; Oduro et al., 2008; Tekola et al., 2009) arising from a lack of directly equivalent terms, as well as languages that are predominantly spoken and therefore do not have standardised written formats. Use of overly complex words and medical terminology further exacerbates this lack of understanding.(Villafranca et al., 2017) Studies have also highlighted a lack of universal tools for assessing understanding of trial participants (Afolabi et al., 2014; Appelbaum, 2010; Lindegger et al., 2006; Sand et al., 2010) and this in itself presents a barrier to identifying areas for improvement. Several studies have highlighted linguistic factors as a significant barrier to comprehension, but there is very little literature exploring this particular issue. Maternal health is a key research priority which justifiably attracts large numbers of research studies. However, pregnant women may represent a vulnerable population and in many low or middle income countries, including Zambia, this may be compounded by low levels of educational attainment and literacy.(Zambia Statistics Agency. et al., 2019) By exploring the language barriers to cross-cultural adaptation of recruitment materials, we aim to improve the quality of recruitment materials provided to future participants in maternal health studies in Zambia, and to contribute towards local efforts to strengthen research ethics capacity, which has been identified as a key priority by the Zambia National Health Research Policy and the Zambian National Health Regulatory Authority.(National Health Research Authority., 2020)

6.2.2. Research objective

The overall aim of this study is to understand the language barriers to informed consent, and to demonstrate, via the example of translating maternal health

research materials in Zambia, the importance of developing informed consent information that truly suits the needs of research participants.

6.3. Methods

We used a qualitative study design incorporating a workshop, in-depth interviews, and focus group discussions. This study took place in three phases (Table 6-1), based primarily in Lusaka, Zambia, alongside a timing of delivery in pre-eclampsia trial;(Beardmore-Gray et al., 2020) the research was led by the coordinator of this trial, Alice Beardmore-Gray (ABG), a UK doctor.

Table 6-1 Study phases and participants

Phase	Activity	Participant summary
Phase 1 Lusaka 18th Nov 2019	Workshop with invited participants from a variety of professional backgrounds. We set out to explore how key maternal health research terms, identified from a cross-sectional sample of recruitment materials from different research studies, might be translated from English into Nyanja and Bemba, and how this process might alter their meaning, as part of an initial exploratory exercise to guide the subsequent two phases.	There were 11 participants including ABG (study lead). Five participants were female and six were male. Nine were Zambian and two were British. Four were Obstetric researchers, three were research assistants, and four were translators with a background in teaching and social science. Participants were invited based on their ongoing involvement with a clinical trial evaluating timing of delivery in pre-eclampsia.
Phase 2 13th May – 1st July 2021	In-depth interviews with key informants to understand in more detail the challenges involved with translating consent documents for a Zambian population.	A total of eight interviews took place. The age range of participants was 30 to 69, three were female and five were male. Most (six) had degrees, two had diplomas. Their occupations included language teacher (three participants), research coordinator (four participants) and one community engagement officer.
Phase 3 21st and 29th June 2021	Focus group discussions with local community advisory boards at primary health clinics to interrogate findings from Phases 1 and 2 with individuals who would be representative of potential research participants.	A total of two focus group discussions (20 participants in total, ten in each group) took place. The mean age of participants was 28 years, twelve were female and six were male (information not provided for two participants). Eight participants had attended tertiary level education, with the remainder having attended secondary level education.

6.3.1. Sampling strategy and data collection methods

The cross-sectional sample of recruitment materials collected during Phase One was obtained by inviting researchers working in Zambia and neighbouring countries, to submit English language examples of recruitment materials they had previously developed (and translated) to inform individuals considering participation in their research studies (predominantly clinical trials). Researchers were identified via ongoing research being conducted at University Teaching Hospital, Lusaka, ongoing research conducted by the Department of Women and Children's Health at King's College London, and via the Global Women's Research Society international conference. Researchers were asked to provide examples of participant information leaflets which were collated, read, and analysed by the study lead (ABG). All relevant examples of recruitment materials provided were included in the sample. Summative content analysis (see Section 1.3.3. Data analysis) was used to identify the most commonly occurring terms related to research and pregnancy (details shown in Table 6-2). Phase Two in-depth interviews were significantly delayed due to the Covid-19 pandemic. An initial convenience sample of key informants was used, whereby individuals were invited to participate if they had prior experience of either translating recruitment materials or enrolling participants into research studies. During data collection, additional informants were invited to participate via snowball sampling. This comprised inviting other individuals, suggested by key informants, who were likely to have relevant insight and expertise, such as community engagement officers or research coordinators. Interviews were conducted in English, the working language in Zambia, by the study lead (ABG). A semi-structured interview guide was used (Appendix 5) and each interview was audio recorded and then transcribed. The interviews took place at times and locations convenient to the participants, primarily office spaces and meeting venues in Lusaka, Zambia. Phase Three focus group discussions were facilitated by three of the professional language teachers/translators who had participated in the interview phase, supported by the study lead (ABG). Focus group participants were invited by asking community advisory board (CAB) members to participate if they wished. CAB members were volunteers who formed part of pre-existing community

groups, linked to primary healthcare facilities in Lusaka, Zambia. CAB members linked to Kanyama first level hospital and Chawama first level hospital were selected as these are two of the busiest primary healthcare facilities in Lusaka and both facilities had enrolled participants into the previously mentioned timing of delivery in pre-eclampsia trial. Invitations were sent out to CAB members via text message, and responding individuals were then invited to participate in a focus group discussion. Two initial focus groups were planned, as a purposeful sample, following on from the workshop and key informant interviews. A focus group guide was developed following the Phase Two interviews and adapted from the interview topic guide (Appendix 5). Focus group discussions took place in outdoor meeting spaces attached to two first level hospitals (Kanyama and Chawama) in Lusaka, and were audio recorded and transcribed. Focus groups were conducted in a mixture of English, Nyanja, and Bemba and were translated at the time of transcription by a Zambian research assistant.

6.3.2. Ethical considerations

Ethical approval for this study was provided by King's College London (MRSP-20/21-22350) and University of Zambia (1517-2020). Written informed consent was sought from all participants before any interviews or focus group discussions were conducted and participation in the study was entirely voluntary. Electronic copies of interview and focus group transcripts were stored on a password protected hard drive. Participants were anonymised and referred to by initials or numbers only.

6.3.3. Data analysis

Content analysis was chosen to analyse the sample of recruitment materials as a recognised method of rapidly identifying commonly occurring language. A summative approach was taken, identifying the number of times that pregnancy related phrases and research terms arose in the sample of recruitment materials.(Hsieh & Shannon, 2005) During the Phase One workshop (conducted in English), participants discussed the interpretation of these commonly occurring terms, and explored how they might be translated into Nyanja and Bemba. No formal analysis of workshop data was performed; however, it was used to inform

the design of Phases Two and Three. Interview transcripts from Phase Two were uploaded to NVivo 12 for data coding. A framework analysis approach was used to analyse interview data.(Srivastava & Thomson, 2009) The theory underpinning this framework was drawn from the conceptual framework for the process of obtaining informed consent outlined by Bhutta,(Bhutta, 2004) theories of reading and language proficiency,(Mweli, 2020) and models for translation and cross-cultural adaptation such as those outlined by Brislin,(Brislin, 1970) and Flaherty and colleagues.(Flaherty et al., 1988) These theories were combined into one overarching framework (Figure 6-1) which guided data analysis, and was developed further during the analysis process, informing the final thematic framework shown in Figure 6-2. Focus group data were analysed using a simple inductive thematic analysis approach. The themes identified were compared and contrasted to findings from the interview data. By collecting data using different methods (workshop, interviews, and focus group discussions) and from different sources (e.g. research professionals and community members) we were able to triangulate our data (Carter et al., 2014) and test the validity of our findings from each phase, thereby enhancing the trustworthiness of our data. Focus group discussions with community members were chosen as a method of interrogating the findings from the workshop and interviews, and to seek differing perspectives and suggestions from individuals likely to represent potential research participants (as part of a local community linked to primary healthcare facilities involved in recruiting to clinical trials).

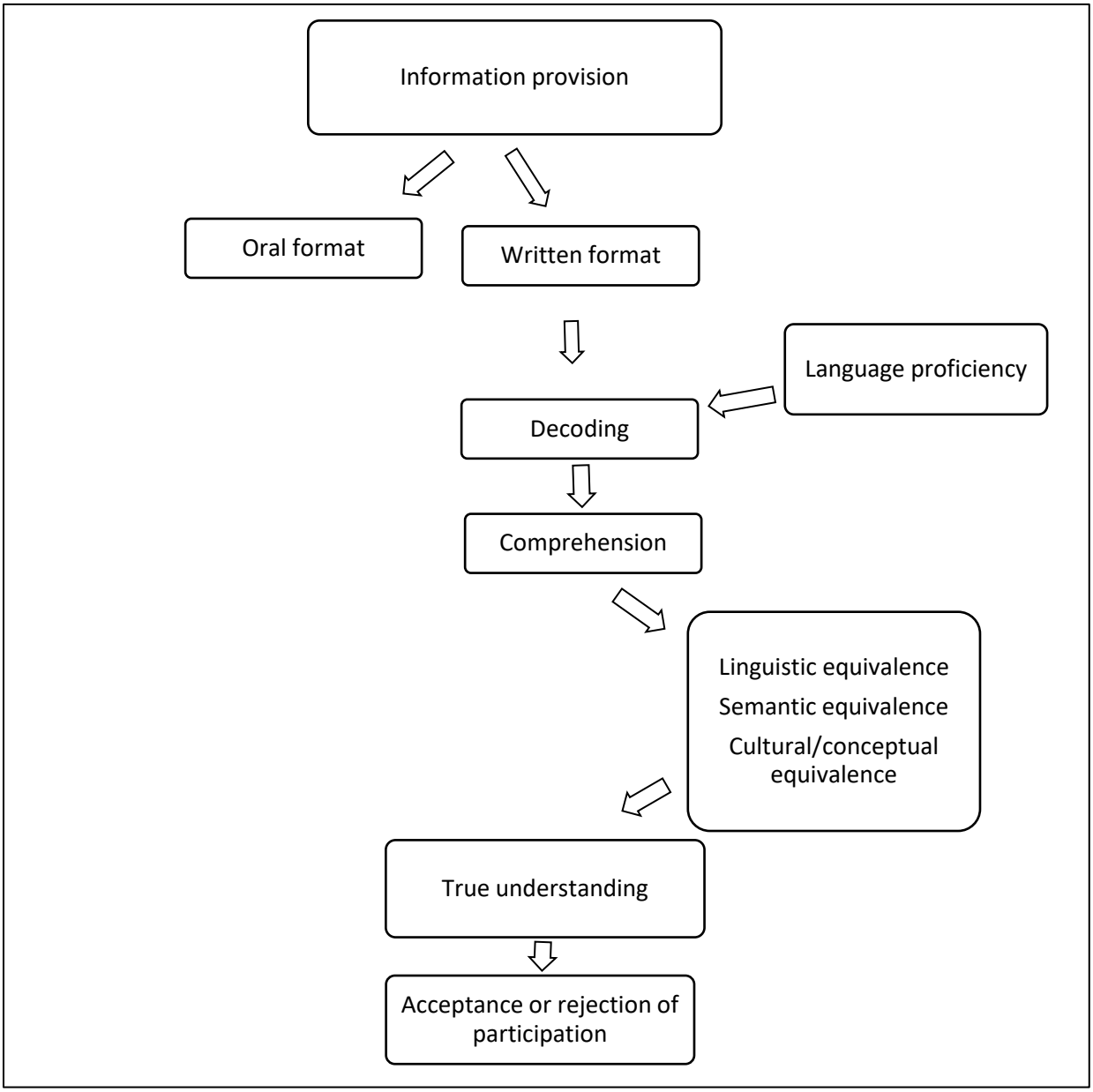


Figure 6-1 Theoretical framework (Brislin, 1970; Flaherty et al., 1988; Villafranca et al., 2017; Zambia Statistics Agency. et al., 2019)

6.3.4. 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.

6.3.5. Patient and public involvement

Patients and the public were not involved in the design or implementation of this study. However, the initial phase, a multi-disciplinary workshop, incorporated individuals from a range of professional backgrounds including social scientists and language teachers in addition to clinicians and researchers. Subsequent phases involved professional translators and members of the public in the form of community advisory boards, with the overall findings and recommended actions reflecting their lived experience and perspectives.

6.4. Results

6.5. Phase One: initial workshop

Content analysis of 13 different recruitment documents, from different maternal health studies, identified the most frequently occurring terms across this sample, which were organised into relevant themes such as pregnancy-specific terms, research concepts, and confidentiality (Table 6-2). The workshop focused on how these different terms could be translated for a Zambian population, and the potential difficulties that might be encountered when doing so. Through our discussion with workshop participants, we were able to identify which commonly occurring terms were most difficult to translate. For example, participating translators highlighted the lack of equivalent terms (in Nyanja or Bemba) for words such as “pre-eclampsia”, “proteinuria”, and “contractions”, as well as differing interpretations of words such as “research”, “benefits” and “risks”. The word “consent” itself was also raised as a term which could be interpreted differently depending on the context, with some communities being less familiar with the concept of individualised consent than others.

Table 6-2 Content analysis of recruitment documents

Theme	Frequency (documents/13)
Pregnancy specific	
Pregnancy; pregnant women	9
Pre-eclampsia	5
Blood pressure; high blood pressure	6
Delivery; childbirth	6
Placenta; umbilical cord	4
Complication; adverse birth outcomes	5
Urine sample; protein level in the urine	4
Ultrasound	3
Contractions	1
Planned early delivery; preterm birth	2
Trial participation	
Take part; you are being invited to take part in a research project; participation; participating	11
Withdraw; you are free to decline to participate; you are free to withdraw from the study at any time	10
You are not forced to participate in this study; you do not have to take part in this research if you do not wish to do so	3
Your decision will not affect the affect the care you receive in any way; there is no penalty if you choose not to take part	5
We would like to invite you to take part; we request your co-operation; we would like to invite you to participate in this study	3
You can receive care whether you take part in our study or not; you do not have to be in the research study to receive health care	2
Voluntary Consent	
Your participation is entirely voluntary; I consent voluntarily as a participant in this research	10
Consent; consent form	7
Permission	3
Informed choice	2
If you agree to take part	1
Risk	
Concerns	5
Dangerous	2
Risk; risk factors	9
Serious complications/consequences	5
Side effects	4
Discomfort	5
No risk	4
Suffer	3
Problems	6
Benefit	
Benefit; benefits to you; important benefits	8
Benefit others; benefit to society	2
Direct benefit; may not help you directly; no personal benefit	4

Improve; improve care; improve health/outcomes	4
Possible/potential benefits	6
Healthcare related	
Your health; your baby's health	6
Care; improve care	6
Symptoms and signs	2
Treatments/Treating	5
Severe problems	2
Samples	3
Results	4
Medicine	3
Injection	4
Infection	3
Condition	3
Drug/study drug	2
Healthcare; healthcare providers; health facilities; health information	5
Swelling	2
Test	3
Swab	2
Research concepts	
What is the purpose of the study	9
Study	11
Academic collaborators	1
Analysis/Analysed	1
Chance; 50/50 Chance	4
Collect	7
Research	10
Published/publications	3
Knowledge	3
Measure/measurements	3
Presentation at international meetings/conference	2
Sponsor	3
Title of research	1
Confidentiality/data management	
Anonymous/Anonymised	4
Confidential	11
Data	5
Protected; kept under lock and key	6
Information; information about you; information that is collected about you and your baby	13
Results	4
Personal information/details; contact information/details	7
Identity	4
Identify	2
Data collected about you; data collection forms; data manager	3

Independently performed back translations of participant information leaflets that had already been translated by the participating translators (for the timing of

delivery in pre-eclampsia trial) were also discussed, with important examples of discrepancies shown in Table 6-3. The translators performing these initial translations each worked as professional teachers of either Nyanja, Bemba, or both, in the public education system in Zambia, and each had at least five years' experience of translating research documents for clinical trials. Although some of these discrepancies may be related to errors, rather than specific language barriers (for example, the addition of the word "funerals" in the first example provided), this highlights the importance of performing back translation (not always required by ethical review bodies), and allowing sufficient time for translators and researchers to meet face-to-face and discuss their work (an important process which, according to the translators interviewed, was frequently ignored by researchers). This interactive workshop highlighted several concerns regarding current procedures for designing and translating research documents, and the lived experiences of the participants suggested this was a common and widespread issue. The group therefore proposed further exploration of the language barriers to adaptation of maternal health recruitment materials in Zambia via in-depth interviews, followed by community focus group discussions to develop locally driven solutions that may be generalisable to other researchers working in similar settings.

Table 6-3 Examples of back translations

Original (English)	**Back translation (from Nyanja translation)**
We appreciate your time and are grateful for your help. However, there will not be any financial compensation for taking part in this study. By choosing to take part in this study you will be helping us to help other women like you in the future.	We are very thankful for giving us your time and all the help that you have rendered to us. Even if things are like this, they will be no funerals of any kind because you have taken part in this research study.
If you take part in the study we will collect some personal information. This will only be used by members of the research team if they need to contact you. This information will be kept confidential. This means that only members of the research team will have access to it, and it will not be shared with anybody else. The data will be protected according to UK Data Protection Laws.	I agree that my suggestions that I will give should be made use of in this lesson (the way my suggestions have been presented) I am aware that my suggestions will be kept following the best recommended practices of keeping secrets.

CRADLE-4 Phase 1: The feasibility and acceptability of planned early delivery in pre-eclampsia in a Low and Middle Income Setting.	Reviewing the advantages of early childhood delivery on the poor women and those at the centre of fending for their families. This is usually centered on the women with complications of swelling of feet and other body parts, excess proteins in the blood and urine and high blood pressure.
You have been invited to take part in this study because you have pre-eclampsia, but your condition does not require that your baby be delivered immediately.	Therefore, you are requested to take part in this study so as to help us get the facts regarding this matter.

6.5.1. Phases Two and Three: Interviews and focus group discussions

The initial theoretical framework was modified throughout the coding process, with the final thematic framework used for data analysis shown in Figure 6-2.

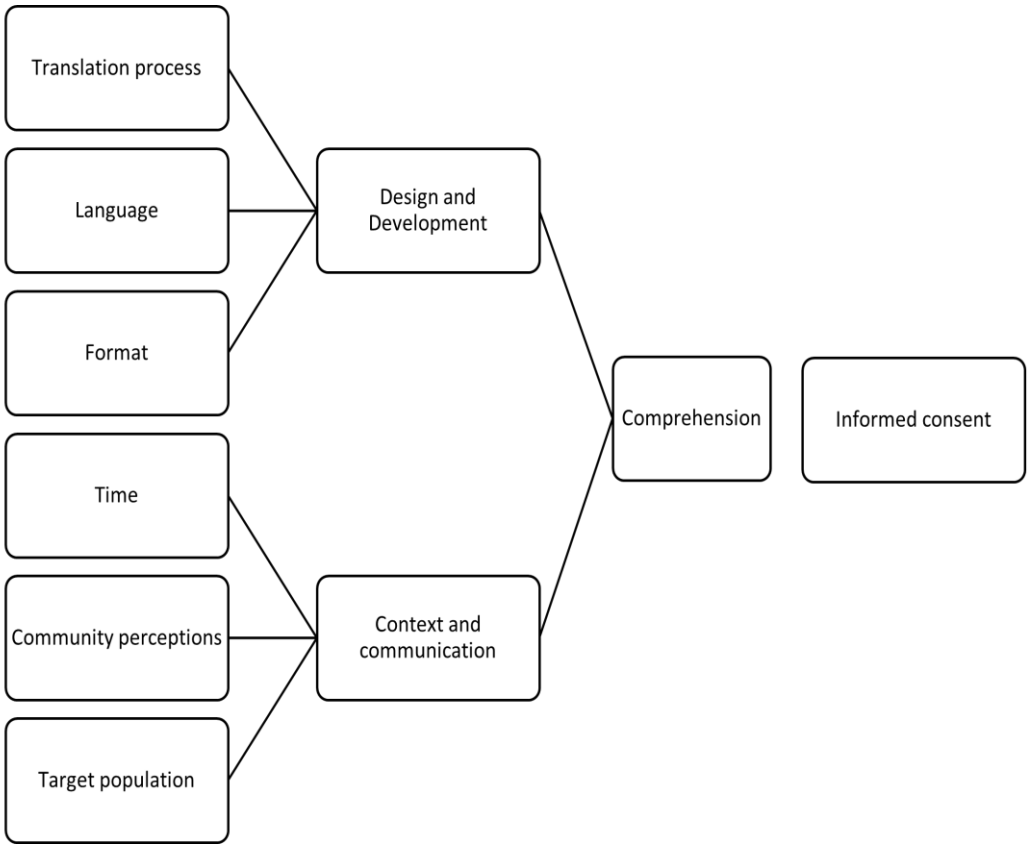


Figure 6-2 Thematic framework

6.5.1.1. Design and development of recruitment materials

The interview participants working as research coordinators felt they were not given sufficient opportunity to contribute to the design of recruitment materials at an early stage, stating that they are often invited to review documents only after they have already been finalised and submitted to the ethics committee (Table 6-4, quote D1). Information leaflets were criticised as being too long and wordy, with emphasis placed on the need to present key messages more succinctly using alternative methods such as flyers, community announcements, and household visits. The translation process itself was identified as a significant issue, due to an over-emphasis on literal word for word translations, rather than communicating the true meaning of the information. This issue was felt to be exacerbated by poor interactions between researchers and translators. The professional translators interviewed spoke of pressure to produce work within a tight timeframe, compounded by a lack of face-to-face meetings with researchers meaning that research principles and scientific concepts were often not thoroughly understood by the individual translating the document (Table 6-4, quote D2). Language itself was an important barrier, primarily due to a lack of equivalence – often there is simply no equivalent word in the local language for a particular English medical term. As a result, translators may try to explain the term using multiple words and phrases which ultimately distort or change the meaning (Table 6-4, quote D3). Furthermore, a clear distinction was made between "play" language and "formal" language with some translators criticising the overuse of formal language in translated documents, rendering them incomprehensible to the intended recipients who use different, more colloquial versions. Finally, the presence of multiple different languages in Zambia (72 in total) was identified as a further challenge, as most documents will be translated into just a few of these languages which will be understood to varying degrees by different individuals depending on their family background and where they live.

Focus group participants also felt that information in recruitment documents should be shortened and simplified, and that lengthy information relating to the

sponsoring institution and data protection was not necessary. Many participants felt that verbal explanations, audio-visual aids, and flip charts could enhance information provision, but agreed with interview participants that written documentation was an important component of the process that should not be eliminated. Participants felt that greater emphasis needed to be placed on the voluntary nature of study participation, with statements such as “you do not have to take part if you do not want to” given greater prominence and translated clearly and directly to ensure the meaning was clear. Participants also stated that language related to funding needed to be clarified, as direct translation of the English phrasing implied possible financial incentives could be provided by taking part. Participants also provided examples of different terms that may be used to explain pregnancy or birth depending on the context, and that whilst informal terms were sometimes considered less “respectful”, they were often better understood by their community (Table 6-4, quote D4). There was tension between some translators who wished to preserve the formal, grammatically correct version of their language as taught in schools, and focus group participants who preferred more colloquial terms. A suggested solution was using more informal terms in brackets so that both the official and colloquial terms could be presented and communicated effectively, depending on the user. Focus group participants also suggested creating a glossary of certain words at the start of any document, using local terms to explain in detail medical terms such as pre-eclampsia or proteinuria for the reader. Participants expressed specific preferences for different translations of particular words, examples of which are presented in Table 6-5. Throughout, more informal versions were preferred, and alternative terms suggested which were sometimes different from the versions originally provided by translators.

Table 6-4 Illustrative quotes

Design and development	
D1.“what I noticed is that we just receive the consent, you can’t change anything in the consent”	Interview participant
D2. “There are people, some people, would have sent work, you work on their consignment, you just send back. You’ve never met face-to-face. They have no time to sit with you”	Interview participant
D3. “pre-eclampsia in our local language, we don’t have it, it’s not there, so a translator need to have a rich vocabulary and full understanding for you to come up with the correct translation”	Interview participant
D4. “here in Lusaka they don’t use kubeleka, but instead they say (abala) so for this word, it will be difficult for the community to understand”	Focus group participant
Context and communication	
C1. “you will find that some people, when they find these women who maybe can’t read on their own and they have to read for them, so you will find that most of the time, there is this issue of inadequate information being given and it will be like fast done”	Interview participant
C2. “you need to get consent from the husband and yet the pregnant woman is an adult, so they can consent on their own but they will not consent, they want consent from their husband or from their parents”	Interview participant
C3. “people need to understand, what is ultrasound, what is this machine, why are you doing this on me? What is its effect”	Interview participant
C4. “HIV, where you are doing blood draws so they would, from communities, they would, they would think you are selling their blood”	Interview participant
C5. “looking at the community where we come from, the people that read this information trust me, most of them can’t read, most of them can’t even read the local language”	Focus group participant

Table 6-5 Suggested terms from focus group discussions

English	**Nyanja**
Pre-eclampsia	Bvuto la kutamanga kwamagazi ndikupezeka kwa dso kudya za mthupi mumitundo pa mene muzimai ali ndi pakati
Stroke	Sitoloko
Low birthweight	Mwana opepoka
Stillborn baby	Nthayo/makanda/ana
Premature baby	Mwana osakosa/osafikapo
Swelling of the legs	Kubvimba kwa mendo
Fitting	Kukunyuka
Urine	Mkhozo/mitundo
Protein in the urine	Kupezeka kwa zakudya zamthupi mu mitundo
High blood pressure	Kutamanga Kwamagazi (Bipi)
This research is brought to you by	Atibweretsera phunziro ndi…/ Akubweretserani…
What are the risks of taking part	Ciyopyezo kuipa/ Kodi kuipa kotengaku mbali ndi kwabwanji?
Research study	Maphunzilo/ Kufunafuna/ Kufufuza
Benefit	Ubwino/Phindu
What are the benefits of taking part?	Ubwino otengako mbali ndiwabwanji?
What is the purpose of the study	Colinga caphunziro ndi ciani?
Why have I been called/invited to take part?	Ndilifukwa ciani/ndaitanidwa kuti ndi tengeko mbali?
What will happen if I take part?	Kodi ndi ciani cizacitika ndi katengaka mbali
Consent form	Cipepala cobvomekeza
Randomisation	Magulu awiri/ Komputa iza zisankila/ Magulu losadzisankhira
Healthy	Umoyo wabwino
Address	Adelesi
Analyse results	Kusanda sanda
Problem/suffering	Mabvuto
The doctor will have to induce labour	Cilikidwa kuyambisidwa

6.5.1.2. Context and communication

The way in which information is communicated to participants, as well as the context into which it is being delivered, was highlighted by both interview and focus group participants as an important area needing improvement. Some interview participants felt that potential participants are not given sufficient time to consider the information provided, with decisions often expected on the same day that a

study is explained for the first time by research teams. Furthermore, some researchers described often needing to verbally explain recruitment materials to illiterate participants. They felt that this makes it difficult to standardise the information provided to potential participants and risks potential participants receiving insufficient or even inaccurate information (Table 6-4, quote C1). When considering the context into which translated documents are being introduced, all of the interview participants raised the importance of the target population and the need to consider the levels of literacy, the languages used, the age and gender of potential participants (for example many pregnant women require their husband's consent before participating in any study), and also the common misconceptions that may be prevalent within that community surrounding healthcare interventions or research studies (Table 6-4, quotes C2 to C4). Many interview participants highlighted the fact that use of inappropriate language or poorly designed forms will compound this issue, and risks both limiting the number of potential participants enrolled into a study and undermining the validity of the informed consent of those who do decide to take part.

Focus group participants raised similar concerns, recalling having previously been given brochures or leaflets to read, and not having the time or inclination to do so. Having more in-depth discussions, with audio-visual aids, and the opportunity for further discussions to ask questions at a later date were suggested as measures that may improve participant comprehension. Consistent with interview findings, focus group participants highlighted the importance of understanding the target community and in particular mentioned the fact that, in their experience, most individuals in their community could not read the local language (Table 6-4, quote C5). They felt that simple information should be provided in ways that are easy to understand such as flip charts and pictures. However, the background and education of potential participants was also highlighted as an important factor to consider when choosing the most appropriate information format – with participants suggesting that in some communities, video consent may be deemed suspicious or inappropriate. Geographical region was also highlighted as important,

with preferred terms changing depending on which area of the country the research is being conducted.

6.6. Discussion

Our collaborative workshop highlighted the discrepancies between the original English versions of recruitment materials and translated copies, as well as the difficulty in finding equivalent terms to accurately convey the intended meaning of key research concepts and medical words such as “pre-eclampsia”. We identified several barriers to participant comprehension and informed consent within in-depth interview data, including a lack of time available to translators, poor literacy, and rushed interactions between researchers and potential participants. Researchers working in Zambia felt that the content and layout of recruitment materials were designed by “the owners” in English speaking countries and that they had little opportunity to influence the design or make their voices heard, with translations subsequently regarded as poor quality. In contrast to the grammatically correct, formal translations often used by professional translators, focus group participants expressed a clear preference for translated versions of recruitment materials to use more informal language, and that this should vary depending on the target population of a study. Furthermore, whilst workshop participants suggested audio-visual aids as a potential solution, interview and focus group participants felt that although they may be a helpful supplement, it was important to have hard copies of written information to refer back to and maintain trust.

Previous research on informed consent has focused primarily on identifying gaps in participants’ understanding and evaluating community perceptions of research. Our findings correlate with those described by other studies, which found that there were widespread misconceptions regarding the purpose of research, the benefits and risks of taking part, and the use of research samples such as blood samples.(Molyneux et al., 2004; Molyneux & Bull, 2013) If the content of research documents does not address people’s fears and beliefs (for example around blood tests or ultrasound scans) and explain in detail what is expected of participants and why, participants may base their decision on whether to participate or not on

misinformation. Previous studies highlighted a need to further investigate the language barriers to effective communication about research, as well as to develop pre-tested and standardised tools that can be used to explain research concepts in a way the local community can understand. However, ours is the first study to our knowledge which explores these barriers, with a focus on translating recruitment materials. We therefore build upon the issues raised by previous work, exploring the specific difficulties relating to language and conceptual equivalence in more detail, adding voices from a cross-section of individuals in Zambia, directly involved in the design and implementation of maternal health research, as well as community representatives of target populations.

There has been a call to action within the global health community to redress the systemic imbalances that are perpetuated by Eurocentric institutions and practices.(Buyum et al., 2020) However, there are very few worked examples that demonstrate how these inequities may cause harm to research participants, and even fewer examples that suggest ways of dismantling these practices.(Khan et al., 2021) This study provides a practical and tangible example of ways in which researchers and ethical review boards can begin the process of change right away. A recent scoping review highlighted the financial, administrative, and regulatory barriers to good quality ethical review in low and middle income countries;(Chaudhry et al., 2022) our study provides relevant findings that may be used to address some of these concerns. A collaborative, multidisciplinary research programme in Kenya has successfully implemented a systematic approach to translating contextualised informed consent templates, drawing on community engagement processes within their research programme, which has received positive engagement from researchers and ethics committees.(Boga et al., 2011) We present our own summary of recommended actions for institutions, researchers, and translators, in Figure 6-3, which represents the perspectives of the Zambian participants in this study, and could be used to inform a similar approach in a Zambian setting.

Research institutions and ethics committees	Researchers	Translators
• Adopt a more flexible and adaptive approach to templates • Support research teams to develop recruitment materials that are context-specific •Ensure study protocols allow sufficient time and funding to support a robust translation process and consent process including community engagement activities • Ensure strong oversight mechanisms to verify the quality and appropriateness of translated materials •Support further research into alternative methods of providing participant information, such as pictures and videos	• Set aside sufficient time and funding to develop recruitment materials •Meet face-to-face with translators and local language experts, ensuring the true meaning of recruitment materials can be understood •Involve community representatives and local researchers from the outset, piloting early versions of translated materials and responding dynamically to feedback • Move away from lengthy word documents with information that may be considered irrelevant by potential participants • Consider a glossary of key terms at the start of any document, using simple and informal terms to explain important concepts or medical terms • Consider the most appropriate format for the intended recipients, including flip charts and videos if appropriate	• Move away from literal, word for word translations • Explore, and be guided by, local dialects and preferences for more informal language

Figure 6-3 Summary of recommended actions

6.6.1. Strengths and limitations

The initial research question and subsequent study design were influenced by the experiences of the study lead (ABG) when translating recruitment materials for the feasibility study informing the main timing of delivery in pre-eclampsia trial,(Beardmore-Gray et al., 2020; Beardmore-Gray et al., 2021) which suggested the specific difficulties encountered during this process may represent a wider issue. This was explored further during the course of data collection and analysis, acknowledging the potential biases that may have been carried forwards from this initial experience. Collecting data from different sources helped to counteract any inherent individual bias. For example, the assumption that participants might prefer information provided in alternative formats was dispelled by both interview and

focus group participants who felt it was important to have a written, hard copy of any recruitment materials. In their position as a trial coordinator, it is possible that interview and focus group participants may have viewed the study lead (ABG) as possessing a certain level of authority, and this in turn may have influenced the responses of the participants. Steps taken to counteract this included informal interview settings and using local translators to help facilitate focus group discussions. In their position as a researcher based in Zambia during the time period that this study took place, the study lead was able to connect with and seek out key informants within the local research community and seek guidance from local experts working in social science research. Language teachers and translators represented an important group of participants for this research. Whilst they had previous professional experiences of translating research materials, it was clear that the objective of this study was to understand and learn from their experiences, rather than engage them in a professional capacity, thus limiting the potential for any conflict of interest. Focus group participants were invited to attend from local community advisory boards (CABs). These groups are local volunteers who are often consulted to gain community input and perspectives on healthcare interventions and research studies.(Mwinga & Moodley, 2015) Whilst this meant they were well-placed to participate in the focus group discussions facilitated as part of this study, participants outside of this well-established model may have provided a wider array of insights.

The views of both interview and focus group participants likely represent an urban population, though many interview participants had experience of a wide range of research studies conducted over different time periods and in different areas of the country. Interview and focus group participants had many experiences of research, given that they lived in Lusaka, the capital city, where many of the healthcare facilities have ongoing involvement in several research projects. A more remote setting in areas where participants are less familiar with research may have provided different findings. However, given that the aim of this study was to specifically explore issues when translating, using, and understanding participant

information documents, the selected population is likely appropriate for the research objectives. Inclusion of ethical review board members, or study principal investigators, who are responsible for approving many of the recruitment materials used in global health studies, could have added an additional and important perspective on the issues explored in our study. Engaging these key stakeholders would be important in any future research, and when implementing our recommended actions.

6.7. Conclusions

Our study has identified that current methods of designing and translating recruitment materials for potential research participants in maternal health studies in Zambia, do not always facilitate true understanding, and therefore do not serve the needs of their intended recipients. This problem requires researchers and ethics committees to re-evaluate their current practice and move away from viewing translation as merely a tick-box exercise required to gain ethical approval, but a collaborative and dynamic process that can be adapted to suit the needs of the communities, countries, and languages in which the research is taking place.

Chapter 7 Planned early delivery versus expectant management to reduce adverse pregnancy outcomes in pre-eclampsia in a low and middle income setting: Study protocol for a randomised controlled trial (CRADLE-4 Trial)

This chapter matches the published paper, incorporating all relevant supplementary material, except when specified as an appendix.

7.1. Abstract

Background

Pre-eclampsia is a pregnancy complication characterised by high blood pressure and multi-organ dysfunction in the mother. It is a leading contributor to maternal and perinatal mortality, with 99% of these deaths occurring in low and middle income countries. Whilst clear guidelines exist for management of early onset (<34 weeks) and term (≥37 weeks) disease, the optimal timing of delivery in pre-eclampsia between 34^{+0} – 36^{+6} weeks is less clear. In a high income setting, delivery may improve maternal outcomes without detriment to the baby, but this intervention is yet to be evaluated in a low or middle income setting.

Methods

The CRADLE-4 Trial is a non-masked, randomised controlled trial comparing planned early delivery (initiation of delivery within 48 hours of randomisation) with routine care (expectant management) in women with pre-eclampsia between 34^{+0} - 36^{+6} weeks' gestation in India and Zambia. The primary objective is to establish whether a policy of planned early delivery can reduce adverse maternal outcomes, without increasing severe neonatal morbidity.

Discussion

The WHO recommends delivery for all women with pre-eclampsia from 37 weeks onwards, based on evidence showing clear maternal benefit without increased neonatal risk. Before 34 weeks, watchful waiting is preferred, with delivery recommended only when there is severe maternal or fetal compromise, due to the neonatal risks associated with early preterm delivery. Currently, there is a lack of

guidance for clinicians managing women with pre-eclampsia between 34^{+0} - 36^{+6} weeks. Early delivery benefits the mother but may increase the need for neonatal unit admission in the infant (albeit without serious morbidity at this gestation). On the other hand, waiting to deliver may increase the risk of stillbirth, fetal growth restriction, and hypoxic brain injury in the neonate as a result of severe maternal complications. This is especially true for low and middle income countries where there is a higher prevalence of adverse events. The balance of risks and benefits therefore needs to be carefully assessed before making firm recommendations. This is the first trial evaluating the optimal timing of delivery in pre-eclampsia in a low income country (LIC) and a lower-middle income country (LMIC), where resources and disease burden are considerably different.

Trial registration

ISRCTN 10672137. Registered on 28th November 2019.
http://www.isrctn.com/ISRCTN10672137

7.2. Background

Pre-eclampsia is a pregnancy specific disorder which complicates 2-8% of pregnancies worldwide (Steegers et al., 2010) and up to 12% of pregnancies in low and middle income countries.(Poon et al., 2019) Pre-eclampsia is responsible for 76,000 maternal deaths and 500,000 perinatal deaths each year (Poon et al., 2019) with the overwhelming majority (99%) of these occurring in Sub-Saharan Africa and South Asia.(Duley, 2009)

Pre-eclampsia is a multi-system disorder. It arises due to inadequate perfusion of the uteroplacental unit, leading to hypoxic placental tissue and endothelial dysfunction. The resulting systemic vascular inflammation leads to widespread organ involvement in the mother as well as growth restriction and even stillbirth in the fetus.(Steegers et al., 2010) Its clinical course is difficult to predict, and the development of symptoms is usually an indicator of end-stage organ damage. The only definitive management of pre-eclampsia is delivery of the dysfunctional

placental unit – thereby ending the pregnancy. Given the progressive and unpredictable nature of the condition, timely intervention and delivery is key.

Delivery at 37 weeks onwards is recommended by the WHO for all women with pre-eclampsia irrespective of disease severity.(World Health Organization, 2011) Prior to 34 weeks (which is an important milestone for fetal lung maturity) expectant management is preferable due to the neonatal risks associated with early preterm birth.(World Health Organization, 2011) Therefore, delivery before 34 weeks' gestation is usually only initiated if there are signs of severe maternal or fetal compromise.

Guidance on the optimal timing of delivery in late preterm pre-eclampsia (between 34^{+0} - 36^{+6} weeks' gestation) is less clear and is likely to be context dependent. In different settings, the risks and benefits of delivery may vary according to the prevalence and character of serious adverse events and the facilities available to manage them.

Currently, a policy of close surveillance is pursued until either 37 weeks' gestation is reached (at which point delivery is recommended) or an indication for immediate delivery (evidence of severe maternal or fetal compromise) develops. It is likely that planned early delivery would benefit the mother as this is the cure to the disease process, however this must be balanced against any potential risks associated with late preterm delivery to the neonate.

In high income settings, previous randomised controlled trials have shown that planned early delivery between 34^{+0} and 36^{+6} weeks' gestation in pre-eclampsia reduces the risk of severe complications in the woman.(Bernardes et al., 2019; Broekhuijsen et al., 2015; Chappell, Brocklehurst, et al., 2019) An increase in neonatal unit admissions amongst infants in the planned delivery group has been reported, though serious neonatal morbidity remains uncommon at this gestation.(Chappell, Brocklehurst, et al., 2019) Planned early delivery has only been

shown to increase respiratory distress syndrome in the neonate when the study population included women with gestational hypertension with a longer time to delivery interval in the usual care arm.(Broekhuijsen et al., 2015) This, and the fact that antenatal corticosteroid use was less prevalent in this study may explain the difference in neonatal respiratory morbidity between the two arms.

This question is yet to be evaluated in a low and middle income setting. Planned early delivery at this gestation may increase risk to the neonate given the lack of neonatal intensive care facilities. In addition, the availability of antenatal corticosteroids and indeed their impact on neonatal outcomes is yet to be fully evaluated in low and middle income countries.(Althabe et al., 2015; Vogel et al., 2017) However, in settings where the disease burden and incidence of serious complications (in particular eclampsia, renal insufficiency, placental abruption, and stillbirth) are related, in part, to inadequate surveillance and delayed intervention, planned early delivery may in fact confer even greater benefit for the woman and the infant to that seen in a high income setting. Severe disease in this setting implies time to delivery intervals will be shorter, and the benefit of removing maternal harm relatively greater than the risk of immaturity. Given the disproportionate number of maternal and perinatal deaths occurring in low and middle income countries, it is imperative that interventions designed to reduce mortality and morbidity are developed and tested within these settings, where their impact may be considerably different.

There is therefore a need to compare a policy of planned early delivery to expectant management for late preterm pre-eclampsia in low and middle income settings. This trial aims to establish whether planned early delivery in women with pre-eclampsia between 34^{+0} and 36^{+6} weeks' gestation can reduce adverse pregnancy outcomes in India and Zambia.

7.3. Methods/Design

7.3.1. Trial objectives

The aim of this trial is to establish whether planned early delivery in pre-eclampsia between 34^{+0} and 36^{+6} weeks can reduce adverse pregnancy outcomes compared to expectant management in a low and middle income setting.

7.3.2. Primary objectives

The primary objectives of the study are:

1. To evaluate whether planned early delivery for women with pre-eclampsia between 34^{+0} and 36^{+6} weeks of gestation can reduce maternal mortality and morbidity based on a composite of outcomes during pregnancy and delivery, until primary hospital discharge.
2. To evaluate the impact of the intervention on short term neonatal outcomes. These will be assessed based on a composite of stillbirth, neonatal death, and neonatal unit admission for >48 hours due to neonatal morbidity, until primary hospital discharge.

7.3.3. Secondary objectives

The secondary objectives of the study are:

1. To evaluate the impact of the intervention on individual components of the primary outcomes and other secondary short-term outcomes for the mother and baby.
2. To evaluate the impact of the intervention on health resource use and cost.
3. To assess how the intervention influences the experiences of women.
4. To evaluate how the effectiveness of the intervention and its implementation is influenced by external factors (specifically resource availability and health system factors).

7.3.4. Trial design

This will be a pragmatic, multicentre, randomised controlled trial of planned delivery versus expectant management in 872 women with pre-eclampsia between 34^{+0} and 36^{+6} weeks of gestation inclusive.

7.3.5. Study setting

The trial will be conducted in five tertiary hospitals across India and Zambia, including their referring district healthcare facilities (sites listed on http://www.isrctn.com/ISRCTN10672137). An initial six-month feasibility study was conducted across the proposed trial sites. This was a mixed-methods study consisting of semi-structured interviews with a cross-section of healthcare providers, focus group discussions with pregnant women and their relatives, and a retrospective case notes audit evaluating gestation specific maternal and neonatal outcomes in women with pre-eclampsia. The results of this feasibility study directly informed the development of the interventional phase protocol.

Recruitment is anticipated to take 22 months based on an assumption that approximately 45 participants will be recruited per month (across all sites), with some allowance for unforeseen events and centres recruiting slower than expected. Daily visits by the research team to the relevant clinical areas at each healthcare facility will ensure that all potentially eligible participants are screened. In addition to this, key personnel at each of the referring healthcare facilities will be provided with a basic mobile phone and airtime in order to facilitate referrals of potentially eligible participants. The development of culturally appropriate trial materials for both participants and key members of their household will help to engage and inform potential participants. Dissemination of trial posters and flowcharts will ensure that clinical staff are well informed and aware of trial procedures. If necessary, additional strategies to boost trial recruitment (such as additional sites or small financial incentives for clinical staff will be considered).

7.3.6. Selection and withdrawal of participants

7.3.6.1. Inclusion criteria

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

- Able to give valid written, informed consent
- Viable ongoing pregnancy at time of recruitment

- Clinical diagnosis of pre-eclampsia confirmed by the obstetric team: must fulfil minimum criteria of hypertension and proteinuria after 20 weeks' gestation. Hypertension will be defined as a systolic blood pressure of ≥ 140mmHg and/or a diastolic blood pressure of ≥90mmHg (or on anti-hypertensive drug at enrolment). Proteinuria will be defined as a 'positive' (≥ 1 + protein) urine dipstick result.(Brown et al., 2018)
- Gestational age between 34^{+0} and 36^{+6} confirmed by a doctor (as determined by known last menstrual period date validated by early or late ultrasound scan if available)

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

7.3.6.2. Exclusion criteria

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

7.3.7. Recruitment, eligibility, and consent

Members of the research team will provide a full verbal explanation and written description (in the relevant local language) to women who meet the inclusion criteria (as above). Additionally, participant information videos in local languages have been developed to aid comprehension amongst both trial participants and their relatives. 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 member of the research team.

7.3.8. Study periods

A woman's participation in the study may be from 34 weeks' gestation until primary discharge of the woman and her baby after birth, as outlined in Figure 7-1 below. Long-term follow-up will be considered by obtaining permission to contact participants later, but only after further ethical approval and governance has been

ascertained. Both the maternal and neonatal short-term outcomes will be collected quickly as the time period from randomisation to outcome collection will not exceed 14 weeks (participants will be followed up until primary discharge of mother and baby post-delivery) and in many cases will be less. Outcome collection will end 42 days after the final participant has been recruited (or sooner if primary discharge of mother and baby occurs before this endpoint).

Procedure	**Screening**	**Randomisation**	**Delivery**	**Postnatal hospital discharge**
Assessment of eligibility	x			
Informed Consent	x	x		
Baseline Data collection		x		
Decision regarding timing of delivery		x	x	
Data collection until discharge from hospital			x	x

Figure 7-1 Schedule of participant enrolment, interventions, and assessment in the trial (SPIRIT figure)

7.3.9. Withdrawal of participants

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. For a woman allocated to the expectant management group, if clinical needs dictate delivery prior to 37 weeks' gestation based on local criteria, 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 be monitored by her attending clinician, this will not constitute withdrawal from the study.

7.3.10. Assessment of outcomes

Outcomes will be recorded on the web-based database after a review of case notes by trained members of the research team. This will be done contemporaneously and completed no later than 24 hours after the mother and baby have been discharged. Confirmation of maternal and neonatal outcome data will be undertaken with an additional sign-off by the site's principal investigator for each participant and constant communication with the relevant clinical teams.

7.3.11. Co-primary outcomes

7.3.11.1. Primary short-term maternal outcome

Maternal mortality and morbidity based on the miniPIERS composite (Payne et al., 2014) (see Table 7-1 for full list) of adverse maternal outcomes (with the addition of severe hypertension) during pregnancy and delivery until primary hospital discharge.

Table 7-1 Full definitions of individual components of the primary short-term maternal outcome

Outcome	Definition
Mortality	Maternal death occurring before primary discharge from hospital
Hepatic dysfunction	Elevated liver enzymes (alanine transaminase or aspartate transaminase ≥ 70 IU/L)
Hepatic haematoma or rupture	Blood collection under the hepatic capsule as confirmed by ultrasound or laparotomy
Glasgow coma score < 13	Based on Glasgow Coma Scale scoring system (Teasdale & Jennett, 1974)
Stroke	Acute neurological event with deficits lasting longer than 48 hours
Cortical Blindness	Loss of visual acuity in the presence of intact pupillary response to light
Reversible Ischaemic Neurologic Deficit (RIND)	Cerebral ischaemia lasting longer than 24 hours but less than 48 hours revealed through clinical examination
Retinal detachment	Separation of the inner layers of the retina from the underlying retinal pigment epithelium (RPE, choroid) and is diagnosed by ophthalmological exam
Acute renal insufficiency	For women with an underlying history of renal disease: defined as creatinine >200 uM; for women with no underlying renal disease: defined as creatinine >150 uM
Dialysis	Including haemodialysis and peritoneal dialysis
Postpartum haemorrhage (PPH) requiring transfusion or hysterectomy	Occurrence of PPH that required transfusion or hysterectomy
Placental Abruption	Any occurrence of abruption diagnosed clinically or based on placental pathology report
Platelet count < 50,000 without blood transfusion	Measurement of platelet count recorded as less than 50,000 without patient being given a blood transfusion
Transfusion of blood products	Includes transfusion of any units of blood products: fresh frozen plasma (FFP), platelets, red blood cells (RBCs), cryoprecipitate (cryo) or whole blood. Includes request for transfusion even if products unavailable at time of request
Positive inotropic support	The use of vasopressors to maintain a systolic blood pressure >90 mmHg or mean arterial pressure >70 mmHg
Myocardial ischaemia/infarction	ECG changes (ST segment elevation or depression) with ischaemic symptoms with or without typical enzyme changes
Eclampsia	Any episode of seizure antepartum, intrapartum or before postpartum discharge as follow-up beyond discharge is not possible
Require >50% oxygen for greater than one hour	Oxygen given at greater than 50% concentration based on local criteria for longer than 1 hour

Intubation other than for Caesarean section	Intubation may be by endotracheal tube insertion or continuous positive airway pressure
Severe breathing difficulty	Suspected pulmonary oedema where x-ray confirmation is unavailable may be diagnosed by presence of chest pain or dyspnoea, crackles in the lungs and SaO_2 <90%
Pulmonary Oedema	Clinical diagnosis with x-ray confirmation or requirement of diuretic treatment and SaO_2 <95%
Severe hypertension	Systolic blood pressure of ≥160mmHg between randomisation and post-delivery discharge

7.3.11.2. Primary short-term perinatal outcome

Composite of one or more of antenatal/intrapartum stillbirth or neonatal death (but not deaths due to congenital anomalies) or neonatal unit admission >48 hours due to neonatal morbidity (necessitating admission to the neonatal unit according to local guidelines) until primary hospital discharge.

7.3.12. Secondary outcomes

Secondary maternal outcomes will include assessment of:

- Individual components of the primary outcome
- Mode of onset of birth (spontaneous, induced or pre-labour caesarean section)
- Primary indication for delivery in both arms
- Intensive care unit admission
- Length of stay in hospital (prior to delivery and after delivery)
- Time from randomisation to delivery (process outcome)
- Use of magnesium sulfate
- Use of antenatal corticosteroids for fetal lung maturity
- Use of antihypertensive medications

Secondary perinatal outcomes will include assessment of:

- Individual components of the primary outcome
- Mode of delivery (vaginal vs. all others)
- Gestational age at delivery
- Birthweight
- Birthweight centile

- Admissions to neonatal unit (and primary indication)
- Total number of nights in hospital and number of nights in each level of care for babies admitted
- Sepsis - with evidence of confirmed infection
- Course of antibiotics given for possible serious bacterial infection (according to the WHO Integrated Management of Childhood Illness (IMCI) guidelines)(Robinson, 1996)
- Apgar score at 5 and 10 minutes post birth
- Need for neonatal resuscitation
- Hypoxic Ischaemic Encephalopathy and Grade
- Neonatal seizures requiring anti-convulsants
- Respiratory Distress Syndrome
- Supplementary oxygen and duration required
- Use of continuous positive airway pressure ventilation and duration required
- Invasive ventilation support and duration required
- Administration of surfactant
- Hypoglycaemia (<2.6 mmol) requiring intervention
- Hypothermia (Temperature <36.5 degrees Celsius)
- Neonatal jaundice requiring phototherapy
- Necrotising enterocolitis (diagnosed at surgery or resulting in death)
- Nasogastric feeding required and indication
- Exclusively breast-fed at discharge from hospital

7.4. Trial procedures

7.4.1. 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, in her preferred language). The local research team at each site are fluent in English and the relevant local languages spoken by the majority of the population across the trial sites (Bemba and Nyanja at the Zambian sites, Kannada

at the Indian sites). The participant information leaflet (examples provided in Appendix 6 and 7) will be read aloud to women who are unable to read it themselves. Partners and relatives will be included in the discussion but may not consent on the woman's behalf. Additionally, three short video clips addressing key topics (pre-eclampsia, trial participation, and the neonatal unit) will be made available to all potentially eligible participants, particularly those with limited literacy. Written informed consent will be given using an informed consent form, completed, signed (thumbprints also accepted), and dated by the woman and signed by the member of the research team who obtained informed consent. After written informed consent has been obtained, a member of the research team will enter the baseline maternal details onto the online database and perform randomisation, communicating the results directly to the woman and her clinical team. Antenatal, intrapartum, and postpartum care will be in accordance with local guidelines and capacity at each site. Delivery will typically be through induction according to local protocol (most commonly oral or vaginal administration of misoprostol). The schedule of care for each group will be as follows:

7.4.2. Intervention (planned delivery) group

The intervention is planned delivery, to be undertaken as soon as feasible (aimed to be commenced within 48 hours) after randomisation. Use of antenatal corticosteroids for fetal lung maturity will be at the discretion of the clinician, in accordance with local guidelines (confirmed as readily available across all facilities). Postnatal care will be in accordance with local protocols and guidelines.

7.4.3. Control (expectant management) group

Expectant management involves close monitoring of the maternal and fetal condition until the woman reaches 37 weeks, or a crisis develops necessitating delivery. Delivery is recommended if the woman develops severe pre-eclampsia. This is in accordance with WHO guidelines which are followed at all of the proposed trial sites.(World Health Organization, 2011)

7.4.4. Time of delivery - adherence to protocol:

Following randomisation to either the planned delivery group or expectant management group, the time of 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 protocol for both study groups to be reviewed and protocol deviations to be identified and investigated.

7.4.5. Sample size

The sample size for the CRADLE-4 study is calculated on the ability to detect a clinically important reduction in the primary maternal outcome: a short-term composite based on the presence of one or more of 22 maternal morbidities. Based on data acquired at the sites prior to start of the main trial, we anticipate an event rate of 80% for the primary maternal outcome in the expectant management arm. We have calculated that a sample size of 558 would provide 90% power to detect a 15% relative risk reduction. If the trial is recruiting well, we will continue to recruit 872 participants which would give 90% power to detect a 12.5% relative risk reduction and greater precision to detect secondary outcomes. The Data Monitoring Committee (DMC) will review the primary event rate and usual safety data and make a recommendation to continue or stop. A one-sided non-inferiority analysis is planned for the primary neonatal composite. Our data acquired at the sites prior to starting the main trial showed an event rate of 24% for the primary neonatal outcome. Complete data on 480 women (240 per group) are required for 90% power to exclude a difference against planned delivery of 10% or more. To exclude a difference of 7.5%, 852 women (426 per group) are needed. The calculation uses a one-sided significance test and confidence interval and assumes that the true event rate is 24%. This is in line with the planned sample size as detailed above.

7.4.6. Randomisation

Randomisation will be managed by a secure web-based randomisation facility hosted by MedSciNet. The allocation ratio of intervention

(planned early delivery) to control (expectant management) will be 1:1. Participants will be stratified by centre and minimised by parity (0 or ≥1), single/multi-fetal pregnancy (singleton or multi-fetal), and gestational age (34^{+0}-34^{+6}, 35^{+0}-35^{+6}, 36^{+0}-36^{+6}) at randomisation. MedSciNet will write the randomisation programme and hold the allocation code. Following randomisation, a clinician will then arrange for delivery or ongoing expectant management as the randomisation indicates.

7.4.7. Masking

Due to the nature of this study, masking of clinicians, nursing staff, and participants is not possible. In view of arrangements for the conduct of the trial at these sites, it is not feasible to arrange for a separate team of outcome assessors masked to intervention allocation. Data analysis will be conducted masked to group allocation.

7.4.8. Data collection

Much of the outcome data for this trial are routinely recorded clinical items that can be obtained from the clinical notes. No additional blood or tissue samples are required for this study. Outcomes will be recorded prospectively using case report forms (CRFs). When possible, online versions will be used (eCRFs) and outcomes therefore recorded directly on the trial database. If, due to power shortages or lack of internet connectivity this is not feasible, paper case report forms will be used, and data then directly transcribed into the database.

7.4.9. Assessment of safety

The DMC will ensure the wellbeing of study participants and will periodically review study progress and outcomes, as well as reports of unexpected serious adverse events (SAEs). The DMC will, if appropriate, make recommendations regarding continuance of the study or modification of the study protocol.

7.4.10. Adverse events

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

7.4.10.1. Serious adverse events

A serious adverse event is any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires participant hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity

7.4.10.2. Expected SAEs

Expected SAEs are those events which are expected in the patient population or as a result of the routine care/treatment of a patient. The following events are expected in women with pre-eclampsia and their infants and will be recorded as part of outcome collection (during a woman's participation in the trial - from randomisation until primary hospital discharge of either mother or baby) but do not require reporting as SAEs:

Expected maternal SAEs

- Hepatic dysfunction
- Hepatic haematoma or rupture
- Coma/impaired consciousness (Glasgow coma score <13)
- Maternal stroke
- Cortical blindness
- Reversible ischaemic neurological deficit
- Retinal detachment
- Acute renal insufficiency or failure
- Postpartum haemorrhage requiring transfusion or hysterectomy
- Placental abruption
- Platelet count <50,000
- Severe uncontrolled hypertension
- Myocardial ischaemia/infarction
- Eclampsia

- Severe breathing difficulty
- Pulmonary oedema
- Sepsis
- Venous thrombo-embolism
- Admission to hospital for pregnancy and any related pregnancy complications
- Admission to ITU for pregnancy and any related pregnancy complications
- Any pregnancy related complication requiring surgical management

Expected infant SAEs

- Congenital anomaly
- Low birth weight
- Requirement for supplemental oxygen or ventilation support
- Sepsis confirmed by positive cerebrospinal fluid or blood cultures
- Necrotising enterocolitis
- Seizures
- Hypoxic ischaemic encephalopathy
- Hypoglycaemia
- Admission to neonatal unit for any indication

7.4.10.3. Unexpected SAEs

An unexpected SAE is any event that meets the definition of a SAE and is not detailed in the list above as expected. The following events, whilst not entirely unexpected in this population, are nevertheless serious enough that they should be reported. However, we anticipate that these will be more related to the disease process in this setting and not directly related to the intervention. With this in mind, they will be aggregated and reviewed on a 3-monthly basis by the DMC:

- maternal death
- neonatal death
- antepartum or intrapartum stillbirth

7.4.11. Safety reporting procedures

All SAEs (described above) will be recorded from randomisation to postnatal discharge from hospital of mother and baby. Unexpected SAEs for both the mother and infant will be recorded and reported to the DMC as described above. Details of the SAE should be recorded on an SAE form (either electronically via the study database or in paper format). Paper forms will be emailed to the trial coordinating team. An SAE occurring to a participant will be reported to the research ethics committee that gave a favourable opinion of the study where in the opinion of the Principal Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs will be submitted within 15 working days of the Principal Investigator becoming aware of the event, using the Health Research Authority (HRA) report of serious adverse event form. All reported SAEs will be reviewed by the DMC at regular intervals throughout the study. The Principal Investigator will inform all Investigators concerned of relevant information that could adversely affect the safety of participants.

7.4.12. Data 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 central trial research team 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.

7.4.13. Statistical analysis

The primary analysis for all maternal outcomes will be by the intention to treat principle with participants analysed in the groups to which they are assigned regardless of deviation from the protocol or intervention received. We will analyse the difference between arms in the randomisation to delivery interval (3 monthly) to ensure intervention compliance. Women in the expectant management arm will

frequently be delivered prior to 37 weeks of gestation due to clinical need and this will not be considered a protocol deviation.

The primary analysis for all perinatal and infant outcomes will be both an intention to treat and a per-protocol analysis, since the hypothesis under examination for these outcomes is a non-inferiority hypothesis. The per-protocol analysis will exclude babies of women who do not receive the allocated intervention as per protocol and will be further defined in the Statistical Analysis Plan (Appendix 11).

All outcomes will be analysed adjusting for minimisation factors at randomisation where possible.(Kahan & Morris, 2012) Where possible, continuous outcomes will be adjusted for baseline measurements of the same variable.(Vickers & Altman, 2001) Binary outcomes will be analysed using log binomial regression models. Results will be presented as adjusted risk ratios with associated confidence intervals (CI). If the model does not converge, logistic regression with robust variance estimation will be used.(Huber, 1967) Continuous outcomes will be analysed using linear regression models. Results will be presented as differences in means with associated CIs. 95% CIs will be presented for all primary outcomes and 99% CIs for secondary outcomes.

For the analysis of perinatal outcomes, we will treat all infants (singletons or multiples) separately, adjusting standard errors for clustering by mother. Pre-specified subgroup analyses will be undertaken for gestation at randomisation (test for trend) and for single vs. multi-fetal pregnancy, country, and region (with a region being tertiary centre and referring healthcare facilities). The consistency of the effect of planned delivery vs. expectant management across subgroups will be assessed using a likelihood ratio test for interaction. Loss to follow-up is expected to be about 5% for the short-term outcomes. A secondary per-protocol analysis will look at the primary outcomes according to the treatment actually received and time of randomisation.

The primary maternal outcome is maternal mortality and morbidity based on miniPIERS (Payne et al., 2014) plus severe hypertension (Table 7-1) during pregnancy or before hospital discharge. The maternal mortality and morbidity component of the primary outcome will be reported separately, as will the severe hypertension component. Additionally, a maternal mortality and morbidity composite of components detected by a clinical diagnosis only will be reported separately (outlined in further detail in the statistical analysis plan).

Health care resource use will include information collected on the management of pre-eclampsia, maternal hospital length of stay related to pre-eclampsia and delivery, maternal intensive care unit admissions, and perinatal neonatal unit admissions and hospital length of stay. Health care resource use will be costed using published sources and will be reported in United States Dollars (USD); costs will be reported in local currencies where possible. Mode of onset and mode of delivery will also be included in the costing. Means and standard deviations will be reported for health care resource items and costs. Linear regression and bootstrapping will be used to calculate the difference between treatment groups and 95% confidence intervals, adjusting for minimisation factors at randomisation.

7.4.14. End of trial

The end of the intervention phase will be when the last participating mother and infant have been discharged from hospital, or 42 days after the final participant has been recruited (whichever occurs sooner). For regulatory purposes the end of the trial is defined as the date when the study database is locked. An end of study declaration will be made to the approving research ethics committees within three months of this date.

7.4.15. Early cessation

In the light of interim data and other evidence from relevant studies, the DMC will inform the Trial Steering Committee (TSC) if, in its view, there is proof beyond reasonable doubt that the data indicate that the trial should be terminated. A

decision to inform the TSC of such a finding will in part be based on statistical considerations.

7.4.16. Evaluation of women's experiences

A purposeful sample of participants will be approached for consent to a qualitative interview exploring their experience of the trial intervention (or usual care arm).

7.4.17. Evaluation of implementation

The impact of external factors (specifically resource availability and health system factors) on the effectiveness of the implementation of the intervention will be assessed by conducting an audit of key resources available at each participating healthcare facility at regular (six-monthly) intervals during the trial, which will be reported using descriptive statistics. A subgroup analysis of the main trial results by site will identify any meaningful variations by site, which may be influenced by local resource availability.

7.4.18. Data handling

Anonymised data be will collected by the local research team under the supervision of the trial coordinator.

When possible, all anonymised data will be directly entered onto a secure, online database (MedSciNet). If the low-resource nature of the environments where we will be collecting the data means this is not possible, the local research team will be trained to accurately transfer any paper-based data onto MedSciNet, whilst maintaining confidentiality always.

Consent forms and source data where paper based, will be kept in files in secure areas at each central site. Only healthcare providers involved in trial participants' care, research assistants, the local trial coordinator, and the UK-based trial manager will have access to these. All paper documents will be stored securely and kept in confidence in compliance with the UK Data Protection Act 1998.

All data entered on the MedSciNet database in each facility will be automatically stored and backed-up. Collection and storage of clinical data in the database will be governed by the UK Data Protection Act 1998. All participants will be given a unique trial identifier and no personal information will be entered into the clinical trial database or sample database. Personal contact information will be held on a local database kept in a locked environment, after gaining written informed consent from trial participants.

All MedSciNet data is stored on high capacity servers that are operated by an external company. Servers are stored in locked rooms, with system monitoring 24x7, physical surveillance and surveillance cameras. A tape backup system is used for backing up the database.

The MedSciNet database will remain live for one year following completion of the main trial. A copy of this will then be kept on the KCL (King's College London) server for 20 years following the trial completion date, in accordance with the KCL Data retention schedule.

7.5. Discussion

Management of late preterm pre-eclampsia remains a challenging clinical scenario for clinicians around the world. Current evidence does not address those populations and contexts where the primary disease burden of pre-eclampsia lies. Whilst early onset pre-eclampsia (before 34 weeks' gestation) is typically regarded as a more 'severe' phenotype of the condition, pre-eclampsia at 34 weeks' gestation onwards is responsible for significant maternal and perinatal morbidity.(Kenneth et al., 2010) This is particularly true in low-resource settings where delays in seeking appropriate care and suboptimal quality of care contribute to high rates of maternal and perinatal mortality.(Arsenault et al., 2018) Planned early delivery beyond 34 weeks has the potential to reduce serious maternal complications (such as stroke, eclampsia, and death) as well as poor perinatal outcomes (such as severe growth restriction and stillbirth). Designing a trial

protocol to evaluate this research question in a robust manner, whilst taking into consideration the reality of the trial environment, is challenging and highlights many of the wider barriers to maternal health in low and middle income countries. The feasibility phase identified several key issues which informed the design of the main trial protocol. For example, a lack of availability of first trimester ultrasound scanning impacting upon gestational age assessment and lack of laboratory reagents for performing routine kidney and liver function tests. Diagnostic criteria for pre-eclampsia and outcome definitions required adapting to suit the local context, taking into account limited diagnostic resources (e.g. radiology services) and facilities (e.g. neonatal intensive care). Our intervention, if shown to be beneficial, must be reproducible and feasible to implement within a real-world scenario. The inclusion of two diverse countries (India and Zambia) will produce results that are generalisable to similar settings. Furthermore, ensuring that the trial protocol and procedures reflect the reality of maternity care in a low and middle income setting is essential in order to produce findings that will be of importance to local, national, and international policy makers.

7.6. Trial status

The current CRADLE-4 protocol is version 1.1 (14 November 2019). The trial opened to recruitment on 16 December 2019. The first participant was recruited on 19 December 2019. All trials sites were open by 24 January 2020. Recruitment is ongoing. We anticipate recruitment will be complete by 31 August 2021.

Chapter 8 Planned delivery or expectant management for late preterm pre-eclampsia in low income and middle income countries (CRADLE-4): a multicentre, open-label, randomised controlled trial

This chapter matches the published paper, incorporating all relevant supplementary material, except when specified as an appendix.

8.1. Summary

Background

Pre-eclampsia is a leading cause of maternal and perinatal mortality. Evidence regarding interventions in a low or middle income setting is scarce. We aimed to evaluate whether planned delivery between 34^{+0} and 36^{+6} weeks' gestation can reduce maternal mortality and morbidity without increasing perinatal complications, in India and Zambia.

Methods

In this parallel-group, non-masked, individual randomised controlled trial in nine sites across India and Zambia, we compared planned delivery versus expectant management in women with pre-eclampsia from 34^{+0} to 36^{+6} weeks' gestation. The primary maternal outcome was a composite of maternal mortality or morbidity with a superiority hypothesis. The primary perinatal outcome was a composite of one or more of: stillbirth, neonatal death, or neonatal unit admission >48 hours with a non-inferiority hypothesis (margin of 10% difference). Analyses were by intention to treat, together with a per-protocol analysis for the perinatal outcome. The trial was prospectively registered with ISRCTN 10672137.

Findings

Between Dec 19, 2019, and March 31, 2022, 565 women were enrolled. 284 women (282 women and 301 infants analysed) were allocated to planned delivery and 281 women (280 women and 300 infants analysed) allocated to expectant management. The incidence of the primary maternal outcome was not significantly different, although lower in the planned delivery group (154 [55%]) compared with the

expectant management group (168 [60%]); adjusted risk ratio 0·91, 95% CI 0·79 to 1·05. The incidence of the primary perinatal outcome by intention to treat was lower in the planned delivery group (58 [19%]) compared with the expectant management group (67 [22%]); adjusted risk difference for non-inferiority -3·39%, 90% CI -8·69 to +1·90; p=<0·0001 (non-inferiority). The results from the per-protocol analysis were similar. There was a significant reduction in severe maternal hypertension (aRR 0·83, 95% CI 0·70 to 0·99) and stillbirth (aRR 0·25, 95% CI 0·07 to 0·87) associated with planned delivery. There were 12 serious adverse events in the planned delivery group and 21 in the expectant management group.

Interpretation

It is safe to offer planned delivery to women with late preterm pre-eclampsia, in a low or middle income country setting. Planned delivery reduces stillbirth, with no increase in neonatal unit admissions or neonatal morbidity, and reduces the risk of severe maternal hypertension. It should therefore be considered as an intervention to reduce pre-eclampsia associated mortality and morbidity in these settings.

Funding

UK Medical Research Council and Indian Department of Biotechnology

8.2. Introduction

It is reported that 810 women die every day from preventable causes related to pregnancy and childbirth; the majority of these deaths (94%) occur in low and lower-middle income countries.(World Health Organization, 2019) In particular, women living in Sub-Saharan Africa and South Asia face a disproportionately high risk of dying.(World Health Organization, 2019) Hypertensive disorders of pregnancy are a leading cause of maternal death, with pre-eclampsia representing the most serious of these disorders. Pre-eclampsia complicates around 3-5% of pregnancies (Chappell et al., 2021) and is estimated to cause at least 42,000 maternal deaths (Chappell et al., 2021) and 500,000 perinatal deaths, including 200,000 stillbirths,(Lawn et al., 2016) every year. Pre-eclampsia is typically defined as new onset hypertension after 20 weeks' gestation with evidence of one or more

of proteinuria, maternal organ dysfunction, or uteroplacental insufficiency.(Brown et al., 2018) Pre-eclampsia can lead to severe consequences for the woman and infant, including eclampsia, maternal death and stillbirth. The clinical course is progressive, and difficult to predict, with delivery the only curative treatment. Early detection and timely delivery reduce complications for the woman.(Chappell, Brocklehurst, et al., 2019; Cluver et al., 2017; Koopmans et al., 2009) The timing of delivery must consider the risks (or benefits) of preterm birth for the infant. The WHO recommends delivery at 37 weeks' gestation for all women with pre-eclampsia irrespective of disease severity.(World Health Organization, 2011) Prior to 34 weeks, expectant management is considered preferable due to neonatal risks associated with early preterm birth, with delivery only recommended for severe maternal or fetal compromise.(National Institute for Health and Care Excellence, 2019; World Health Organization, 2011) Between 34 and 37 weeks of pregnancy, the optimal timing of delivery is less clear. Recent evidence from high income settings has demonstrated maternal benefit associated with planned delivery at this gestation, with an increase in neonatal unit admissions (compared to expectant management) but no increase in neonatal morbidity.(Chappell, Brocklehurst, et al., 2019) Fetal death is rare at late preterm gestations in high income settings, with none reported in our recent IPD meta-analysis.(Beardmore-Gray, Seed, et al., 2022) Based on our literature search, no published studies to date have reported a comparison of planned delivery versus expectant management for late preterm pre-eclampsia in a low or lower-middle income country, despite the overwhelming proportion of maternal and perinatal mortality occurring in these settings. The potential risks and benefits of late preterm delivery for the infant in a low-resource setting with varying levels of antenatal, intrapartum, and neonatal care available are likely to be different to those in a high income setting, and therefore this intervention requires careful evaluation. The aim of this trial was therefore to evaluate whether planned delivery between 34 and 37 weeks' gestation, in women with pre-eclampsia without an indication for immediate delivery, could reduce adverse pregnancy outcomes, compared to usual care (expectant management), in sites across India and Zambia.

8.3. Methods

8.3.1. Study design and participants

This was a multicentre trial with individual randomisation, across nine sites in India and Zambia, currently classified as lower-middle income and low income countries, respectively. The four sites in India were tertiary level urban referral hospitals based in the state of Karnataka. The five sites in Zambia were tertiary level urban referral hospitals based in Lusaka, Central, and Copperbelt provinces, including their referring healthcare facilities which serve a mixed urban and rural population. A full site listing is shown in Appendix 8. Ethical approval was obtained from King's College London (HR-19/20-13535), University of Zambia (UNZA-301/2019), BVV Sangha's S Nijalingappa Medical College (SNMCIEC/1·1 /2019-2020) and Women's and Children's Health Research Unit, KLE Academy of Higher Education and Research (KAHER/IEC/2019-20/D-251119016). Prior to designing the protocol for the interventional phase of the trial, we conducted a 6-month feasibility and acceptability study, seeking to understand the barriers and facilitators to our proposed intervention across the trial sites, including the acceptability of the intervention to pregnant women and their supporting relatives.(Beardmore-Gray et al., 2021) This directly informed trial design, enabling us to develop pragmatic methods of diagnosing pre-eclampsia (in accordance with ISSHP recommendations for low-resource settings (Brown et al., 2018)), determining gestational age, and defining clinical outcomes suitable for the local context.

A pregnant woman was eligible if she had a clinical diagnosis of pre-eclampsia and a gestational age between 34^{+0} and 36^{+6} weeks, as confirmed by a doctor, with a singleton or multi-fetal pregnancy and at least one viable fetus. Women with any other co-morbidity (including pre-existing hypertension, diabetes, and HIV) or having had a previous caesarean section, or with the fetus in any presentation, were eligible. Women were excluded if a decision had already been made to initiate delivery within the next 48 hours, as recommended for pre-eclampsia with severe features. Site research teams sought written consent from eligible women after a full verbal and written description of the trial in her preferred language,

supplemented by three short video-clips when available. A full version of the published study protocol is available: https://doi.org/10·1 186/s13063-020-04888-w. There were no substantial changes to the published study design, methods, or outcomes after the start of the trial. The trial is closed to recruitment and all follow-up has been completed.

8.3.2. Randomisation and masking

Baseline participant details were entered onto the trial database by local research assistants. Participants were randomly assigned to planned delivery or expectant management in a 1:1 ratio by a secure web-based randomisation facility hosted by MedSciNet. Randomisation was stratified by centre and minimised by parity, singleton/multi-fetal pregnancy, and gestational age (34^{+0}-34^{+6}, 35^{+0}-35^{+6}, 36^{+0}-36^{+6}). MedSciNet wrote the randomisation programme and held the allocation code. The randomised allocation was generated by the web-based programme (using a tablet computer or other internet-enabled device) and then directly communicated to the woman and her clinical team. Due to the nature of the intervention, masking of clinicians and participants was not possible.

8.3.3. Procedures

The intervention consisted of initiation of delivery within 48 hours of randomisation (to enable corticosteroid administration to accelerate fetal lung maturation if necessary) and expectant management comprised usual care, with delivery at 37 weeks' gestation or sooner if clinically indicated, in accordance with the WHO guidelines. This included both inpatient and outpatient monitoring depending on local capacity, clinical judgement, and women's preferences. Use of antenatal corticosteroids was left to the discretion of the clinical team, in line with local guidance. Method of induction, mode of delivery, intrapartum care, and postnatal care followed local clinical practice at each trial site. Outcomes were recorded on the web-based trial database contemporaneously by site research teams up until maternal and infant primary discharge from hospital. Each participant record was cross-checked by the trial coordinator and any queries resolved with local site teams with retrospective case notes review if required. The end of the intervention

phase was defined by the date when the last participating woman and infant were discharged from hospital, or 42 days after the final participant was recruited (whichever occurred sooner).

8.3.4. Outcomes

There was one primary maternal outcome and one primary perinatal outcome. The primary maternal outcome was a composite of maternal multi-organ pre-eclampsia associated morbidity based on miniPIERS outcomes (including maternal death, central nervous system, cardiorespiratory, haematological, hepatic, renal variables, and placental abruption, listed in full in our trial protocol (Beardmore-Gray et al., 2020)) modified to suit our trial environment,(Beardmore-Gray et al., 2020; Beardmore-Gray et al., 2021; Payne et al., 2014) with the addition of recorded systolic blood pressure of at least 160mmHg post-randomisation (on any occasion). The primary perinatal outcome was a composite of neonatal death, antenatal or intrapartum stillbirth or neonatal unit admission >48 hours due to neonatal morbidity (as defined by a clinical indication for admission to the neonatal unit according to local site guidelines). Secondary maternal outcomes included individual components of the composite primary outcome (miniPIERS outcomes or recorded systolic blood pressure of ≥160mmHg), miniPIERS outcomes detected by clinical diagnosis only, onset of labour, need for antihypertensives prior to delivery, primary indication for delivery and process outcomes such as length of stay and time from randomisation to initiation of delivery. Secondary perinatal outcomes included individual components of the composite outcome, any admission to the neonatal unit, number of nights in each category of care, total number of nights in hospital, birthweight, birthweight centile, birthweight less than tenth or third centile, gestational age at delivery, Apgar score at five minutes after birth, need for respiratory support, need for supplemental oxygen, confirmed diagnosis of sepsis, antibiotics given for possible serious bacterial infection, hypoxic ischaemic encephalopathy (all grades), and respiratory distress syndrome. Research teams undertook standard assessments of safety, with reporting of adverse events and serious adverse events as specified in the trial protocol and following the usual governance procedures for a clinical trial.

8.3.5. Statistical analysis

Assuming an anticipated composite adverse maternal outcome incidence of 80% in the expectant management group, based on data from the CRADLE-4 feasibility study,(Beardmore-Gray et al., 2021) a sample size of 558 women would provide 90% power to detect a 15% relative risk reduction of the primary maternal outcome in the planned delivery group with a two-sided 5% significance level and 90% power. With an anticipated 10% loss to follow-up, the overall inflated target for recruitment was 620 women. Assuming a composite adverse perinatal outcome incidence of 24%, based on data from the CRADLE-4 feasibility study,(Beardmore-Gray et al., 2021) complete data on 480 women would be required for 90% power to exclude a difference against planned delivery of 10% or more (based on a non-inferiority analysis using a one-sided 5% significance test and 90% confidence interval). This was in line with the planned sample size and overall recruitment target. 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 outcomes was by both intention-to-treat and per protocol since the hypothesis under examination for these outcomes was non-inferiority. All outcomes were analysed adjusting for minimisation factors at randomisation, which were gestational age at randomisation, twin pregnancy, and parity. Binary outcomes were analysed using log binomial regression models with results presented as adjusted risk ratios with associated confidence intervals (CI). Continuous outcomes were analysed using linear regression models with results presented as differences in means with associated CIs. 95% CIs are presented for all primary outcomes and their main components. 99% CIs are presented for secondary outcomes, in order to minimise the risk of a Type 1 error.

For all perinatal outcomes, all infants (singletons or multiples) were treated separately, adjusting standard errors for clustering by mother.(Rogers, 1994) Pre-specified subgroup analyses were done for primary outcomes based on gestation at randomisation (test for trend), singleton vs. multi-fetal pregnancy, country, and

region (with a region being tertiary centre and referring healthcare facilities). To allow for clinical and logistical delays, we did a pre-specified sensitivity analysis on the primary outcomes excluding women and infants randomised to the planned delivery group where initiation of delivery was more than 96 hours post-randomisation. Data analyses were done with STATA version 17. An independent data monitoring committee reviewed trial progress and conduct, including all reported serious adverse events, at regular intervals throughout the study. No formal interim analysis was planned, and guidance for early cessation of the trial followed the Haybittle-Peto principle that overwhelming evidence is needed in favour of one treatment option, such that randomisation is no longer ethical. The trial was prospectively registered with ISRCTN registry, ISRCTN 10672137.

8.3.6. 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.

8.4. Results

Between 19th December, 2019, and 31st March, 2022, 881 women were screened, and 584 women were found to be eligible, of whom 565 were enrolled (Figure 8-1), across four referral sites in Karnataka State, India and five referral sites and their linked primary healthcare facilities in Lusaka, Central, and Copperbelt provinces in Zambia (Appendix 8). 284 women were allocated to planned delivery and 281 to expectant management (Figure 8- 1). For the intention-to-treat analysis, data from 282 women and 301 infants in the planned delivery group and 280 women and 300 infants in the expectant management group were included. Follow-up to maternal and infant discharge continued until 12th May 2022. Two women allocated to planned delivery withdrew consent, and one woman was lost to follow-up in the expectant management group (Figure 8-1).

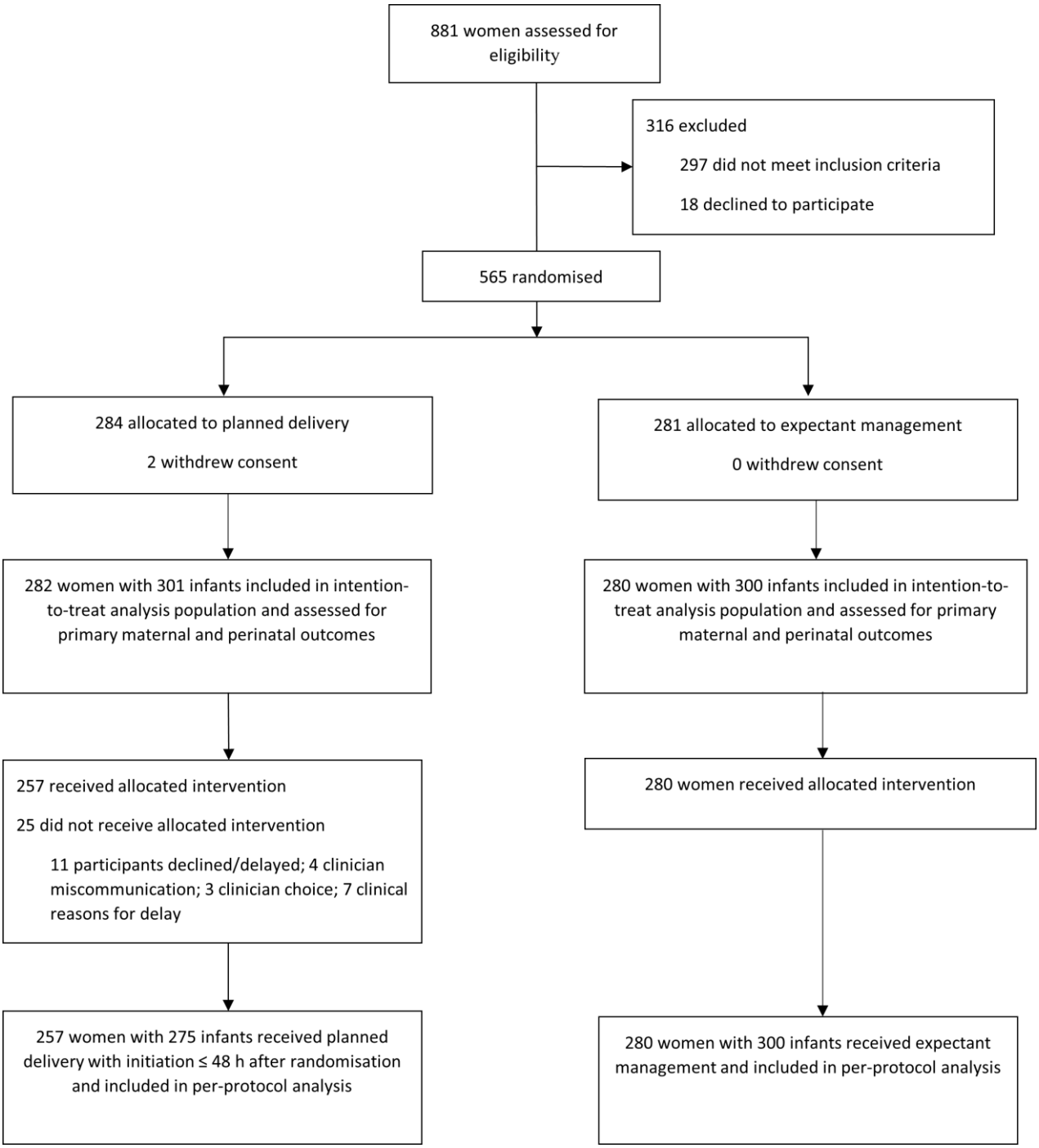


Figure 8-1 Trial profile

Baseline maternal characteristics appeared balanced between the two groups (Table 8-1). A high proportion of women in each group had their pregnancy dated using the self-reported date of their last menstrual period (122 [43%] and 142

[51%]). Only five [2%] women in the planned delivery group and 15 [5%] women in the expectant management group were prescribed aspirin at any stage during their pregnancy.

Table 8-1 Baseline maternal characteristics at enrolment

Characteristic	**Planned delivery n=282**	**Expectant management n=281**
Maternal age, years	28·53 (6·66)	28·07 (6·32)
Ethnicity		
Black – African	204 (72·3%)	202 (71·9%)
Asian – Indian	78 (27·7%)	79 (28·1%)
Educational level		
None	6 (2·1%)	4 (1·4%)
Primary	76 (27·0%)	70 (24·9%)
Secondary	159 (56·4%)	157 (55·9%)
Tertiary	41 (14·5%)	50 (17·8%)
No previous births*	110 (39·0%)	106 (37·7%)
One or more previous birth (≥24 weeks)	172 (61·0%)	175 (62·3%)
Previous caesarean section	53/172 (30·8%)	42/175 (24·0%)
High blood pressure in a previous pregnancy		
No	140/184 (76·1%)	120/186 (64·5%)
Yes	37/184 (20·1%)	51/186 (27·4%)
Unknown	7/184 (3·8%)	15/186 (8·1%)
Body Mass Index, kg/m^2	26·9 (5·8)	27·5 (6·1)
First trimester weight recorded	50 (17·7%)	61 (21·7%)
Tobacco use (any)	0	0
Pre-existing chronic hypertension	18 (6·4%)	29 (10·3%)
Pre-existing chronic renal disease	0	0
Human immunodeficiency virus positive	12 (4·3%)	12 (4·3%)
Pre-pregnancy diabetes	2 (0·7%)	2 (0·7%)
Gestational diabetes	3 (1·1%)	6 (2·1%)
Aspirin prescribed during pregnancy	5 (1·8%)	15 (5·3%)
Gestational age determined by:		
Last menstrual period	122 (43·3%)	142 (50·5%)
Early scan (before 24 weeks)	102 (36·2%)	96 (34·2%)
Late scan (at or after 24 weeks)	58 (20·6%)	43 (15·3%)
Median gestational age, weeks	35·7 (34·9, 36·4)	35·6 (34·9, 36·3)
Gestational age category*		
34 to <35 weeks	81 (28·7%)	78 (27·8%)
35 to <36 weeks	83 (29·4%)	90 (32·0%)
36 to <37 weeks	118 (41·8%)	113 (40·2%)
Singleton pregnancy*	263 (93·3%)	261 (92·9%)

Highest systolic blood pressure leading to pre-eclampsia diagnosis, mmHg	158·2 (13·9)	157·7 (13·9)
Highest diastolic blood pressure leading to pre-eclampsia diagnosis, mmHg	103·3 (9·6)	103·0 (9·5)
Severity of systolic hypertension at diagnosis		
≤149 mmHg	70 (24·8%)	80 (28·5%)
150-159 mmHg	97 (34·4%)	76 (27·0%)
≥160 mmHg	115 (40·8%)	125 (44·5%)
Proteinuria at diagnosis (dipstick)		
1+	120 (42·6%)	114 (40·6%)
2+	126 (44·7%)	121 (43·1%)
3+	28 (9·9%)	38 (13·5%)
4+	8 (2·8%)	8 (2·8%)

Data are n (%), mean (SD), or median (IQR). *Minimisation factors used to ensure balance at randomisation.

The proportion of women with the primary maternal outcome (Table 8-2) was lower in the planned delivery group (154 [55%]) compared to the expectant management group (168 [60%]), but this did not reach statistical significance (aRR [adjusted risk ratio] 0·91, 95% CI [confidence interval] 0·79 to 1·05). Planned delivery was associated with a similar incidence in the primary perinatal outcome compared to the expectant management group (58 [19%] versus 67 [22%]; aRR 0·88, 95% CI 0·64 to 1·21) (Table 8-2). The risk difference (RD) was less than 10% (RD -3·39% [90% CI -8·67 to +1·90, p value for non-inferiority <0·0001]); hence we can conclude non-inferiority of planned delivery compared to expectant management. The per-protocol analysis produced similar findings (aRR 0·88, 95% CI 0·64 to 1·23; non-inferiority risk difference -3·22%, 90% CI -8·61 to 2·18).

Table 8-2 Primary maternal and perinatal outcome

	Planned delivery	Expectant management	Risk ratio* (95% CI)	P value
Primary maternal outcome				
Intention to treat	154/282 (54·6%)	168/280 (60·0%)	0·91 (0·79 to 1·05)	0·182
Individual components:				
Post-randomisation severe hypertension	123 (43·6%)	146 (52·1%)	0·83 (0·70 to 0·99)	0·035
Maternal morbidity and mortality	61 (21·6%)	66 (23·6%)	0·92 (0·68 to 1.25)	0·601
Maternal morbidity and mortality detected by clinical diagnosis only[†]	14 (5·0%)	24 (8·6%)	0·58 (0·31 to 1·09)	0·091
Primary perinatal outcome				
Intention to treat	58/301 (19·3%)	67/300 (22·3%)	0·88 (0·64 to 1·21)	0·441
Per protocol	52/275 (18·9%)	67/300 (22·3%)	0·88 (0·64 to 1·23)	0·456
Non-inferiority:			**Risk difference* (90% CI)**	**P value for non-inferiority**
Intention to treat	58/301 (19·3%)	67/300 (22·3%)	-3·39% (-8·67 to 1·90)	p<0·0001
Per protocol	52/275 (18·9%)	67/300 (22·3%)	-3·22% (-8·61 to 2·18)	P<0·0001
Individual components:			**Risk ratio* (95% CI)**	**P value**
Stillbirth	3/301 (1·0%)	12/300 (4·0%)	0·25 (0·07 to 0·87)	0·029
Neonatal death[‡]	7/301 (2·3%)	5/300 (1·7%)		
Neonatal unit admission for >48hs	51/301 (17·1%)	52/300 (18·1%)	1·00 (0·71 to 1·41)	0·994

CI - confidence interval. *Analysis adjusted for gestational age at randomisation, twin pregnancy, parity. [†] Any one of: maternal death, hepatic haematoma or rupture, Glasgow coma score <13, Stroke, Cortical blindness, Reversible ischaemic neurologic deficit, retinal detachment, postpartum haemorrhage requiring transfusion or hysterectomy, placental abruption, myocardial ischaemia/infarction, eclampsia, requiring >50% oxygen for greater than one hour, severe breathing difficulty, pulmonary oedema. [‡] Excluding deaths due to congenital anomalies. Not tested due to pooled event rate <5% (as per Statistical Analysis Plan for this variable). P values are presented for superiority testing unless indicated otherwise.

Prespecified analysis of individual components of the primary maternal and perinatal composite outcomes demonstrated a statistically significant reduction in post-randomisation severe hypertension in women allocated to planned delivery (aRR 0·83, 95% CI 0·70 to 0·99), with a reduction in the same direction (but not statistically significant) seen in the maternal morbidity and mortality component (aRR 0·92, 95% CI 0·68 to 1·25). We demonstrated a significant reduction in stillbirth associated with planned delivery (aRR 0·25, 95% 0·07 to 0·87), with no statistically significant differences observed in neonatal death (7 [2%] versus 5 [2%]) or neonatal unit admission for >48 hours (aRR 1·00, 95% CI 0·71 to 1·41) between the two groups. The reduction in stillbirth was driven by a marked difference in antepartum stillbirths, with none occurring in the planned delivery group and ten occurring in the expectant management group. The number need to treat for planned delivery to prevent one antepartum stillbirth was 33 (95% CI 18 to 193).

Prespecified analysis of selected individual components of the maternal morbidity composite did not demonstrate statistically significant differences in the proportion of women in the planned delivery group who experienced eclampsia (aRR 0·50, 99% CI 0·08 to 3·07), placental abruption (aRR 0·38, 99% CI 0·07 to 2·15) and postpartum haemorrhage requiring transfusion or hysterectomy (aRR 0·69, 99% CI 0·20 to 2·40) (Table 8-3), although event rates for these clinical endpoints were lower in the planned delivery group. Other secondary descriptive maternal outcomes presented in Table 8-3 and Table 8-4 show that there was one (0%) maternal death and four (1%) women admitted to the intensive care unit in the planned delivery arm, compared to three (1%) maternal deaths and ten (4%) women admitted to the intensive care unit in the expectant management arm. The majority (264 [99%]) of women allocated to planned delivery had trial allocation documented as their primary indication for delivery. Women allocated to expectant management were most frequently delivered due to reaching 37 weeks' gestation (81 [34%]), severe maternal symptoms (71 [30%]) and fetal compromise (33 [14%]). The mean time from randomisation to initiation of delivery was 2·37 (SD 6·06) days for women in the planned delivery group, compared to 5·54 (SD 7·55) days for women in the

expectant management group. A high proportion of women across both groups received antenatal corticosteroids (168 [60%] versus 148 [53%]), with rates of antihypertensive use (275 [98%] versus 274 [98%]) and magnesium sulfate administration (81 [29%] versus 96 [34%]) also similar between the two groups. The mean length of stay for women allocated to planned delivery (6·38 days, SD 4·75) was significantly lower compared to those allocated to expectant management (8·19 days, SD 5·07; adjusted mean difference -1·81, 99% CI -2·88 to -0·74).

Table 8-3 Secondary maternal outcomes (selected)

Selected Individual components (non-exclusive):	**Planned delivery n=282**	**Expectant management n=280**	**Effect measure* (99% CI)**	**P value**
Eclampsia	3 (1·1%)	6 (2·1%)	aRR 0·50 (0·08 to 3·07)	0·329
Placental abruption	3 (1·1%)	8 (2·9%)	aRR 0·38 (0·07 to 2·15)	0·152
Postpartum haemorrhage requiring transfusion or hysterectomy	7 (2·5%)	10 (3·6%)	aRR 0·69 (0·20 to 2·40)	0·449
Platelet count <50 x 10^9 per litre without blood transfusion	5/238 (2·1%)	4/250 (1·6%)	aRR 1·31 (0·24 to 7·27)	0·681
Hepatic dysfunction[ɬ]	30/171 (17·5%)	32/179 (17·9%)	..	..
Acute renal insufficiency[ɬ]	5/176 (2·8%)	5/190 (2·6%)	..	..
Maternal death	1 (0·4%)	3 (1·1%)	..	..
Maximum systolic blood pressure post-randomisation, mmHg	158·32 (14·01)	160·46 (15·94)	..	..
Onset of labour	**n=282**	**n=280**		
Induced	139 (49·3%)	104 (37·1%)	..	..
Pre-labour caesarean section	127 (45·0%)	136 (48·6%)	..	..
Spontaneous	16 (5·7%)	38 (13·6%)	..	..
PROM and augmentation	0	2 (0·7%)	..	..
Need for anti-hypertensives before delivery	275 (97·5%)	274 (97·9%)	..	..
Antenatal corticosteroids (any)	168 (59·6%)	148 (52·9%)	..	..

Complete course received	106 (37·6%)	106 (37·9%)	··	··
Primary indication for delivery‡ (non-exclusive)	**n=266**	**n=240**		
Trial allocation to planned delivery arm	264 (99·2%)	0	··	··
Reaching 37 weeks' gestation	3 (1·1%)	81 (33·8%)	··	··
Severe maternal symptoms	4 (1·5%)	71 (29·6%)	··	··
Fetal compromise on ultrasound	5 (1·9%)	13 (5·4%)	··	··
Fetal compromise on cardiotocography	1 (0·4%)	16 (6·7%)	··	··
Fetal compromise on intermittent auscultation	4 (1·5%)	33 (13·8%)	··	··
Maternal haematological abnormality	0	3 (1·3%)	··	··
Maternal biochemical abnormality	0	8 (3·3%)	··	··
Maternal hypertension not controlled by maximal therapy	4 (1·5%)	30 (12·5%)	··	··
Intrauterine fetal death	0	6 (2·5%)	··	··
Other	1 (0·4%)	10 (4·2%)	··	··
Process outcomes	**n=282**	**n=280**		
Time from randomisation to initiation of delivery, days	2·37 (6·06)	5·54 (7·55)	MD -3·18 (-4·63 to -1·72)	p<0·0001
Time from randomisation to delivery, days	3·01 (6·06)	5·89 (7·59)	MD -2·88 (-4·34 to -1·42)	p<0·0001
Length of stay, days	6·38 (4·75)	8·19 (5·07)	MD -1·81 (-2·88 to -0·74)	p<0·0001

Data are n (%) or mean (SD). PROM – pre-labour rupture of membranes. CI – confidence interval. aRR – adjusted risk ratio. MD – mean difference. *Risk ratios are adjusted for gestational age at randomisation (34, 35, 36 weeks), parity (multiparous vs. primiparous) and multifetal pregnancy. ǂ Not tested due to missing data >20% in both groups. ‡ Excluding women who went into spontaneous labour.

Table 8-4 Additional baseline enrolment characteristics and secondary descriptive maternal outcomes

Baseline characteristics at enrolment	**Planned delivery n=282**	**Expectant management n=281**
Previous pregnancy	184 (65·2%)	186 (66·2%)
High blood pressure in a previous pregnancy?	37 (13·1%)	51 (18·1%)
If history of high blood pressure in previous pregnancy, was there a diagnosis of:		
Pre-eclampsia	20 (7·1%)	28 (10·0%)
Unsure	16 (5·7%)	20 (7·1%)
Eclampsia	1 (0·4%)	3 (1·1%)
Tobacco use	0	0
Aspirin taken during this pregnancy	5 (1·8%)	15 (15·3%)
Started in 1st trimester	1 (0·4%)	9 (3·2%)
Started in 2nd trimester	4 (1·4%)	5 (1·8%)
Started in 3rd trimester	0 (0·0%)	1 (0·4%)
Secondary maternal outcomes	n=282	n=280
Antenatal corticosteroids (any)	168 (59·6%)	148 (52·9%)
Complete course received	106 (37·6%)	106 (37·9%)
Intensive care unit admission	4 (1·4%)	10 (3·6%)
Length of intensive care unit stay, nights	2·5 (1·5, 3·0) n=4	1·5 (1·0, 2·0) n=10
Obstetric high dependency unit admission	51 (18·1%)	58 (20·7%)
Length of high dependency unit stay, nights	1·0 (1·0, 2·0) n=51	1·0 (1·0, 3·0) n=58
Components by detected by a clinical diagnosis only (non-exclusive)	**n=282**	**n=280**
Maternal death	1 (0·4%)	3 (1·1%)
Hepatic haematoma or rupture	0	0
Glasgow coma scale score <13	0	1 (0·4%)
Stroke	0	0
Cortical blindness	0	1 (0·4%)
Reversible ischaemic neurological deficit	0	0
Retinal detachment	0	1 (0·4%)
Postpartum haemorrhage requiring transfusion or hysterectomy	7 (2·5%)	10 (3·6%)
Placental abruption	3 (1·1%)	8 (2·9%)
Myocardial ischaemia/infarction	0	0
Eclampsia	3 (1·1%)	6 (2·1%)
Require >50% oxygen for greater than 1 h	2 (0·7%)	4 (1·4%)
Pulmonary oedema	0	2 (0·7%)
Severe breathing difficulty	0	3 (1·1%)
Resource-dependent components		

Hepatic dysfunction	30/171 (17·5%)	32/179 (17·9%)
Acute renal insufficiency	5/176 (2·8%)	5/190 (2·6%)
Dialysis	0	0
Transfusion of any blood product	28 (9·9%)	27 (9·6%)
Platelet count <50 x 10^9 per litre without blood transfusion	5/238 (2·1%)	4/250 (1·6%)
Positive inotropic support	0	3 (1·1%)
Intubation (other than for caesarean section)	0	2 (0·7%)
Other secondary maternal outcomes		
Magnesium sulfate: randomisation to delivery	81 (28·7%)	96 (34·3%)
Highest blood pressure recorded: randomisation to delivery	n=282	n=280
Mean (SD) systolic blood pressure (mmHg)	152·75 (13·96)	157·03 (15·79)
Mean (SD) diastolic blood pressure (mmHg)	97·57 (10·13)	100·06 (10·82)
Systolic blood pressure ≥160mmHg (randomisation to delivery)	89 (31·6%)	121 (43·2%)
Highest blood pressure recorded: delivery to post-delivery discharge	**n=281**	**n=279**
Mean (SD) systolic blood pressure (mmHg)	149·72 (16·51)	148·73 (17·30)
Mean (SD) diastolic blood pressure (mmHg)	96·85 (12·17)	96·15 (12·47)
Systolic blood pressure ≥ 160mmHg (delivery to post-delivery discharge)	73 (26·0%)	73 (26·2%)
Antihypertensive drugs administered (study entry to delivery)	**n=282**	**n=280**
None	7 (2·5%)	6 (2·1%)
One oral agent	5 (1·8%)	12 (4·3%)
Two or more oral agents	270 (95·7%)	262 (93·6%)
One or more intravenous agent	39 (13·8%)	59 (21·1%)
Antihypertensive drugs administered (non-exclusive)		
Hydralazine	11 (3·9%)	26 (9·3%)
Labetalol	64 (22·7%)	79 (28·2%)
Methyldopa	175 (62·1%)	175 (62·5%)
Nifedipine	211 (74·8%)	211 (75·4%)
Atenolol	0	2 (0·7%)
Amlodipine	11 (3·9%)	16 (5·7%)
Induction methods used	n=139	n=106
Prostaglandin gel/pessary	27 (19·4%)	21 (19·8%)
Oral misoprostol	31 (22·3%)	31 (29·2%)
Vaginal misoprostol	57 (41·0%)	37 (34·9%)
Foley catheter	46 (33·1%)	35 (33·0%)
Artificial rupture of membranes	2 (7·2%)	2 (1·9%)
Oxytocin	10 (7·2%)	12 (11·3%)

Other (mifepristone)	6 (4·3%)	4 (3·8%)
	n=282	**n=280**
Progression to HELLP syndrome	1 (0·4%)	1 (0·4%)
Estimated blood loss at delivery (mls)	316 (212) n=225	322 (209) n=218
Not measured	57 (20·2%)	62 (22·1%)

HELLP syndrome: Haemolysis, elevated liver enzymes, and low platelet count syndrome

The proportion of vaginal deliveries was similar between the two groups (aRR 0·95, 99% CI 0·74 to 1·24) (Table 8-5). Secondary perinatal outcomes showed the median gestational age at delivery was 252 days compared to 255 days for infants born to women in the planned delivery group and expectant management group respectively (Table 8-5). Median infant birthweight for infants in the planned delivery group was 2340g (IQR 2000 to 2700) compared to 2300g (IQR 2000 to 2700) in the expectant management group. Birthweight centile was significantly higher in those with planned delivery (MedD [median difference] 4·4, 99% CI 0·5 to 8·8), with fewer infants born less than the 10th centile (aRR 0·85, 99% CI 0·64 to 1·13). Proportions of overall neonatal unit admission were similar between the two groups (119 [40%] versus 124 [43%]) with only four infants (two in each group) requiring acute-level (invasive ventilation) care. Overall, no statistically significant differences in short-term neonatal complications were observed between the two management groups. Markers of respiratory morbidity such as the proportion of infants needing respiratory support (24 [8%] versus 24 [8%], aRR 0·98, 99% CI 0·49 to 1·99), supplemental oxygen (43 [14%] versus 55 [19%], aRR 0·77, 99% CI 0·48 to 1·24) or with respiratory distress syndrome (28 [9%] versus 29 [10%]) were similar between the two groups, and lower in the planned delivery group. Rates of other secondary perinatal outcomes were also similar (Table 8-6). Mean number of nights in hospital was 4·68 (SD 4·70) days and 5·18 (SD 5·50) days for infants in the planned delivery group and expectant management group, respectively (Table 8-5).

Table 8-5 Secondary perinatal outcomes (selected)

Outcome	**Planned delivery n=301**	**Expectant management n=300**	**Effect measure* (99% CI)**	**P value**
Antepartum stillbirth	0	10 (3·3%)	..	..
Intrapartum stillbirth	3 (1·0%)	2 (0·7%)	..	..
Gestation at birth, days	252 (246 to 257)	255 (248 to 259)	MedD -3·0 (-4·0 to -1·0)	p<0·0001
Gestation at birth	**n=301**	**n=300**	..	..
34 to <35 weeks	58 (19·3%)	30 (10·0%)	..	..
35 to <36 weeks	78 (25·9%)	82 (27·3%)	..	..
36 to <37 weeks	123 (40·9%)	88 (29·3%)	..	..
≥37 weeks	42 (14·0%)	100 (33·3%)	..	..
Vaginal birth	115 (38·2%)	119 (39·7%)	aRR 0·95 (0·74 to 1·24)	0·650
Birthweight, g	2340 (2000 to 2700)	2300 (2000, 2700)	..	..
Birthweight centile†	22·8 (7·7 to 55·8)	16·9 (3·8 to 41·9)	MedD 4·4 (0·5 to 8·8)	0·003
Small for gestational age (<10th centile) †	97 (32·3%)	115 (38·3%)	aRR 0·85 (0·64 to 1·13)	0·137
Small for gestational age (<3rd centile) †	35 (11·6%)	64 (21·3%)	..	..
Livebirths	**n=298**	**n=288**		
Apgar score at 5 minutes	9·0 (8·0, 9·0)	9·0 (8·0, 9·0)	MedD 0·0 (0·0 to 0·0)	0·178
Need for resuscitation	36 (12·1%)	45 (15·6%)	aRR 0·78 (0·46 to 1·33)	0·227
Any admission to neonatal unit	119 (39·9%)	124 (43·1%)	aRR 0·97 (0·77 to 1·24)	0·784
Number of nights in neonatal unit	3·63 (4·58) n=119	4·15 (5·15) n=124	MD -0·53 (-2·21 to 1·15)	0·412
Number of nights in each level of care‡	**n=298**	**n=288**	..	..
Acute care	7·50 (6·36) n=2	1·50 (0·71) n=2	..	..
Subacute care	4·68 (4·44) n=90	4·91 (5·25) n=104	..	..
Kangaroo mother care	4·68 (3·31) n=41	4·48 (3·66) n=42	..	..
Normal care	3·15 (1·98) n=243	3·37 (2·61) n=234	..	..
Total number of nights in hospital	4·68 (4·70) n=298	5·18 (5·50) n=288	..	..
Need for respiratory support	24 (8·1%)	24 (8·3%)	aRR 0·98 (0·49 to 1·99)	0·949

Endotracheal ventilation	2 (0·7%)	2 (0·7%)	··	··
Continuous positive airway pressure (CPAP)	23 (7·7%)	24 (8·3%)	··	··
Need for supplemental oxygen	43 (14·4%)	55 (19·1%)	aRR 0·77 (0·48 to 1·24)	0·157
Confirmed diagnosis of sepsis [§]	1 (0·3%)	1 (0·3%)	··	··
Antibiotics for possible serious bacterial infection	35 (11·7%)	34 (11·8%)	··	··
Hypoxic ischaemic encephalopathy (HIE)	14 (4·7%)	14 (4·9%)	··	··
Respiratory distress syndrome	28 (9·4%)	29 (10·1%)	··	··

Data are n (%), mean (SD), or median (IQR). CI – confidence interval. MedD – median difference. aRR – adjusted risk ratio. *Risk ratios are adjusted for gestational age at randomisation (34, 35, 36 weeks), parity (multiparous vs. primiparous) and multifetal pregnancy. Median differences are unadjusted. [ǂ] Calculated using Intergrowth centiles.(Villar et al., 2014) [‡]Infants may have received more than one level of care, including normal care on the postnatal ward. [§]Positive blood cultures.

Table 8-6 Secondary descriptive perinatal outcomes

Outcome	Planned delivery n=301	Expectant management n=300
Mode of birth		
Spontaneous vaginal (cephalic)	112 (37·2%)	115 (38·3%)
Spontaneous vaginal (breech)	1 (0·3%)	0
Assisted vaginal (vacuum)	2 (0·7%)	4 (1·3%)
Assisted vaginal (forceps)	0	0
Assisted vaginal (breech)	0	0
Caesarean section	186 (61·8%)	181 (60·3%)
Baby sex		
Male	163 (54·2%)	151 (50·3%)
Female	138 (45·8%)	149 (49·7%)
Gestation at birth		
34 to <35 weeks	58 (19·3%)	30 (10·0%)
35 to <36 weeks	78 (25·9%)	82 (27·3%)
36 to <37 weeks	123 (40·9%)	88 (29·3%)
<37 weeks	259 (86·0%)	200 (66·7%)
≥37 weeks	42 (14·0%)	100 (33·3%)
Principal recorded indication for neonatal unit admission (/infants admitted)	**n=119**	**n=124**
Weight less than 1·8kg	18 (15·1%)	29 (23·4%)
In respiratory distress	22 (18·5%)	17 (13·7%)
Temperature >38 degrees Celsius	1 (0·8%)	0
Hypoglycaemia unresponsive to feeds	4 (3·4%)	0
Congenital anomalies	1 (0·8%)	2 (1·6%)
Asphyxia	19 (16·0%)	26 (21·0%)
Hypothermia	1 (0·8%)	0
Jaundice	7 (5·9%)	9 (7·3%)
Other	46 (38·7%)	40 (32·3%)
Other secondary perinatal outcomes (/livebirths)	**n=298**	**n=288**
Apgar score at 10 minutes	9·0 (9·0, 9·0) n=199	9·0 (9·0, 9·0) n=186
Need for supplemental oxygen	43/298 (14·4%)	55/288 (19·1%)
Days of supplemental oxygen required	2·79 (2·55) n=43	3·33 (5·27) n=55
Antibiotics given for possible serious bacterial infection	35 (11·7%)	34 (11·8%)
Number of days given	5·0 (3·0 to 7·0) n=35	7·0 (5·0 to 7·0) n=34
Hypoxic ischaemic encephalopathy (HIE)	14 (4·7%)	14 (4·9%)
Grade 1	7 (2·3%)	10 (3·5%)
Grade 2	6 (2·0%)	4 (1·4%)
Grade 3	1 (0·3%)	0

Neonatal seizures requiring anticonvulsants	3 (1·0%)	3 (1·0%)
Administration of surfactant	0	1 (0·3%)
Hypothermia	11 (3·7%)	8 (2·8%)
Hypoglycaemia requiring intervention	10 (3·4%)	9 (3·1%)
Neonatal jaundice requiring phototherapy	25 (8·4%)	27 (9·4%)
Necrotising enterocolitis	0	0
Nasogastric feeding	16 (5·4%)	20 (6·9%)
Indication	**n=16**	**n=20**
Prematurity	6 (37·5%)	8 (40·0%)
Infant on respiratory support	8 (50·0%)	10 (50·0%)
Hypoglycaemia	1 (6·3%)	2 (10·0%)
Phototherapy	1 (6·3%)	0
Exclusively breast-fed at discharge	279 (93·6%)	269 (93·4%)
Number of infants admitted to each level of care		
Acute care	2 (0·7%)	2 (0·7%)
Subacute care	90 (30·25)	104 (36·1%)
Kangaroo mother care	41 (13·8%)	42 (14·6%)
Normal care	243 (81·5%)	234 (81·3%)
Number of nights in each level of care	**n=298**	**n=288**
Acute care	7·50 (6·36) n=2	1·50 (0·71) n=2
Subacute care	4·68 (4·44) n=90	4·91 (5·25) n=104
Kangaroo mother care	4·68 (3·31) n=41	4·48 (3·66) n=42
Normal care	3·15 (1·98) n=243	3·37 (2·61) n=234
Total number of nights in hospital	4·68 (4·70)	5·18 (5·50)

There was a total of 33 serious adverse events (affecting 32 pregnancies) during the trial (Table 8-7). They comprised 4 maternal deaths (1 in the planned delivery group compared to 3 in the expectant management group); 14 neonatal deaths (8 in the planned delivery group compared to 6 in the expectant management group) which included two linked to congenital anomalies, and 15 stillbirths (3 in the planned delivery group compared to 12 in the expectant management group). None of these serious adverse events were deemed to be unexpected or related to the intervention.

Table 8-7 Serious Adverse Events

	Planned delivery n=282	**Expectant management n=280**
Serious adverse events (SAEs)*	12 (4·2%)	21 (7·5%)
Event		
Pregnancy complicated by SAE	12 (4·2%)	20 (7·1%)
Maternal death	1 /12 (8·3%)	3/20 (15·0%)
Neonatal death prior to discharge	8/12 (66·7%)	6/20 (30·0%)
Antepartum stillbirth	0	10/20 (50·0%)
Intrapartum stillbirth	3/12 (25·0%)	2/20 (10·0%)
Characteristics	**n=12**	**n=21**
Severity		
Mild	0	0
Moderate	0	0
Severe	12 (100%)	21 (100%)
Causality		
Not related	9 (75·0%)	21 (100%)
Possibly	3 (25·0%)	0
Probably	0	0
Action taken		
Intervention stopped prior to the event starting	0	0
Outcome		
Fatal	12 (100%)	21 (100%)
Not resolved	0	0
Resolved	0	0
Resolved with sequelae	0	0

*There were 32 pregnancies complicated by 33 SAEs (one pregnancy was complicated by both an antepartum stillbirth and a maternal death).

In prespecified subgroup analyses (unpowered), we found no significant interaction between the incidence of the primary maternal or perinatal outcome and gestational age at randomisation, singleton or multifetal pregnancy, country, or region (Figure 8-2).

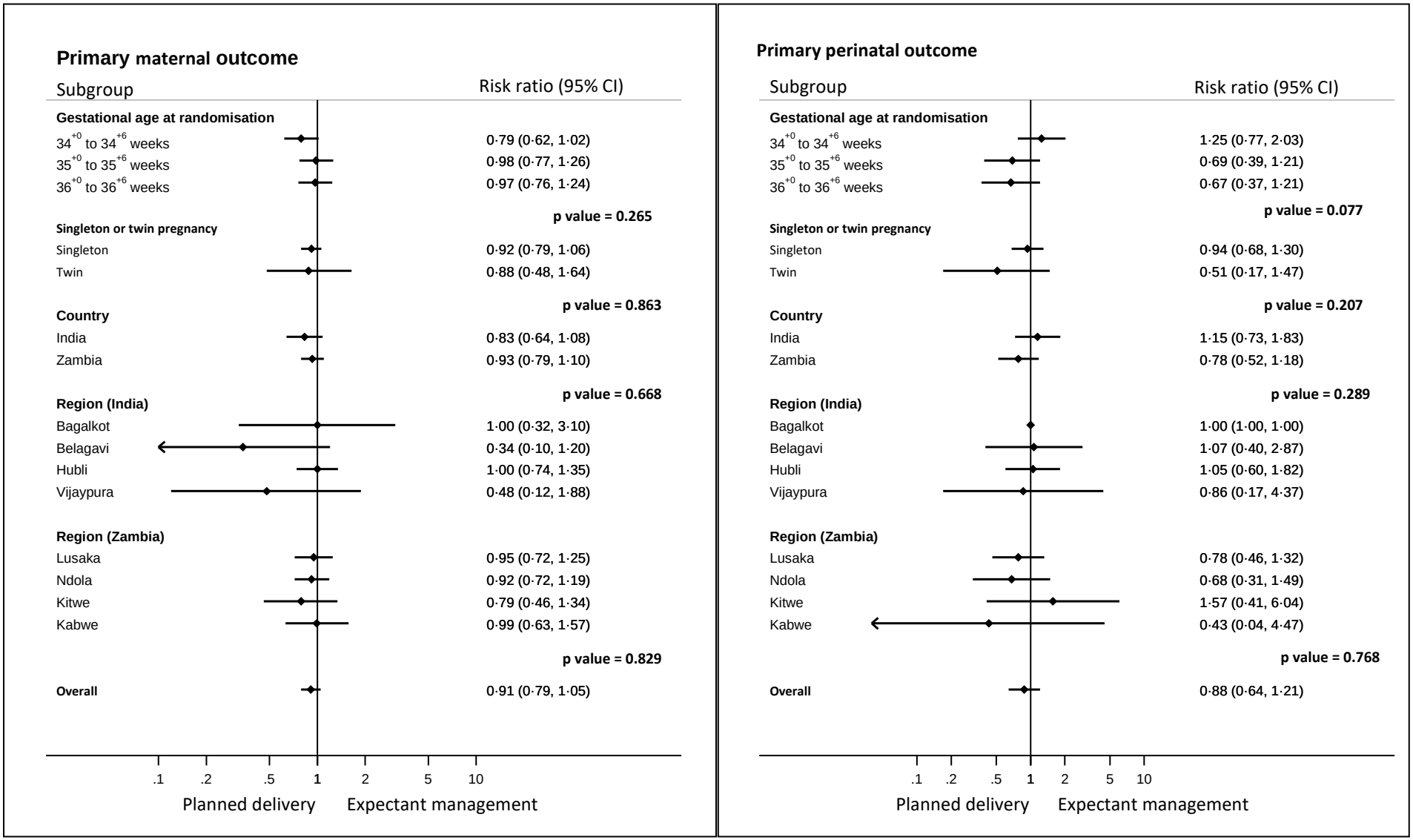


Figure 8-2 Subgroup analysis

Table 8-8 presents time from randomisation to initiation of delivery and delivery for each gestational age category by week. A prespecified sensitivity analysis excluding women or infants randomly allocated to the planned delivery group with initiation of delivery after 96 hours did not alter our findings in any way (Table 8-9).

Table 8-8 Time from randomisation to initiation of delivery and delivery

	Planned delivery n=282	**Expectant management n=280**
Time from randomisation to initiation of delivery, days	2·37 (6·06)	5·54 (7·55)
Time from randomisation to delivery, days	3·01 (6·06)	5·89 (7·59)
By gestational age at randomisation		
34^{+0} to 34^{+6}		
n (%)	81 (28·7%)	78 (27·9%)
Days from randomisation to initiation of delivery	4·62 (9·71)	7·54 (10·48)
Days from randomisation to delivery	5·30 (9·54)	7·96 (10·51)
35^{+0} to 35^{+6}		
n (%)	83 (29·4%)	90 (32·1%)
Days from randomisation to initiation of delivery	2·04 (4·78)	5·91 (7·13)
Days from randomisation to delivery	2·73 (4·92)	6·20 (7·19)
36^{+0} to 36^{+6}		
n (%)	118 (41·8%)	112 (40.0%)
Days from randomisation to initiation of delivery	1·05 (1·60)	3·86 (4·53)
Days from randomisation to delivery	1·64 (1·83)	4·21 (4·57)

Data are n (%) or mean (SD).

Table 8-9 Sensitivity analysis of women who had delivery initiated within 96 hours of randomisation

Outcome	**Planned delivery**	**Expectant management**	**Risk ratio* (95% CI)**	**P value**
Primary maternal outcome	147/266 (55·3%)	168/280 (60·0%)	0·92 (0·80 to 1·06)	0·273
Primary perinatal outcome	53/285 (18·6%)	67/300 (22·3%)	0·86 (0·62 to 1·20)	0·385

*Analysis adjusted for gestational age at randomisation, twin pregnancy, parity.

8.5. Discussion

In this randomised controlled trial of planned delivery versus expectant management for women with late preterm pre-eclampsia in India and Zambia, we demonstrated that planned delivery significantly reduces severe maternal hypertension, with an important but non-significant reduction in maternal morbidity and mortality. For the infant, we found that planned delivery did not increase perinatal mortality or morbidity, and significantly reduced the risk of stillbirth, particularly those in the antenatal period. Secondary maternal and perinatal outcomes were consistent with our main findings, showing fewer short-term maternal complications with no difference in short-term neonatal complications. Overall, best estimates of these secondary treatment effects were in the direction favouring planned delivery, with no indication of harm to the infant. Planned delivery did not increase rates of operative delivery and was associated with a significant reduction in maternal hospital stay and equivalent neonatal hospital stay.

Based on our literature search, this is the first trial to be published evaluating optimal timing of delivery in pre-eclampsia between 34^{+0} and 36^{+6} weeks' gestation in low and lower-middle income countries, and is strengthened by its relevance to settings where the vast burden of pre-eclampsia-related morbidity and mortality exists. The inclusion of two different countries with different healthcare systems and populations strengthens the generalisability of our results, such that they are likely to be applicable across many similar settings in both Sub-Saharan Africa and South Asia. Reassuringly, the proportion of infants requiring neonatal unit stay, respiratory interventions, or with neonatal morbidity was not increased by the intervention, suggesting planned delivery can be safely implemented in countries with more limited neonatal resources. Our trial sites incorporated tertiary level hospitals and their local network of primary level health facilities, serving a mixed urban and rural population, in accordance with national referral pathways. Thus we anticipate our findings would apply to women across different geographical contexts. Our low loss to follow-up rate (one participant) and low rate of missing

data, alongside robust in-country oversight from the trial coordinator, provides confidence in the quality and completeness of our data.

Recent trials evaluating interventions that have been proven to work in a high income setting, such as therapeutic hypothermia for moderate and severe neonatal encephalopathy,(Thayyil et al., 2021) have shown that such interventions may have a different impact in a low-resource setting. These results highlight the importance of generating evidence from low and middle income countries before implementing interventions, and the importance of gaining a thorough understanding of the trial environment. The varied disease phenotypes in different populations and settings may also provide new insights into the efficacy of interventions. Our trial was conducted in settings with variable resource availability, demonstrated by monthly site audits highlighting differences in access to blood pressure monitors, urinalysis sticks, laboratory reagents and neonatal unit equipment between sites, with more rural healthcare facilities often lacking these key resources. The six-month feasibility and acceptability study which preceded the interventional phase of the trial enabled us to design a pragmatic protocol and analysis plan, suited to the context. This strengthened our engagement with local healthcare partners, the consent process, and our ability to screen and enrol the target number of participants; it also enabled accurate detection of clinical outcomes and adaptation of definitions where necessary. This initial phase enhanced our successful delivery of the trial despite the challenges of working in these settings and more broadly, the COVID-19 pandemic. However, a larger sample size might have enabled demonstration of a statistically significant reduction in adverse maternal outcomes, associated with planned delivery, as seen in studies across high income settings. The planned delivery group had a lower proportion of infants with the primary perinatal outcome (19% vs. 22%), despite a lower than anticipated (24%) event rate in the expectant management group. There was no evidence of harm to the infant, which supports our conclusion that planned delivery can be safely recommended. Although there were fewer serious adverse events in the planned delivery group (12) compared to the expectant management group (21), the high number of

serious adverse events overall demonstrates the unacceptably high levels of maternal and perinatal mortality in these settings.

A further challenge during the trial was reaching women with late preterm pre-eclampsia before they developed severe features of the disease. Delays in detection, diagnosis, and referral across local sites meant it was sometimes difficult for site research teams to reach these women at an earlier stage in their disease, and may in part explain the smaller than anticipated difference in maternal outcomes between the two groups. Additionally, the small mean difference in time from randomisation to initiation of delivery between the two groups highlights the rapidly progressive and unpredictable nature of pre-eclampsia, particularly in these settings, such that women allocated to expectant management frequently deteriorated and required delivery prior to 37 weeks' gestation. This narrow time difference between the groups, which is similar to that found in other studies,(Beardmore-Gray, Seed, et al., 2022; Chappell, Brocklehurst, et al., 2019) may also explain the lack of a statistically significant difference in overall maternal outcomes between the two groups. Importantly, other clinical outcomes such as post-partum haemorrhage or operative delivery were not increased in the planned delivery group, indicating no additional harm to the woman associated with the intervention.

The largest reported study to date (the PHOENIX Trial (Chappell, Brocklehurst, et al., 2019)) comparing planned delivery to expectant management for pre-eclampsia between 34^{+0} and 36^{+6} weeks' gestation, conducted in a high income setting, found that planned delivery significantly reduced adverse maternal outcomes but increased the primary perinatal outcome of neonatal unit admission. Overall, the prevalence of serious adverse outcomes in this setting was rare. When incorporated into a larger IPD meta-analysis,(Beardmore-Gray, Seed, et al., 2022) combining data from six randomised controlled trials evaluating planned delivery from 34 weeks' gestation onwards, these findings remained consistent, with the results of this IPD meta-analysis showing a significant reduction in adverse maternal outcomes

associated with planned delivery from 34 weeks' gestation, but an increase in short-term neonatal complications, primarily respiratory distress syndrome. These findings may in part be explained by the wide variation in antenatal corticosteroid use observed in these trials, with those studies conducted later in the observed period showing greater antenatal corticosteroid use, and no difference in respiratory morbidity between management groups. The high rates of antenatal corticosteroid use in our CRADLE-4 Trial demonstrate that this intervention is widely available in these settings and may in part explain the similar neonatal outcomes observed in both management groups. Although use of antenatal corticosteroids beyond 34 weeks requires further evaluation,(WHO ACTION Trials Collaborators, 2022) the recently published ACTION-I trial demonstrated that antenatal dexamethasone for women in low-resource countries at risk of preterm birth significantly reduced the risk of neonatal death or stillbirth, with no increase in the incidence of possible maternal bacterial infection.(WHO ACTION Trials Collaborators et al., 2020) The CRADLE-4 Trial fills a critical knowledge gap in the evidence relating to timing of delivery, with none of these previous studies evaluating the intervention in a low or lower-middle income country. Our findings are consistent with current evidence and supported by a clear biological rationale; planned delivery is well-established to provide maternal benefit in the context of pre-eclampsia,(Cluver et al., 2017) as well as being associated with higher rates of vaginal delivery demonstrated in recent trials.(Beardmore-Gray, Seed, et al., 2022; Chappell, Brocklehurst, et al., 2019) The significant reduction in severe maternal hypertension observed with planned delivery in this trial is likely to be of clinical benefit, since we know that severe hypertension is associated with an increased risk of adverse maternal outcomes.(Magee et al., 2016)

In contrast to previous studies, we have demonstrated that planned delivery between 34^{+0} and 36^{+6} weeks' gestation for pre-eclampsia in a low or lower-middle income setting does not increase harm compared to expectant management, but also significantly reduces the risk of stillbirth, with no increase in short-term neonatal complications or neonatal death. In the recently published IPD meta-

analysis (1,790 participants) (Beardmore-Gray, Seed, et al., 2022) comparing planned delivery to expectant management in late preterm pre-eclampsia in high income settings, there were no stillbirths. In the CRADLE-4 Trial, 15 women (2·7 %) experienced a stillbirth. This highlights the different context in which we evaluated planned delivery, and the high rates of pre-eclampsia-associated perinatal mortality that occur in settings with fragile healthcare systems and limited resources. An estimated 2·6 million stillbirths occur every year, 98% in low or lower-middle income countries,(Lawn et al., 2016) with extensive psychological, physical, and economic consequences.(Heazell et al., 2016) The number needed to treat to prevent one stillbirth in our trial was 33 (95% CI 18 to 193), considerably lower than the number needed to treat (n=544) (Middleton et al., 2020) to prevent one stillbirth via post-dates induction of labour in the UK; clinicians and women may therefore feel there is sufficient rationale to offer planned delivery to women with pre-eclampsia from 34 weeks' gestation onwards. Despite often limited neonatal unit resources, we have demonstrated that in pre-eclampsia after 34 weeks' gestation, delivery offers clinical benefit to the infant as well as to the woman. Our secondary perinatal outcomes provide reassuring evidence to support this, showing low rates of neonatal complications overall and no difference in neonatal unit admissions or length of stay between the two groups. Supporting a policy of planned delivery, we found a reduction in the proportion of infants born small for gestational age in the planned delivery group, with similar birthweights in each group. This is consistent with a similar intervention for infants with suspected intrauterine growth restriction (Boers et al., 2010) which found, at two years of age, that normal birthweight (increased with planned delivery) increased the chance of a normal neurodevelopmental score.(van Wyk et al., 2012) Two-year follow-up of infants in the PHOENIX Trial, demonstrated that neurodevelopmental scores were within the normal range for infants in both management groups,(Beardmore-Gray, Greenland, et al., 2022) consistent with two-year and five-year follow-up of infants in the HYPITAT-II trial which demonstrated no significant differences at five years of age between infants in the planned delivery and expectant management groups.(Zwertbroek et al., 2019; Zwertbroek et al., 2020) A formal healthcare

resource use analysis will be published separately, alongside qualitative data exploring women's experiences of participating in the trial; however, the process outcomes presented here such as length of stay and level of neonatal care required would suggest that planned delivery may be cost-saving for the healthcare system, consistent with the cost-savings for a high income setting reported by the PHOENIX Trial.(Chappell, Brocklehurst, et al., 2019; Hunter et al., 2022)

These findings have important implications for healthcare professionals working in these settings, and for women who develop pre-eclampsia. Given the strong body of evidence to support planned delivery from 34 weeks' gestation for maternal benefit, combined with the new findings from this trial demonstrating both infant safety and a reduction in the risk of stillbirth, we conclude that it is safe for clinicians to offer planned early birth to women with late preterm pre-eclampsia, even without severe features, in a low or lower-middle income country setting, from 34 weeks' gestation onwards. Further research must focus on identifying local barriers and facilitators to implementation, engaging communities to raise awareness of pre-eclampsia and understanding the social and economic factors that may influence a woman's decision to seek antenatal care, as well as the wider determinants of the health system and its ability to provide safe, timely and good quality care. This should include accurate gestational age determination and precise diagnosis of pre-eclampsia. We anticipate our findings will be incorporated into national and international guidance on timing of delivery in pre-eclampsia, and a recently held policy lab focused on implementation strategies indicated positive engagement and commitment from key stakeholders. Context matters: we have demonstrated that even in resource limited settings, planned delivery can be safely and effectively implemented, and is recommended to reduce adverse pregnancy outcomes in late preterm pre-eclampsia, particularly stillbirth. This should form part of a concerted global effort to end all maternal and perinatal deaths from preventable causes.

Chapter 9 Discussion and conclusions

A discussion of the specific findings generated by each study are presented in Chapters 3 to 8 of this thesis. In this Chapter, I summarise the overall findings, referring to the objectives described in Chapter 2. I discuss the strengths and limitations of this thesis as a whole, and identify potential directions for future work.

9.1. Summary of key findings

Throughout this thesis, I present new evidence to address the question of when to offer delivery to women with late preterm pre-eclampsia in low and middle income countries. The first objective was to synthesise the current available evidence, via an IPD meta-analysis. The results of this study, which included six randomised controlled trials, all conducted in high income countries, demonstrated a significant reduction in a composite outcome of maternal morbidity and mortality associated with planned delivery from 34 weeks' gestation onwards. This was associated with an increase in the primary composite perinatal outcome, primarily driven by an increase in respiratory distress syndrome. When interpreting these results, it is important to note the variation between the included trials, particularly with respect to use of antenatal corticosteroids. The largest, and most recent trial included had higher rates of antenatal corticosteroid administration, and no difference in neonatal respiratory morbidity.(Chappell, Brocklehurst, et al., 2019) In my analysis, expectant management was found to significantly increase the risk of infants being born small for gestational age (SGA), compared to planned delivery. This is an important finding to consider, given the known association between SGA and stillbirth,(Flenady et al., 2016; Gardosi et al., 2013; Lawn et al., 2016) as well as the impact of fetal growth restriction on long-term neurodevelopmental outcomes.(Eixarch et al., 2008; Murray et al., 2015; van Wyk et al., 2012) I would therefore suggest that the risk of worsening fetal growth restriction and severe maternal morbidity associated with expectant management outweighs the risk of neonatal respiratory morbidity associated with planned delivery, particularly since

this risk can be mitigated against by appropriate use of antenatal corticosteroids, and is unlikely to lead to long-term respiratory disease when occurring in this late preterm period.

The second objective was to evaluate the longer-term impact of planned early delivery for pre-eclampsia on infant neurodevelopment. In Chapter 4, I present the two-year follow-up of infant and maternal outcomes after a randomised controlled trial of planned early delivery or expectant management for late preterm pre-eclampsia, conducted in the United Kingdom.(Chappell, Brocklehurst, et al., 2019) At two years of age, neurodevelopmental assessment for infants in both management groups was within the normal range. For infants in both management groups, the mean composite PARCA-R score was towards the lower end of the normal range, which is consistent with our knowledge that pre-eclampsia itself is a risk factor for neurodevelopmental delay, irrespective of timing of delivery.(Johnson et al., 2015; Warshafsky et al., 2016) The mean difference in composite PARCA-R scores between the two management groups was small (-2.43); however, the 95% confidence interval (-5.36 to 0.50) crossed the pre-specified margin for non-inferiority (4 standardised score points), meaning it was not possible to definitively conclude non-inferiority of planned delivery for this outcome. A larger sample size may have provided a tighter confidence interval and hence increased certainty in concluding that there was no significant difference in composite PARCA-R scores between the two groups. However, this small difference (-2.43) is unlikely to be clinically meaningful; five-year follow-up of infants in the HYPITAT-II trial, which evaluated planned delivery between 34 and 37 weeks in women with any hypertensive disorder of pregnancy, showed that the small differences in neurodevelopmental assessment observed at two years were no longer present at the age of five.(Zwertbroek et al., 2019; Zwertbroek et al., 2020) Therefore, a longer period of follow-up of the cohort of infants I discuss in my analysis may have provided more information on whether the small differences observed at two years of age led to any meaningful impact at school age. However, this comes with logistical and financial challenges and a potential increase in attrition. In low and

lower-middle income settings this may be even more challenging, though potentially feasible with sufficient funding, human resources, and meaningful community engagement. In any setting, one must consider other factors influencing infant neurodevelopment such as malnutrition, infection, and parental education level and income. In countries such as India and Zambia, the prevalence of early childhood infections such as diarrhoeal illness, pneumonia, and malaria remains high, alongside high rates of stunting and malnutrition.(The World Bank, 2022) These conditions may therefore be additional confounding causes of neurodevelopmental delay (Fink et al., 2013; Kihara et al., 2006) amongst this already high-risk population of infants, making it difficult to elucidate the impact of planned delivery alone.

The third objective was to assess the feasibility and acceptability of the proposed intervention (planned delivery), prior to implementing a trial comparing planned delivery to expectant management for late preterm pre-eclampsia in low and lower-middle income settings. Through a retrospective case note audit, key stakeholder interviews, and focus group discussions, I was able to assess the current disease burden associated with pre-eclampsia at the proposed trial sites, establishing a need to evaluate the intervention as well as the safety of initiating late preterm delivery in these settings. Importantly, thematic analysis of qualitative data from interviews and focus group discussions highlighted the serious consequences of pre-eclampsia experienced by women, their families, and healthcare providers. The proposed intervention was acceptable to the majority of stakeholders. However, I was able to identify potential barriers to implementation, such as myths and misconceptions surrounding pre-eclampsia, financial concerns, and a preference for spontaneous labour. I was also able to ascertain the level of resources available to manage women with pre-eclampsia across the proposed trial sites. Whilst key resources such as anti-hypertensives, magnesium sulfate, antenatal corticosteroids, and continuous positive airway pressure ventilation for infants appeared readily available, I also identified a number of challenges. These included relying on last menstrual period to determine gestational age, limited access to laboratory

resources, limited access to blood products, and limited cot space and ventilators on the neonatal unit. During this initial phase, a particular challenge was encountered when translating participant information leaflets and consent forms from English into two Zambian languages (Nyanja and Bemba). An exploratory workshop held in Lusaka, Zambia, with researchers, translators, and clinicians highlighted the fact that this was a widespread issue, requiring further attention. This led to the Lost in Translation study, described in Chapter 6 and addressing the fourth objective of this thesis, which sought to understand the factors influencing participant comprehension of recruitment materials used in maternal health research studies conducted in Zambia. This study explored the language barriers to informed consent in Zambia, specifically focusing on the translation process, and the way in which this can potentially undermine understanding amongst research participants. Key informants and local community groups expressed concerns regarding the layout and format of recruitment materials, the length, and the language used, as well as the time given to consider the information. Translators highlighted the difficulty in achieving conceptual equivalence when translating from English into their local languages, with community groups also highlighting their difficulty in reading and understanding overly formal, written versions of their language.

Utilising these findings, and meeting the fifth objective of this thesis, I was able to design a clinical trial protocol to evaluate planned early delivery compared to expectant management for women with pre-eclampsia between 34^{+0} and 36^{+6} weeks' gestation in India and Zambia. The eligibility criteria were designed to be as pragmatic as possible, given the limited diagnostic capabilities at many of the trial sites. Proteinuria was therefore defined as 1+ or more on urine dipstick, without a requirement for quantitative assessment, and gestational age was accepted based on last menstrual period, so long as the doctor caring for the woman agreed with the estimated due date. The informed consent process was supplemented by videos (in Nyanja and Bemba) at Zambian sites which explained pre-eclampsia, preterm birth, and trial participation. Videos were not produced for Indian sites due to

budget and time constraints; however, the large research teams at these sites were able to spend additional time counselling potential participants when required. Once enrolled into the trial, initiation of planned delivery or expectant management followed local protocols at each site. Clinical outcomes were adapted to suit the resources available; for example, incorporating outcomes such as "severe breathing difficulty" as a proxy for pulmonary oedema when radiological diagnosis is not possible, and using the WHO definition of possible serious bacterial infection in the neonate, when evidence of positive blood or cerebrospinal fluid cultures is lacking.(Robinson, 1996) The statistical analysis plan was also designed to account for variation in resource availability, prespecifying separate analyses of the maternal mortality and morbidity component of the maternal composite outcome, such that components based upon a clinical diagnosis would be analysed separately to those reliant upon additional resources (i.e. hepatic dysfunction, acute renal insufficiency, thrombocytopaenia, and need for inotropic support and intubation).

The final objective was to undertake a randomised controlled trial across sites in India and Zambia to compare planned delivery to expectant management for women with pre-eclampsia, without severe features, between 34^{+0} and 36^{+6} weeks' gestation. This trial (the CRADLE-4 Trial) enrolled 565 women across nine sites in India and Zambia and randomly allocated 284 women to planned delivery and 281 women to expectant management. The intention-to-treat analysis population included 282 women (301 infants) in the planned delivery group and 280 women (300 infants) in the expectant management group. Planned delivery was associated with a reduction in the primary maternal outcome (a composite of maternal morbidity and mortality based on miniPIERS outcomes, with the addition of severe hypertension), which did not reach significance. However, the risk of developing severe maternal hypertension post-randomisation was significantly reduced. Analysis of individual components either favoured planned delivery, or showed that there was no difference between the two groups. Analysis of the primary perinatal outcome demonstrated non-inferiority of planned delivery with respect to the composite perinatal outcome. Planned delivery significantly reduced the risk of

stillbirth, driven by a large difference in antepartum stillbirth between the two groups (0 in the planned delivery group compared to 10 in the expectant management group). Reassuringly, there was no difference in short-term neonatal morbidity, neonatal unit admission, or neonatal hospital stay. Rates of operative delivery were similar between the two groups, and planned delivery was associated with a significant reduction in hospital stay for the woman.

It is clear, based on the review of evidence from high income settings (Chapter 3), that planned delivery reduces adverse maternal outcomes. Results from the Phase 1 feasibility study (Chapter 5) demonstrated the high level of maternal and perinatal morbidity associated with late preterm pre-eclampsia at the main trial sites, and findings from the interventional phase of the trial demonstrate an important reduction in these adverse outcomes, consistent with current evidence. The IPD meta-analysis was not able to provide conclusive evidence to support planned delivery in a high income setting from an infant perspective, and two-year follow-up of infant outcomes from the PHOENIX Trial was limited by small numbers and short follow-up time. I have demonstrated, through the CRADLE-4 Trial, that planned delivery between 34 and 37 weeks in a low income country and a lower-middle income country is safe, feasible, and acceptable. I have shown that in settings where the majority of perinatal losses occur, planned delivery significantly reduces stillbirth. Moreover, I have demonstrated that neonatal outcomes are similar between infants in the planned delivery group and expectant management group, with no increase in neonatal deaths, neonatal unit admission, or need for respiratory support associated with planned delivery. This provides reassuring evidence that even in settings where resources are limited, late preterm delivery can be managed safely and is likely to be preferable, compared to watching and waiting, in the context of pre-eclampsia.

9.2. Strengths and limitations

Within this thesis, I compare and contrast evidence from high income countries with evidence from a low income country and lower-middle income country. In doing so, I highlight the importance of evaluating interventions in the regions and

populations most affected by pre-eclampsia. Listening to local communities, and generating local evidence, is key to this. Planned delivery for late preterm pre-eclampsia is likely to have greater benefit in low and lower-middle income countries, compared to high income countries. Whilst high income countries have the privilege of being able to provide intensive monitoring to women with pre-eclampsia, enabling early detection of complications and timely delivery, women living in low and lower-middle income countries do not always access or receive adequate antenatal surveillance, and thus face a far greater risk of mortality, morbidity, and stillbirth. The CRADLE-4 Trial demonstrates the different impact that planned delivery has in settings with different healthcare systems and resources to those in high income settings. Whilst delivering a clinical trial in low-resource settings brings complex challenges, the work presented in this thesis illustrates how assessment of feasibility and acceptability enables design of a robust interventional trial, and demonstrates that it is possible to deliver good quality evidence despite resource limitations. Furthermore, the high rate of adverse pregnancy outcomes in low and lower-middle income countries, as demonstrated in the CRADLE-4 Trial, increases the likelihood of demonstrating differences in clinical outcomes that are meaningful to those settings, thereby increasing the impact and usefulness of the evidence generated. The low loss to follow-up rate and high data completeness is testament to the professionalism and dedication of the research teams involved in data collection, as well as the extensive research capacity building that took place throughout the duration of the trial.

The overall aim of this thesis was to evaluate the impact of planned delivery in late preterm pre-eclampsia on pregnancy outcomes in a low income and lower-middle income country. To answer this question, I have used multiple different methodologies, strengthening my own knowledge and understanding of different research methods and how they may be used to address particular topics.
IPD meta-analysis enables data from multiple trials to be harmonised in order to answer a specific question – in this case the impact of planned delivery for pre-eclampsia from 34 weeks' onwards on maternal and perinatal outcomes. The

advantage of using IPD meta-analysis techniques is that data relating to a specific population or condition can be extracted from large datasets, and combined with others in order to generate a larger sample size, whilst harmonising inclusion criteria and outcome definitions. This is particularly useful when evaluating relatively rare conditions, such as pre-eclampsia, with typically small event rates (i.e. low rates of eclampsia and maternal mortality in high income settings).(Burke et al., 2017) Previous reviews evaluating timing of delivery in hypertensive disorders of pregnancy have grouped all types of hypertensive disease together. In my IPD meta-analysis, I was able to present outcomes for women with pre-eclampsia specifically. This is important, as pre-eclampsia is a more severe disease phenotype and therefore women with pre-eclampsia represent a population who may require different clinical management. However, variation in clinical practice over time, as well as the conduct and quality of individual trials, can make it difficult to draw direct comparisons between studies. This was evident in the IPD meta-analysis I performed, due to the wide variation in antenatal steroid use between the included trials, which is likely to have influenced the primary perinatal outcome.

The importance of assessing long-term outcomes has been previously described, and the two-year follow-up presented in Chapter 4 of this thesis provides new and important data that may help inform women and clinicians who are considering planned delivery for pre-eclampsia from 34 weeks' gestation onwards, in a high income setting. I have been able to develop an understanding of the different modalities of assessing infant neurodevelopment such as the PARCA-R questionnaire described in this study,(Johnson, Bountziouka, Linsell, et al., 2019; Martin et al., 2013) as well as statistical techniques that can be used to deal with missing data (e.g. multiple imputation).(Bodner, 2008) However, I was not able to undertake long-term follow-up of infants born to women who participated in the CRADLE-4 Trial. This was partly due to the funding and time available, as well as logistical concerns about how feasible it would be to conduct long-term follow-up at the trial sites. As demonstrated by the smaller subset analysed as part of the PHOENIX Trial two-year follow-up, high loss to follow-up limits the potential value

of such findings, in addition to the presence of other confounding factors that may influence childhood development. Given that the difference in time from randomisation to delivery between the two management groups (mean difference -2.88 days) in the CRADLE-4 Trial was similar to that seen in the PHOENIX Trial (median difference -4 days), it is possible that the two-year outcomes for infants born to women enrolled in the CRADLE-4 Trial would show a similar pattern to that seen in infants born to women enrolled in the PHOENIX Trial, despite the differences between these two settings. Nevertheless, assessing infant neurodevelopment at two or five years after women were enrolled into the CRADLE-4 Trial might have provided further information to guide women and clinicians in low and lower-middle income countries, and could have increased confidence that planned delivery remains safe, and non-detrimental to infants, in the long-term as well as the short-term. Furthermore, a longer period of short-term follow-up of infants in the CRADLE-4 Trial, for example until six weeks post birth, may have enabled detection of any late neonatal deaths or complications in either management group. However, given the similar neonatal outcomes between infants in the planned delivery group and the expectant management group at discharge, a longer period of follow-up is unlikely to have changed the overall interpretation of the main trial findings, and may have been constrained by differential case ascertainment. In the future, as routine data collection on infants and children becomes more widespread, this may be a more feasible option for understanding the longer-term impact of pregnancy interventions.

The use of qualitative research methods has been an integral component of this thesis, particularly in developing the CRADLE-4 clinical trial protocol. Whilst quantitative data provides important information to answer questions such as "what proportion of women experience eclampsia?" or, "what proportion of infants are admitted to the neonatal unit?", it cannot provide us with key details to understand *why* and *how* women and infants are dying.(O'Cathain et al., 2015; Onwuegbuzie & Leech, 2005) The reasons underlying the high maternal and neonatal mortality rates in low and lower-middle income countries are multi-

factorial and cannot be fully understood without exploring the attitudes, beliefs, and lived experiences of affected communities. This requires thorough qualitative evaluation; the qualitative component to the feasibility and acceptability study presented as part of this thesis provided a unique and powerful insight into maternity care and the impact of pre-eclampsia at the proposed trial sites and was essential in designing and implementing the main trial successfully. The CRADLE-4 Trial also incorporated a qualitative assessment of women's experiences of participating in the trial, and analysis of this data is ongoing. Building on this work, the Lost in Translation study provides further insight into the informed consent process, highlighting the lack of local Zambian words to describe hypertensive disorders of pregnancy, and the potential issues this can cause when translating recruitment materials. This is a relatively unexplored problem and applies not just to the CRADLE-4 Trial, but to the wider community of researchers working across high and low income settings. The CRADLE-4 Trial began before data collection and analysis of the Lost in Translation study was complete, limiting my ability to fully incorporate the lessons learned from the Lost in Translation study into the recruitment materials developed for the CRADLE-4 Trial. However, I plan to follow the recommendations developed as part of the Lost in Translation study when designing participant information for any future research studies, and I hope that they will be shared and used widely by other researchers working in Zambia and beyond.

The use of multiple methodologies as part of this thesis may limit the extent to which each one can be fully explored and honed. However, establishing the optimal timing of delivery in late preterm pre-eclampsia in low and lower-middle income settings, requires a multi-faceted approach. Furthermore, this thesis has developed my skills as a clinical researcher. It has equipped me with the ability to approach a research question from different perspectives and select a variety of methods to address the issue holistically.

A potential limitation of the work presented in this thesis is the applicability and generalisability of the findings from the CRADLE-4 Trial to other low and lower-middle income countries. The trial was conducted in five urban referral hospitals across three of Zambia's provinces, and in four urban referral hospitals across one Indian state. Further trials, conducted in a wider variety of settings, might give greater confidence in the findings I have discussed. However, the pragmatic design of the CRADLE-4 Trial took account of the real-world setting in which it was implemented and, other than the intervention, followed local clinical practice at each site. Resources varied between the trial sites, with only one of the sites in Zambia having a fully operational neonatal intensive care unit. The short-term perinatal outcomes demonstrated that planned delivery did not increase the risk of neonatal unit admission or neonatal respiratory distress. This is reassuring, and would suggest that planned delivery for late preterm pre-eclampsia is beneficial, irrespective of the resources available. It is therefore likely to be safe and effective across all settings, even in low income countries with more fragile healthcare systems than those represented in the trial. Preliminary results of the planned health economic analysis are shown in Appendix 9 and suggest no increased cost to the health system associated with planned delivery, and a net cost-saving for antenatal and maternal care. This analysis will be submitted for publication alongside the resources audit of participating CRADLE-4 Trial sites, and will be key to informing policy-makers on the potential cost-savings associated with planned delivery, and its impact on resource use across the healthcare system, prior to initiating implementation on a wider scale.

9.3. Personal insight

Whilst coordinating the interventional phase of the trial, I lived in Lusaka, Zambia. During this time, I worked clinically as a postgraduate doctor attached to a firm within the Obstetrics and Gynaecology department, assisting with the on-call duties once a week. I kept a weekly log and reflected on the cases that I became involved with. Participating in the clinical care of women in this setting gave me a privileged insight into the local healthcare system. I observed the excellent skills and knowledge of my local colleagues, who worked hard to provide women with the

best possible care. I also experienced the challenges they faced; for example, lack of running water overnight and consequently limited sterilisation facilities, lack of power, lack of blood products, lack of gloves, stockouts of essential medicine, incredibly high patient turnover, and a limited ability to provide intrapartum fetal monitoring. Being able to experience these issues first hand, enabled me to contextualise my research findings, and interpret the evidence based on my own lived experience of providing maternity care at a tertiary government hospital in Zambia.

9.4. Future directions

The new evidence generated as part of this thesis, will, I hope, be translated into a tangible improvement in pregnancy outcomes for women and their infants – particularly across the trial sites, but also similar settings in Sub-Saharan Africa and South Asia. I have demonstrated that planned delivery for late preterm pre-eclampsia in a low and lower-middle income setting provides clinical benefit to women, with a significant reduction in the risk of stillbirth and no increase in adverse neonatal outcomes. However, demonstrating that an intervention is effective is only the first step in improving outcomes. In order to mobilise the knowledge generated as a result of this research, I will be guided by the 7Cs framework which identifies seven core impact principles.(Sreenan et al., 2019) A funding uplift to support this has been secured. Identifying and collaborating with key stakeholders who can influence change will be an important next step. This will include international and national guideline committees as well as ministry of health representatives and hospital managers. An initial policy lab (Hinrichs-Krapels et al., 2020) brought together around 50 stakeholders from a range of professional disciplines including doctors, midwives, NGO representatives, and district health officials on 14th February 2023 in Lusaka, Zambia. Attendees made several recommendations regarding next steps, which included ongoing efforts to increase awareness and understanding of pre-eclampsia at a community level, involving local safe motherhood action groups, updating national guidelines, and engaging high-level personnel such as the First Lady of Zambia.

Ensuring that these research findings benefit the intended recipients will require ongoing community engagement, in particular addressing many of the barriers to providing good quality antenatal care. For example, it is important to understand and explore why some women register late for antenatal care or do not attend at all, or why some women may choose not to undergo induction of labour, even if medically recommended. These issues are relevant to both high income and low income settings. Promoting uptake of maternity care in order to improve pregnancy outcomes may be achieved through participatory community activities, for example using Theory of Change workshops,(Robbins et al., 2022) and future work should incorporate holistic and collaborative approaches such as this to support implementation of healthcare interventions.

Data collected as part of the CRADLE-4 Trial highlighted several areas of care requiring improvement. In particular, the use of aspirin in the first trimester, and the use of early (<24 weeks) ultrasound scanning to determine gestational age could be enhanced. Evaluation of novel interventions, such as the TraCer device which is a portable ultrasound probe measuring fetal transcerebellar diameter, (Etyang et al., 2020; Maraci et al., 2020) could improve the accuracy of gestational age determination in settings with more limited access to ultrasound. In the future, this may help clinical decision-making around a range of interventions dependent on accurate assessment of gestational age, including planned delivery for pre-eclampsia. Limited access to laboratory testing was a further barrier to diagnosing pre-eclampsia or detecting maternal complications at the trial sites, particularly in Zambia. Low-cost solutions such as point of care creatinine testing may help to counteract this particular barrier, but this requires further evaluation of its feasibility and efficacy in high-risk obstetric populations living in low-resource settings.(Glasmacher et al., 2016; Macedo, 2017) However, vertical solutions, focused on one problem (i.e. timing of delivery) alone, are unlikely to produce improvements, unless all the necessary components of good quality care within the healthcare system are considered. For example, post-partum haemorrhage (PPH) remains the leading direct cause of maternal death globally,(Say et al., 2014) and

was the underlying cause of death for two of the four maternal deaths in the CRADLE-4 Trial. Therefore, future research must focus on how to strengthen the healthcare system as a whole, alongside effective implementation of evidence-based interventions. Whilst the CRADLE-4 Trial provides reassuring evidence that planned delivery can be offered to women with late preterm pre-eclampsia in a low-resource setting, the impact in settings that are more rural and with fewer resources could be explored further. Most of the sites included in the CRADLE-4 Trial were either tertiary referral centres, or primary health facilities serving a mixed rural and urban population, in close proximity to neonatal services if required. However, most national guidelines, including in Zambia, would advocate referral of any woman with pre-eclampsia to higher-level care, if diagnosed in a more remote health facility.(Ministry of Health., 2018) Therefore, initiation of planned delivery for late preterm pre-eclampsia should only be undertaken in a facility that has sufficient resources (i.e. Comprehensive emergency obstetric and newborn care services [CEmONC]) to provide safe maternal and newborn care. Establishing the minimum level of staffing, equipment, and expertise required to deliver the intervention safely will be an important component of implementation.

Placental growth factor (PLGF) testing is now recommended by NICE (National Institute for Health and Care Excellence) in the UK to confirm or rule out a diagnosis of pre-eclampsia.(National Institute for Health and Care Excellence, 2022) Point of care PLGF testing presents an exciting opportunity to evaluate the impact of PLGF testing in a low and lower-middle income setting. Using these tests to more accurately diagnose pre-eclampsia at the bedside, could improve the accuracy of diagnosis and the safety of the intervention, ensuring that only the women with confirmed pre-eclampsia are offered planned delivery. This requires further evaluation, and a pilot study is currently underway at four sites in Zambia to explore the feasibility of a larger randomised trial across several different low and middle income countries. Ultimately, the development of a clinical pathway that incorporates PLGF testing as part of a decision-making tool for timing of delivery

could help target resources in the safest and most effective way, helping clinicians identify which women and infants are most at risk.

Antenatal corticosteroids are an important example of the need to use evidence-based interventions judiciously, in the right populations at the right time. Whilst there is a strong body of evidence supporting the use of antenatal corticosteroids to reduce the risk of neonatal morbidity and mortality at early preterm gestations,(McGoldrick et al., 2020) their use after 34 weeks is more controversial, and no longer routinely recommended.(Norman et al., 2021) This is due to their potential adverse effect on long-term infant neurodevelopment, particularly amongst infants initially exposed to antenatal corticosteroids, who are then born at term.(Raikkonen et al., 2020) Pre-eclampsia represents a clinical scenario where it is usually possible to plan delivery, and thus optimally time administration of antenatal corticosteroids. Data from the CRADLE-4 Trial, where a high proportion of women received antenatal corticosteroids, with reassuring perinatal outcomes, would suggest that planned delivery for women with pre-eclampsia is a clinical situation that merits use of optimally timed antenatal corticosteroids at late preterm gestations. In this particular scenario, when delivery can be planned within 48 hours, the benefits of antenatal corticosteroids likely outweigh the risks. However, further research should aim to establish more clearly the benefits and risks of antenatal corticosteroids at late preterm gestations,(WHO ACTION Trials Collaborators, 2022) in different clinical scenarios including pre-eclampsia, and the long-term impact on infant outcomes, to help guide clinical practice further. Finally, the findings from the Lost in Translation study are an important contribution to the wider movement aimed at decolonising global health research.(Khan et al., 2021) It is vital that researchers, and research ethics committees, re-evaluate the current procedures used to design and translate recruitment materials. Whilst lengthy templates, designed in English-speaking, high income countries, are commonplace, I believe we should be more flexible, and be guided by local needs. This may include written information that has been developed in conjunction with local communities and language experts, but should extend beyond this to

community engagement activities aimed at improving health literacy and understanding of clinical research, as well as specific meetings and household visits (if appropriate) concerning specific studies. The videos used to supplement the informed consent process as part of the CRADLE-4 Trial were a valuable tool to aid participant understanding, but more work is required to formally evaluate different methods of providing information to potential participants as well as assessing their understanding. Ethics committees have a responsibility to ensure that the recruitment materials in use are fit for purpose and serve the needs of the intended recipients, not simply the legal requirements of the study sponsor. Building local research ethics capacity and strengthening the systems currently in place is therefore an important area to focus on in the future.(Chaudhry et al., 2022)

9.5. Conclusions

Based on the research findings explored throughout this thesis, planned delivery should be offered to all women with late preterm pre-eclampsia, irrespective of severity, from 34 weeks' onwards, in low and lower-middle income settings. This intervention significantly reduces the risk of stillbirth by 75%, with no increase in short-term neonatal complications. Translating these findings into an overall reduction in maternal and perinatal mortality, will require ongoing community engagement to share this knowledge, alongside holistic interventions which address the entire pathway of maternity care, as well as the wider social determinants of health. The importance of qualitative methods, and assessing feasibility, when designing future research studies, cannot be over-stated. Finally, the language barriers to informed consent identified during this work should prompt a re-evaluation of the design of recruitment materials, how they are translated, and the ethical review process, alongside efforts to establish greater equity between partners delivering global health research.

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Chapter 10 Appendix

Appendix 1 Two-year follow-up of infant and maternal outcomes after planned early delivery or expectant management for late preterm pre-eclampsia (PHOENIX): a randomised controlled trial: GRIPP2-SF Checklist

Section and topic	Item	Reported
Aim	The aim of Public and Patient Involvement in all aspects of the study was to ensure that the voices of pregnant women (and their wider families) were woven throughout the research, such that the results would be of direct benefit to them.	√
Methods	We worked with Public and Patient Involvement representatives from grant preparation through to dissemination. As the study arose from a commissioned call, we were aware that pregnant women had been involved through the NICE guideline committee and the NIHR HTA prioritisation work, but we additionally worked with representatives (including those with lived experience) from Action on Pre-eclampsia (the patient support group) and Tommy's Charity (a national baby charity). This involvement extended across considerations around research design, development and iteration of participant information resources, research management and troubleshooting (as members of the Co-Investigator Group and Trial Steering Committee), interpretation of the data, and writing and dissemination of the findings.	√
Study results	Examples of how PPI shaped the research included consideration of how to promote recruitment when it was slower than anticipated. A number of the central research team noted that women were often enthusiastic about participation, perceiving the clinical need for this uncertainty to be addressed, but that healthcare professionals could act as gatekeepers to enrolment. We worked with site teams to support them offering the trial to a greater proportion of eligible women, reinforcing that we had made the inclusion criteria as wide as possible for a pragmatic approach. We disseminated the information that around 55% of women who were approached agreed to take part, and with positive quotes from women (about participation)	√

Section and topic	Item	Reported
	included in newsletters, with the women's consent. This enabled a shift towards an inclusive approach to enrolment.	
Discussion and conclusions	Pregnancy studies have had a long history of active PPI input, but for a timing of delivery trial this is particularly crucial as the trade-off between maternal and infant benefits and risks is central to the research question. PPI input has been pivotal around appropriate representation of this balance, accurate depiction of the existing equipoise, and interpretation of the findings when typically benefits may not always go in the same direction for the woman and the baby. PPI has only ever been a positive and essential guiding influence.	√
Reflections/critical perspective	The active involvement of Action on Pre-eclampsia, the patient support group, has been vital at all stages. This has enabled contribution through the Chief Executive Officer, Marcus Green, who combines indirect lived experience (as a partner of a woman with pre-eclampsia) with a powerful conduit to many other voices for whom he constantly advocates. The study has also had involvement of others with lived experience, but we noted that sometimes women transition through various phases of their lives and may choose to be involved for varying durations (not always for the entire length of the study). This has led Action on Pre-eclampsia to set up a research involvement panel, so that those with lived experience can contribute in the way that best suits them	√

Appendix 2 Two-year follow-up of infant and maternal outcomes after planned early delivery or expectant management for late preterm pre-eclampsia (PHOENIX): a randomised controlled trial: Centre at randomisation of responders at two-year assessment

Name	Planned delivery (n=276)	Expectant management (n=251)
St Thomas' Hospital, London	19 (6.9)	22 (8.8)
Darent Valley Hospital	17 (6.2)	15 (6.0)
St Mary's Hospital, Manchester	17 (6.2)	10 (4.0)
Bradford Royal Infirmary	8 (2.9)	4 (1.6)
West Middlesex University	17 (6.2)	15 (6.0)
Nottingham City Hospital	9 (3.3)	9 (3.6)
Leeds Teaching Hospitals - St James'	14 (5.1)	6 (2.4)
Liverpool Women's	11 (4.0)	13 (5.2)
Queens Medical Centre	6 (2.2)	5 (2.0)
Royal Victoria Infirmary	7 (2.5)	10 (4.0)
James Cook University Hospital	9 (3.3)	15 (6.0)
Sunderland Royal Hospital	11 (4.0)	16 (6.4)
University College Hospital	6 (2.2)	10 (4.0)
Birmingham Women's Hospital	6 (2.2)	3 (1.2)
St George's Hospital	5 (1.8)	0 (0.0)
Royal Stoke University Hospital	6 (2.2)	4 (1.6)
Western Sussex Hospitals	5 (1.8)	9 (3.6)
Whittington Hospital	3 (1.1)	2 (0.8)
ABM University Hospitals, Wales	16 (5.8)	11 (4.4)
Birmingham City Hospital	6 (2.2)	2 (0.8)
Birmingham Heartlands Hospital	4 (1.4)	0 (0.0)
Warrington and Halton Hospitals	2 (0.7)	2 (0.8)
Chesterfield Royal Hospital	2 (0.7)	3 (1.2)
Royal United Hospital, Bath	3 (1.1)	3 (1.2)
Kingston Hospital NHS Trust	11 (4.0)	9 (3.6)
Leighton Hospital	4 (1.4)	6 (2.4)
Leicester Royal infirmary	6 (2.2)	6 (2.4)
Shrewsbury and Telford Hospital	0 (0.0)	3 (1.2)
Royal Preston Hospital	1 (0.4)	3 (1.2)
Northampton General	5 (1.8)	3 (1.2)
Gloucestershire Royal Hospital	0 (0.0)	1 (0.4)
St Michael's Hospital, Bristol	2 (0.7)	3 (1.2)
Royal London Hospital	4 (1.4)	1 (0.4)
Whipps Cross Hospital	4 (1.4)	4 (1.6)
New Cross Hospital,Wolverhampton	3 (1.1)	2 (0.8)
Cambridge University Hospitals	2 (0.7)	0 (0.0)
Chelsea and Westminster Hospital	0 (0.0)	3 (1.2)
Royal Bolton Hospital	2 (0.7)	1 (0.4)
St Helier Hospital	2 (0.7)	1 (0.4)

University Hospital, Lewisham	0 (0.0)	2 (0.8)
Epsom Hospital	1 (0.4)	0 (0.0)
Queen Elizabeth Hospital, Greenwich	4 (1.4)	0 (0.0)
Queen's Hospital, Romford	2 (0.7)	2 (0.8)
Croydon University Hospital	11 (4.0)	12 (4.8)
Broomfield Hospital, Chelmsford	3 (1.1)	0 (0.0)

Appendix 3 CRADLE-4 Phase 1 Focus group discussion guide

The purpose of this focus group is:

- To explore women's experiences and understanding of pre-eclampsia and preterm birth through a group discussion.
- To explore women's views surrounding planned early delivery in pre-eclampsia

Reassure the participants that their answers will be anonymous and we would like them to be honest. These questions are a guide only; feel free to explore topics as they arise.

Thank you all for agreeing to participate today.

We're going to start by talking about a condition called pre-eclampsia.	What do you understand about this condition? Do you know anyone who has had pre-eclampsia?
What impact might pre-eclampsia have on a woman's pregnancy and her baby?	How might it affect the mother? How might it affect the baby?
Sometimes women with pre-eclampsia might have their babies early…	What do you understand about this? How do you feel about this? Has this happened to anyone you know? Can you tell me any more about this?
If a woman with pre-eclampsia has her baby early what do you think the advantages and disadvantages might be?	For the woman? For the baby?
Do you know anyone who has had a baby that was born early?	What happened? Can you tell me more about this?
What care might be provided to babies who are born early?	What care might be needed? What care is available here? How might this care be accessed?

	Are there any barriers to accessing this care? Can you tell me more about this?

Pre-eclampsia can be a serious condition for both mother and baby. It can cause very high blood pressure in the mother and in serious cases it can cause fits, strokes, organ failure and sometimes death. Babies whose mothers have pre-eclampsia tend to be smaller and are more likely to be born early. Because of this, most women with pre-eclampsia have their labour started around 37 weeks of pregnancy.

But, because some of the complications of pre-eclampsia can be life-threatening and the condition of both the mother and baby can suddenly worsen, some doctors think it may be better for women with pre-eclampsia to have their babies before this.

We are designing a trial to find out whether, in women with pre-eclampsia between 34 and 37 weeks of pregnancy, planned early delivery causes fewer complications for the mother and/or baby, compared to waiting until 37 weeks (unless a serious problem occurs before this time).

This means that women who agree to participate in the trial will be randomly allocated to planned early delivery or expectant management (watchful waiting).

What do you think about this?	Can you tell me why?
What do you think the advantages and disadvantages of being in the early delivery group might be?	For the mother? For the baby? Can you tell me more about this?
What do you think the advantages and disadvantages of being in the watchful waiting group might be?	For the mother? For the baby? Can you tell me more about this?
Planned early birth is usually started by a process called “Induction”	What do you understand by this? Do you know anyone who has had an Induction? What do you think about Induction? Can you tell me more about this?
Occasionally, planned early birth might happen by caesarean section (for example, if a woman has had a caesarean section in the past)	What do you understand by this? Do you know anyone who has had a caesarean section? What do you think about caesarean section? Can you tell me more about this?
How would you prefer to give birth?	Can you tell me why?
How do you feel about planning early birth in women with pre-eclampsia?	Can you tell me why?
How does your family feel about pregnancy and childbirth?	How might their views influence your preferences? Do you have a husband? How might his views influence your preferences?
How do you get to the hospital?	At short notice? Can you tell me more about this?
How do you pay for your maternity care?	Can you tell me more about this?

How would you feel if you or your baby needed to spend additional time in hospital?	Can you tell me more about this?

Appendix 4 CRADLE-4 Phase 1 Stakeholder interview topic guide

The purpose of this interview is:

- To understand the experience of healthcare providers managing women with pre-eclampsia and their babies in this hospital.
- To explore healthcare providers' views surrounding management of pre-eclampsia and preterm birth
- To find out how healthcare providers feel about planned early delivery in women with pre-eclampsia.

Reassure the interviewee that their answers will be anonymous and we would like them to be honest.

Introductory Questions	
How long have you been working in this healthcare facility?	
What is your role?	
Can you tell me about your understanding of pre-eclampsia?	
Do you work with women or babies that have been affected by pre-eclampsia?	Can you tell me more about your experience of this?
Exploratory Questions	
What is your understanding of how pre-eclampsia is managed in this facility?	At what gestation are women with pre-eclampsia routinely delivered in this hospital? What do you think the advantages and disadvantages of this might be? (If Obstetrician) How do you manage someone with pre-eclampsia?
Can you tell me about your understanding of what happens to women who have pre-eclampsia?	What happens to these women? What is your experience of this?
Can you tell me about your understanding of what happens to the babies of women who have pre-eclampsia?	What happens to these babies? What is your experience of this?
Can you tell me about your experience of the neonatal facilities here?	What happens to babies that are born before term? How are they looked after?

	What are their outcomes? How do you feel about the management of preterm babies in this facility?
How do you feel about the management of pre-eclampsia in this facility?	What works well? What do you find difficult? What could be improved?

After 37 weeks' gestation we know that the World Health Organization recommends delivery in women with pre-eclampsia. But, because some complications of pre-eclampsia can be life-threatening and the condition of both the mother and baby can suddenly worsen, some clinicians think it may be better for women with pre-eclampsia to have their babies earlier than this.

We are designing a trial to find out whether, in women with pre-eclampsia between 34 and 37 weeks of pregnancy, planned early delivery causes fewer complications for the mother and/or baby, compared to waiting until 37 weeks (unless a serious problem occurs before this time).

This means that women who agree to participate in the trial will be randomly allocated to planned early delivery or expectant management (watchful waiting). A similar trial is currently underway in the U.K. but it's important to evaluate the intervention in other settings where the outcomes may be different.

What do you think about this?	What do you think the advantages and disadvantages of early delivery might be? What do you think the advantages and disadvantages of expectant management might be?
How do you think the care provided to women in each group might differ?	How might the care of women in the early delivery group differ from routine management?
What might the advantages and disadvantages be for the babies in each group?	What do you think the advantages and disadvantages of early delivery might be for the baby? What do you think the advantages and disadvantages of expectant management might be for the baby?
What impact do you think the trial will have on the capacity of your unit?	(If obstetrician/midwife) How might it affect labour ward? (If neonatal nurse/doctor) How might it affect the neonatal unit?
What do you hope the trial might achieve?	Can you tell me more about that?
Do you have any concerns or questions about the trial?	Can you tell me more about that?

Appendix 5 Lost in Translation: Interview topic guide

Details:

Date	
Start time	
Finish time	
Location	
Initial(s) of participant(s)	
Age(s)	
Level of education	
Profession	

Notes

Example prompts *What does this term/phrase mean to you?* *What do you understand by this term/phrase?* *How might this term be translated into Nyanja/Bemba?* *Is there an equivalent word?* *Is there an equivalent concept?* **If participant is a translator:** *Can you tell me about your experience of translating research materials from English to Nyanja/Bemba?*	

Have you come across any challenges? *Is there anything you feel that may improve this process?* **If participant is a researcher**: *Can you tell me about your experience of using research materials when gaining consent?* *Have you come across any challenges?* *Is there anything you feel that may improve this process?*	

Appendix 6 CRADLE-4 Trial Participant information leaflet (English)

Who should I contact for further information?

University Teaching Hospital, Lusaka, Zambia &

Levy Mwanawasa Teaching Hospital, Lusaka, Zambia

Prof Bellington Vwalika

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THE CRADLE-4 TRIAL: Can planned early birth in pre-eclampsia (high BP in pregnancy) reduce adverse pregnancy outcomes?

PARTICIPANT INFORMATION LEAFLET

VERSION 1.1. 2019_10_10

Who are we?

We are a team of researchers aiming to improve care for women with high blood pressure in pregnancy. We would like to invite you to take part in this research project. Before you decide whether you want to take part, it is important for you to understand why the research is being done and what your participation will involve.

Please take time to read the following information and discuss it with others if you wish. Please ask a member of the research team if there is anything that is not clear or if you would like more information.

What is the purpose of the study?

Pre-eclampsia is a pregnancy complication. It is associated with high blood pressure and protein in the urine. It can be a serious condition for both mother and baby. For example, it can cause very high blood pressure and in severe cases it can cause fits, stroke and sometimes even death.

Babies whose mothers have pre-eclampsia are smaller and are more likely to be born early. In severe cases pre-eclampsia may cause babies to be stillborn (intra-uterine fetal death). The cause of pre-eclampsia is not known. However, we know that the condition only improves once the baby is delivered.

Once a woman with pre-eclampsia has completed 37 weeks (8 ½ months) of pregnancy it is recommended that she is delivered. Her labour is normally started by induction (using medicines to start labour), between 37 and 38 weeks of

pregnancy (around 8 ½ months). At this time most babies are fully developed and ready to be born.

But, because pre-eclampsia can be serious and the mother and her baby might become unwell suddenly, it may be better for women with pre-eclampsia to deliver their babies earlier.

This study aims to find out whether, in women with pre-eclampsia between 34 and 37 weeks of pregnancy (around 7 ½ to 8 ½ months), planned early birth can reduce complications for the mother and her baby, compared to waiting until 37 weeks (about 8 ½ months) or until a serious problem occurs before this time.

This study may help improve the care of women with pre-eclampsia in the future.

Why have I been invited to take part?

You have been invited to take part in this study because you have pre-eclampsia, but your condition does not require that your baby be delivered immediately.

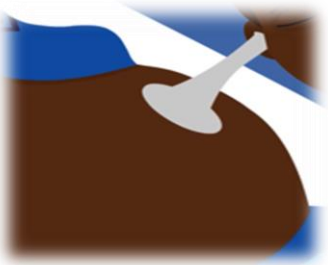
What will happen if I take part?

If you decide you would like to take part we will ask you to sign a consent form. Details about you and your pregnancy will be put into a computer which will randomly allocate you to either the planned early birth group or the watchful waiting group. Random allocation means that you cannot choose which group you want to be in, and neither can your doctor. The computer will randomly allocate you - you will have a 50/50 chance of being in either group.

If you are allocated to the planned early birth group then your labour will be started by your doctor within two days. This is called an induction of labour (using medicines to start your labour). Your doctor might give you some steroid injections to help your baby's lungs mature.

If you don’t go into labour (get labour pains), your doctor may deliver you in other ways, according to the hospital's protocol.

If you are allocated to the watchful waiting group then your doctors will look after you according to their routine protocol. This means you will be admitted to hospital and they will monitor you and your baby.



If you remain well until 37 weeks (about 8 ½ months) then your doctors will recommend delivery at this time. This means they will arrange for your labour to be induced (giving medicines to start your labour) in the same way as for women in the planned early birth group. During your monitoring, your doctors will recommend delivery before 37 weeks (about 8 ½ months) if they are concerned about either you or your baby’s condition. You will still be a part of the study if this happens.

After you have given birth, you and your baby will be cared for in the usual way at the hospital. It will not make a difference which group you belong to.

Information will be collected about yours and your baby’s health until you are both discharged from hospital.

Do I have to take part?

Participation in this study is entirely voluntary. You do not have to take part if you do not want to. If you decide you don't want to take part, this will not affect your care in any way.

What are the benefits of taking part?

The results of this study will provide additional information to improve outcomes for mothers and babies with pre-eclampsia.

We appreciate your time and are grateful for your help. However, there will not be any financial compensation for taking part in this study.

By choosing to take part in this study you will be helping us to help other women like you in the future.

What are the possible risks of taking part?

There are possible risks and benefits for both groups. This is why we feel it is important to do this study to improve care for women with pre-eclampsia.

If you are in the planned early birth group:

After 34 weeks (around 7 ½ months) your baby's lungs are usually mature and we know that babies who are born at this time do well. However, there is a risk that your baby may have problems associated with being born early. They may need to go to the neonatal unit when they are first born. Some of these babies may need help with their breathing or feeding in the first few days of life.

If you are in the watchful waiting (expectant) group:

If you are in this group your doctors will be monitoring you and your baby. During your monitoring, your doctors will recommend delivery if they are concerned about either you or your baby's condition. If this happens they will start your labour early, meaning they will offer you an induction of labour (giving medicines to start your labour). When women have pre-eclampsia, sometimes their babies do not get enough nutrients for them to grow properly and in addition the women can become unwell quickly. If this happens to you, you may need an emergency delivery (either by induction or by caesarean). This may be stressful for you and your baby.

We don't know whether it is better to be in the planned early birth group or the watchful waiting group. This is why we are doing this research.

What if I change my mind about taking part?

You can leave the study at any time, up until 31st August 2021. We will ask you if we may use the information collected about you so far in the analysis of the study. We may also ask if you are happy for the researchers to continue to collect information about the health of you and your baby until you are discharged from hospital However, this is entirely voluntary and you may choose to withdraw all the information collected about you and your baby (up until 31st August 2021) if you wish.

If you decide you no longer want to take part in the study, this will not affect the quality of the routine care provided to you and your baby for the remainder of your pregnancy.

How will you manage the information collected about me and my baby?

If you take part in the study we will collect some personal information. This will only be used by members of the research team if they need to contact you. This information will be kept confidential. This means that only members of the research team will have access to it, and it will not be shared with anybody else.

Any other information collected about you and your baby will be anonymised. This means that you will be given a Study ID number. We will not use your name. It will not be possible to identify you or your baby from these records. The information will be kept on a secure computer. Only members of the research team will have access to it.

The data will be protected according to UK Data Protection Laws.

What will happen to the results of the study?

At the end of the study, the results will be analysed and published in scientific journals and presented at scientific conferences. You and your baby will not be identified in any report or publication about the study.

How is the project being funded and organised?

This study is being funded by the Medical Research Council in the UK and the Department of Biotechnology in India. The study is organised by King's College London in collaboration with the University of Zambia and the KLE Academy of Higher Education and Research, India.

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Appendix 7 CRADLE-4 Trial Participant information leaflet (Nyanja)

Kodi ndizafunsa ndani ngati ndifuna kudziwa zoculuka?

Prof Bellington Vwalika

+260 96 6782971

CIYAMBI –KUFUFUZO -4: KODI KUKONZEKERA KWA UBEREKI WAMASIKU OSAKWANA CUFUKWA CA BVUTO LOTHAMANGA KWA MAGAZI PAMENE MAI ALI NDI PAKATI KUNGACEPETSEDWE?

NYANJA_VERSION 1.1. 2019_10_10

Kodi ndise andani?

Ndise guru yochokela ku cradle 4 yamene iyanganila pazimai alindipakati amene apezeka ndibvuto ya puliekelampusiya.

Nikupemphani kuti mtengeko mbali mkufufuza kwathu. Mukalibe kusankha kutengako mbali, muyenera ku dziwa ncifukwa ninji kufufuza kuli kucitika ndiponso phindu lomwe mungapeze pamene mutengako mbali.

Conde patulani nthawi kuti muwerenge ndi kukambitsirana ndi anzanu ngati mungakonde kutero. Ndinu oloredwa kundifunsa funso lirironse pazomwe simunvetse kapena mfundo zina zirizonse zimene mufuna kudziwa.

Kodi colinga ca cifufuzo ici nciani?

Puliekelampusiya ndi bvuto lomwe limayamba pamene mai akhala ndi pakati. Cizindikiro ca bvutoli ndi kuthamanga kwa magazi ndiponso pamene zakudya zomwe zikalibe kugwiritsidwa nchito mthupi zipezeka mum'kodzo. Bvutoli liri lingakhare ndi ciopsyeso cacikulu kwa mzimai wa pakati ndi mwana osabadwayo.

Mwacitsanzo, ingapangitse magazi kuthamanga kwambiri kotero kuti mai atha kuyamba ukunyuka, kuzizira ziwalo, bvuto la mphewo kapena kufa kumene.

Ana omwe amai ao ali ndi bvuto la puliekelampusiya angabadwe aang'ona kwambiri ndiponso masiku osakwana. Pamene ciopsyezo ca bvuto la puliekelampusiya cipitirira, makanda amenewa amabadwa akufa (nthayo).

Comwe ciyambitsa Puliekelampusiya kuthamanga kwa magazi kotereku sicidziwika. Ngakhale zilitere, tidziwa kuti bvutili limatha pokhapo mai atabereka.

Pamene mai wa puliekelampusiya afika masabata 37 kapena kuti miyezi 8 (isanu ndi itatu) yakukhala ndi pakati, nkofunika kuti abereke. Kawiri- kawiri kuberekaku kumakhala kocito yambitsa pakati pa masabata 37 ndi 38 ya kukhala ndi pakati (pakapita miyezi 8). Panthawi iyi nkuti masiku atakwana kuti mwana nkubadwa.

Koma, cifukwa ca kuti Puliekelampusiya ndi bvuto limene liika moyo wa mai ndi mwana pa cipsyezo mosayembezera, ncofunika kuti azimai abvuto lotere abereke mosataya nthawi.

Colinga ca phunzilo lathu ndi kudziwa ngati nkotheka kuti azimai a Puliekelampusiya omwe akhala ndi pathupi pakati pa miyezi 34 ndi 37 (pakatipa miyezi 7 ndi 8), kukonzekera kwa uberekiwa masiku osakwanira kunga cepetse ngozi kupambana kuyembekezera mpaka masabata 37(miyezi 8) pokhapo ngati kwapezeka bvuto lalikulu isanafike nthawi iyi.

Kufufuza kwathu kungathandize azimai omwe angakhale ndi Puliekelampusiya mtsogolo.

Ncifukwa ciani ndaitanidwa kuti ndi tengeko mbali?

Mwaitanidwa kuti mtengeko mbali mkufufuza kwathu cufukwa muli ndi bvuto la Puliekelampusiya, koma bvuto lanu siritanthauza kuti mwana ayera kubadwa nthawi yomweino ai.

Kodi cidzacika nciani ngati ndi tengako mbali?

Ngati mudzasankha kutengako mbali, mudzafunsidwa kusaina pepala la cibvomerezo.

Mfundo zonena za pathupi panu zidzaikidwa m' kompyuta yomwe idzakuikani mgulu losadzisankhira, lomwe lingakhale gulu la ubereki wa masiku osakwana kapena agulu loyang'aniridwa

Lichedwa gulu losadzisankhira cifukwa, suyenera kusankha wekha gulu lakuti upezemo ngakhale aDotolo omwe sangakusankhireni. Kompyuta ndiyo idzagwira nchito yokuikani m'magulu. Muli ndi mwai olingana kupezeka mgulu lirilonse mwa magulu awiriwa.

Ngati mwapezeka mgulu la ofunika kukonzekeredwa ubereki wa masiku osakwana, kuwawa kwa m'mimba kwa ubereki wanu kudzayambidwa ndi aDotolo pasanapite masiku awiri. Iyi ndi njira yobereketsa mzimai wa pathupi nthawi isanakwane. A dotolo anu angakulaseni nyeleti yokonzekeretsa khanda kubadwa. Ngati mai sayambabe kubereka, a dotolo adzagwiritsira nchito njira zina kulingana ndi ndondomeko za chipatala canu.

Ngati mwapezeka mgulu la kungo yang'aniridwa ndi a dotolo kulingana ndi zoonerapo zao, mudza sungidwa mchipatala kuti muyang'niridwe pamodzi ndi mwana wanu.

Ngati mukhala athanzi mpaka masabata 37 (miyezi 8), mudzayamikiridwa kuti mudzabereke mtakwanitsa masabata 37 (miyezi 8). Kutanthauza kuti ubereki wanu udzakhala oyambitsidwa monga momwe a gulu lija la obereka msasiku osakwana acitira. Ngati bvuto lanu likula musanakwanitse masabata 37 (miyezi 8) a dotolo anu adzakuunikirani kuti mubereke. Mudzakhalabe agulu la phunziro iri ngati zicitika motere.

Pambuyo poti mwaona mwana, inu ndi mwana wanu mudzalandira cisamaliro mnjira imodzi-mozdzi monga m'mene onse asamaliridwa mchipatala. Mfundo zokhudza umoyo wanu ndi wa mwana zidzatenge kufikira pamene mudza tuludzidwa m'chipatala.

Kodi ndi funika kutengako mbali?

Osatengako mbali ngati simufuna kutero. Mungasankhe kutengako mbali kapena ai, muyenera kutengako mbali pokhapo ngati mufuna kutero. Ngati mwasankha kusatengako mbali, ici sicidzasokoneza thandizo lomwe muyera kulandira mnjira iriyonse.

Nanga ubwino otengako mbali ndiotani?

Tikhulupirira kuti zotuluka zakufufuza uku zidzathandiza a dotolo ndi anyamwino ogwira nchito mdziko lathu pa kukhala ndi cidziwitso cozama popereka thandizo lofunikira kwa azimai omwe apezeka ndi bvuto la Puliekelampusiya.

Ndise oyamikira panthawi yanu ndi thandizo lomwe mwatipatsa. Ngakhaleziri tero, sipadzakhala malipiro alionse cifukwa cotengako mbali mkufufuza uku.

Pakutengako mbali, mukutithandiza kuti tikathandize ena amene angadzakumane ndi bvuto lofanana ndi lanu mtsogolo.

Kodi pangakhale kuipa kotani mkutegako mbali?

Pali kuipa ndi ubwino mkutengako mbali m'magulu onse awiri. Ncifukwa cake taganiza kuti tifufuze pofuna kuonjezera cisamaliro kwa azimai omwe ali ndi bvuto la pre-eclamsia.
Ngati muli mgulu la okonzekeredwa ubereki wa masiku osakwana:

Pambuyo pa masabata 34(miyezi 7) maphwaphwa a khanda amakhala olimbabwino ndiponso ana obadwa masiku otere amakula bwino. Ngakhale zili tere, pangakhale zobvuta cifukwa cobadwa msanga nthawi isanafike. Amafunika ukasungidwa kucigawo ca maleredwe pamene angobadwa cabe. Ciwerengero cocepa mwa makanda obadwa motere, amafunika thandizo lopuma ndi kudya mwa masiku ocepa cabe kucokela pamene abadwa.

Ngati muli mgulu loyaning'aniridwa pa ubereki wa masiku osafikapo:
Ngati muli mgulu iri a dotolo anu adzakuyang'anirani pamodzi ndi mwana wanu. Ngati bvuto likula, a dotolo adzaku unikirani kuti mubereke nthawi yomweyo. Ici citanthauza kuti kubereka kwanu kudza yambitsidwa msanga, ndipo ubereki wanu udzakhala ocirikidwa ndi a dotolo. Ngati mai ali ndi Puliekelampusiya, nthawi zina ana ao samalandila zakudya mthupi zokwanira kuti akule bwino ndiponso angadwale nthawi iriyonse. Ngati zikhala tero, mungafunike kubereketsedwa mnjira za cidule (mwina kukakamiza mwana kubadwa kapena kuceka mai munsi mwamimba nkucotsa mwana). Ici cingapereke cisautso cacikulu kwa inu ndi mwana yemwe.
Sitidziwa cabwino nciati pakati pa kupezeka mgulu la okonzeketsedwa kubereka masiku osakwana ndi aja oyang'aniridwa paubereki. Ncifukwacake tiri kufufuza za ici.

Zikhala bwanji ntasitha maganizo pa kutengako mbali?

Mungasiye kutengako mbali mkufufuza uku nthawi iliyonse. Mudzafunsidwa ngati muvomereza kugwiritsako nchito mfundo munatipatsa kufikira nthawiyo mphunziro iri.

Kodi mzagwiritsira nchito motani mfundo zokhuza ine ndi mwana wanga?

Ngati mutengako mbali mkufufuza uku ,tidzatenga keyala yanu. Kayala iyi idzagwiritsidwa nchito ndi ogwira nchito ku bungwe lathu cabe pamene tingafune kulankhula ndi inu.zonsezi zidzasungidwa mwa cinsinsi. Ici citanthauza kuti ogwira nchito mbungwe lathu okha ndiwo adzakhare ndi danga lodziwa nambala yanu ndipo sidzapatsidwa ku munthu wamba wina aliyense.

Mfundo zina zirizone zimene zingatedwe zokhudza inu ndi mwana wanu zidzatengedwa mcinsinsi. Kutanthauza kuti mudzapatsidwa khadi ndi numbala ya cidzindikiro. Sitidzalembapo dzina lanu.sicidzakhala cotheka kukuzindikirani pamodzi ndi mwana wanu pongoyang'ana pa nambala ya khadi. Mfundo zonse zidzasungidwa m'compyuta yocingiriridwa. Abungwe lathu lofufuza ndiwo okha adzakhale ndi mpata otsegula compyutayi.

Zofufuza zathu zonse zidzasungidwa molondola malamulo osunga cinsinsi a UK Data Protection Laws.

Kodi cidzacitika ndi ciyani pa zotuluka za phunziro iri?

Pomaliza kwa kufufuza uku, zotuluka zidzasandidwa-sandidwa ndi kuulutsidwa mkhani zofalitsa za umoyo. Inu ndi mwana wanu simudzazindikiridwa kapena kufalitsidwa mphunziro iri.

Kodi nchito yofufuza iyi itsogoleredwa ndi kulipiridwa ndi bungwe lanji?

Kufufuza uku kulipilidwa ndi a bungwe la Medical Research Council lokhazikitsidwa mu United Kingdom. Kufufuza uku kutsogoleredwa ndi abungwe la king's college London mogwirizana ndi sukukulu lalikulu la maphunziro la m'Zambia (university of Zambia).

Appendix 8 CRADLE-4 recruitment by main site

Site	Planned delivery n=282	Expectant management n=281
Country		
Zambia	205 (72·7%)	202 (71·9%)
India	77 (27·3%)	79 (28·1%)
Zambia (city)		
Kabwe	31 (11·0%)	29 (10·3%)
Kitwe	31 (11·0%)	30 (10·7%)
Lusaka	85 (30·1%)	88 (31·3%)
Ndola	58 (20·6%)	55 (19·6%)
Lusaka (centre[s])		
University Teaching Hospital	24 (8·5%)	26 (9·3%)
Levy Mwanawasa Teaching Hospital	14 (5·0%)	14 (5·0%)
Kanyama 1st level hospital	17 (6·0%)	14 (5·0%)
Chipata 1st level hospital	10 (3·5%)	13 (4·6%)
Chilenje 1st level hospital	6 (2·1%)	6 (2·1%)
Chawama 1st level hospital	4 (1·45)	2 (0·7%)
Matero 1st level hospital	10 (3·5%)	13 (4·6%)
Ndola (centre[s])		
Ndola Teaching Hospital	58 (20·6%)	55 (19·6%)
Kabwe (centre[s])		
Kabwe Teaching Hospital	31 (11·0%)	28 (10·0%)
Mine Hospital	0	1 (0·4%)
Kitwe (centre[s])		
Kitwe Teaching Hospital	31 (11·0%)	30 (10·7%)
India (city and centre)		
Belgaum (Jawaharlal Nehru Medical College)	8 (2·8%)	14 (4·3%)
Bagalkot (S. Nijalingappa Medical College and Hangal Shri Kumareshwar Hospital and Research Centre)	3 (1·1%)	3 (1·1%)
Hubballi (Karnataka Institute of Medical Sciences Hubballi)	59 (20·9%)	59 (21·0%)
Vijaypura (BLDE [Deemed to be University] Shri B. M. Patil Medical College Hospital and Research Centre)	7 (2·5%)	5 (1·8%)

Appendix 9 CRADLE-4 Trial health economic analysis – preliminary results

Appendix 9a Health care cost – mean cost per woman in 2021 United States Dollars (USD)

Health care cost (USD)	**Planned delivery n= 284**	**Expectant management n= 281**	**Effect Size**
	Mean (SD)	Mean (SD)	MD (95% CI)*
Maternal Health care cost			
Antenatal ward	73 (119)	121 (217)	-49 (-76 to -22)
High-dependency and intensive care units	5 (36)	14 (83)	-9 (-20 to 1)
Postnatal ward	200 (206)	192 (161)	6 (-22 to 35)
Delivery	792 (745)	802 (785)	-9 (-75 to 57)
Total maternal cost	1070 (795)	1129 (831)	-61 (-140 to 19)
Infant cost			
Acute care	43 (385)	24 (119)	20 (-25 to 65)
Sub-acute care	311 (970)	341 (883)	-27 (-161 to 107)
Kangaroo care	60 (307)	60 (348)	2 (-51 to 55)
Normal	264 (464)	302 (668)	-39 (-109 to 32)
Total Infant Cost	678 (1441)	727 (1578)	-44 (-244 to 156)
Total infant and maternal cost	1748 (2019)	1856 (2219)	-105 (-340 to 130)

MD: mean difference *Adjusting for centre, parity, singleton versus twin pregnancy, and gestation at randomisation.

Appendix 9b Health care cost Zambia – mean cost per woman in 2021 United States Dollars (USD)

Health care cost (USD)	**Planned delivery n= 205**	**Expectant management n= 202**	**Effect Size**
	Mean (SD)	Mean (SD)	MD (95% CI)*
Total maternal cost	683 (421)	740 (421)	-80 (-150 to -9)
Total Infant cost	206 (295)	239 (436)	-33 (-1069 to 40)
Total maternal and infant cost	889 (567)	979 (660)	-113 (-222 to -3)

MD: mean difference *Adjusting for centre, parity, singleton versus twin pregnancy, and gestation at randomisation.

Appendix 9c Health care cost India – mean cost per woman in 2021 United States Dollars (USD)

Health care cost (USD)	**Planned delivery n= 77**	**Expectant management n= 79**	**Effect Size**
	Mean (SD)	Mean (SD)	MD (95% CI)*
Total maternal cost (USD)	2073 (643)	2124 (791)	26 (-161 to 213)
Total Infant cost (USD)	1905 (2279)	1975 (2497)	170 (-405 to 745)
Total maternal and infant cost (USD)	3978 (2641)	4099 (3078)	196 (-464 to 857)

MD: mean difference *Adjusting for centre, parity, singleton versus twin pregnancy, and gestation at randomisation.

Appendix 10 Ethical approvals

CRADLE-4 Phase 1 (feasibility and acceptability study)

Country	Ethics approval authority	Ethics approval number
Zambia	University of Zambia Research Ethics Committee	014-11-18
India	KLE Academy of Higher Education and Research Institutional Ethics Committee	KAHER/IEC/2019-20/D-2742
UK	King's College London Research Ethics Committee	LRS-18/19-8818

CRADLE-4 Phase 2 (randomised controlled trial)

Country (site)	Ethics approval authority	Ethics approval number
Zambia (all)	University of Zambia Research Ethics Committee	UNZA-301/2019
Zambia	National Health Research Authority	None provided; approval letter received 6th November 2019
India (Belgaum)	KLE Academy of Higher Education and Research Institutional Ethics Committee	KAHER/IEC/2019-20/D-251119016
India (Bagalkot)	BVV Sangha's S Nijalingappa Medical College Institutional Ethics Committee	SNMCIEC/1·1 /2019-2020
India (Vijaypura)	BLDE [Deemed to be University] Shri B. M. Patil Medical College Hospital and Research Centre Institutional Ethics Committee	BLDE(DU)/IEC/504/2020-21
India (Hubballi)	Karnataka Institute of Medical Sciences, Hubli-21, Scientific and ethical committee	None provided; approval letter received 1st January 2021
UK	King's College London Research Ethics Committee	HR-19/20-13535

Lost in translation (qualitative study)

Country	Ethics approval authority	Ethics approval number
Zambia	University of Zambia Research Ethics Committee	1517-2020
UK	King's College London Research Ethics Committee	MRSP-20/21-22350

Appendix 11 Published papers, trial protocol and statistical analysis plan

Planned delivery or expectant management in preeclampsia: an individual participant data meta-analysis

Alice Beardmore-Gray, MBBS; Paul T. Seed, MSc, CStat; Jessica Fleminger, MEng; Eva Zwertbroek, MD, PhD; Thomas Bernardes, MD, PhD; Ben W. Mol, PhD; Cheryl Battersby, PhD, FRCPCH; Corine Koopmans, MD, PhD; Kim Broekhuijsen, MD, PhD; Kim Boers, MD, PhD; Michelle Y. Owens, MD; Jim Thornton, MD; Marcus Green; Andrew H. Shennan, MD; Henk Groen, PhD; Lucy C. Chappell, PhD

OBJECTIVE: Pregnancy hypertension is a leading cause of maternal and perinatal mortality and morbidity. Between 34^{+0} and 36^{+6} weeks gestation, it is uncertain whether planned delivery could reduce maternal complications without serious neonatal consequences. In this individual participant data meta-analysis, we aimed to compare planned delivery to expectant management, focusing specifically on women with preeclampsia.

DATA SOURCES: We performed an electronic database search using a prespecified search strategy, including trials published between January 1, 2000 and December 18, 2021. We sought individual participant-level data from all eligible trials.

STUDY ELIGIBILITY CRITERIA: We included women with singleton or multifetal pregnancies with preeclampsia from 34 weeks gestation onward.

METHODS: The primary maternal outcome was a composite of maternal mortality or morbidity. The primary perinatal outcome was a composite of perinatal mortality or morbidity. We analyzed all the available data for each prespecified outcome on an intention-to-treat basis. For primary individual patient data analyses, we used a 1-stage fixed effects model.

RESULTS: We included 1790 participants from 6 trials in our analysis. Planned delivery from 34 weeks gestation onward significantly reduced the risk of maternal morbidity (2.6% vs 4.4%; adjusted risk ratio, 0.59; 95% confidence interval, 0.36—0.98) compared with expectant management. The primary composite perinatal outcome was increased by planned delivery (20.9% vs 17.1%; adjusted risk ratio, 1.22; 95% confidence interval, 1.01—1.47), driven by short-term neonatal respiratory morbidity. However, infants in the expectant management group were more likely to be born small for gestational age (7.8% vs 10.6%; risk ratio, 0.74; 95% confidence interval, 0.55—0.99).

CONCLUSION: Planned early delivery in women with late preterm preeclampsia provides clear maternal benefits and may reduce the risk of the infant being born small for gestational age, with a possible increase in short-term neonatal respiratory morbidity. The potential benefits and risks of prolonging a pregnancy complicated by preeclampsia should be discussed with women as part of a shared decision-making process.

Key words: expectant management, fetal growth restriction, infant outcomes, neonatal outcomes, obstetrics, planned delivery, preeclampsia, pregnancy hypertension, preterm birth, respiratory distress syndrome

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AJOG at a Glance

Why was this study conducted?

There is limited evidence regarding the optimal timing of delivery in late preterm preeclampsia, and single studies have not produced robust conclusions.

Key findings

Planned delivery from 34 weeks onward in women with preeclampsia significantly reduces maternal morbidity (adjusted risk ratio [RR], 0.59; 95% confidence interval [CI], 0.36−0.98) and the incidence of infants born small for gestational age (RR, 0.74; 95% CI, 0.55−0.99) but increases short-term neonatal respiratory morbidity (adjusted RR, 1.22; 95% CI, 1.01−1.47). The risk of short-term neonatal respiratory morbidity was lower in more recent trials where the use of antenatal steroids was higher.

What does this add to what is known?

This is the first individual patient data meta-analysis to evaluate planned delivery in women with preeclampsia at late preterm gestations. We have quantified the effect of planned delivery from 34 weeks onward on infant outcomes more precisely, demonstrating a reduction in the risk of infants being born small for gestational age but an increase in short-term neonatal respiratory morbidity. Evidence to guide clinical practice in this area is lacking. Our analysis provides more accurate information on the risks and benefits of planned delivery for preeclampsia without severe features from 34 weeks onward.

Introduction

Pregnancy hypertension is responsible for at least 27,800 maternal deaths[1] worldwide every year and 500,000 infant deaths,[2] including approximately 200,000 stillbirths.[3] Although the prevalence of preeclampsia varies throughout the world, it complicates between 2% and 3% of pregnancies in a high-income setting.[4] Estimates for low- and middle-income countries are higher, with up to 12% of pregnancies affected in these settings.[2] Delivery is the only definitive management for this progressive and unpredictable condition, and it is routinely recommended for all women with preeclampsia from 37 weeks gestation onward.[5] At gestations up to 34 weeks, if there are no immediate indications for delivery, expectant management is preferable because of the neonatal risks associated with early preterm birth.[5]

It is less clear whether a policy of expectant management in the late preterm period (34−37 weeks) should be pursued, although if severe features of preeclampsia develop or the woman reaches 37 weeks, delivery is indicated. However, there is uncertainty as to whether a policy of routine immediate delivery at this gestational window (34−37 weeks) could reduce maternal complications without serious neonatal consequences. Several studies have compared these 2 strategies in women with hypertensive disorders of pregnancy (including preeclampsia) from 34 weeks.[6−12] However, it has not been possible to draw firm conclusions from individual studies alone. Recent meta-analyses[13,14] and individual participant data (IPD) meta-analyses[15] of women with hypertensive disorders of pregnancy have shown that planned early delivery from 34 weeks gestation reduces maternal complications, but the neonatal impact remains unclear. These reviews generally grouped all hypertensive disorders of pregnancy together, combining women with chronic hypertension, gestational hypertension, and preeclampsia. However, the underlying pathophysiology of preeclampsia is distinct, with maternal endothelial dysfunction leading to multiorgan complications and potentially severe maternal and fetal outcomes. The optimal timing of delivery in preeclampsia may therefore differ compared with other hypertensive disorders of pregnancy, and the balance of risks and benefits for the infant should also be considered within the context of this rapidly progressive and unpredictable disease. A limited subgroup analysis conducted as part of the previous IPD meta-analysis[15] in women with all types of pregnancy hypertension identified women with preeclampsia as a population in whom planned delivery may confer significant benefit. The authors therefore highlighted a need to evaluate the impact of this intervention specifically in women with preeclampsia. Since this meta-analysis was published, a new trial has been reported,[6] enrolling more women with preeclampsia than all previously included trials combined. This enabled us to conduct an IPD meta-analysis evaluating the timing of delivery on a wider set of maternal and perinatal outcomes in this high-risk group of women with preeclampsia. A meta-analysis evaluating early delivery or expectant management for late preterm preeclampsia was recently published.[16] However, this study was limited by its inclusion of just 3 randomized controlled trials, only 2 of which were used to evaluate the coprimary outcome of neonatal intensive care unit admission. Our IPD meta-analysis is strengthened by its ability to harmonize data to overcome inconsistencies in outcome definitions between trials and to evaluate key outcomes such as neonatal morbidity, in more detail.

Objective

The objective of this study was to undertake an IPD meta-analysis focusing on women with preeclampsia alone. In women with preeclampsia from 34 weeks gestation onward, this study aimed to evaluate the effect of planned early delivery on maternal mortality or morbidity and perinatal mortality or morbidity compared with expectant management using IPD from randomized controlled trials. The use of IPD enabled us to target our review to women with late preterm preeclampsia and to perform subgroup analyses and adjustments that would not be possible with the use of aggregate data, for

example, using blood pressure values to reflect the severity of disease. This is clinically relevant, because the presence of additional risk factors in women with preeclampsia may alter management options.

Methods

Search strategy and study selection

We followed a protocol and statistical analysis plan published in the PROSPERO registry in accordance with PRISMA-IPD guidance.[17] We included studies that were randomized controlled trials comparing planned early delivery with expectant management in women presenting with preeclampsia from 34 weeks gestation onward. Cluster randomized trials or studies with a quasi-randomized design were excluded. To identify the eligible studies, we electronically searched the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, MEDLINE, and ClinicalTrials.gov using the search terms "pre-eclampsia" OR "preeclampsia" AND "delivery" OR "birth" with the limits "human" and "randomized controlled trial." The final search date was December 18, 2021. We did not restrict our search by language. We excluded trials published before the year 2000. This was because of changes in clinical practice, care of women with preeclampsia, and neonatal care over time such that the findings from earlier trials may be difficult to interpret. To ensure that the search was comprehensive, we also hand-searched the reference lists of the retrieved studies and any relevant reviews identified. Two independent review authors (A.B.G. and J.F.) assessed all the studies identified by the search strategy against the study-level inclusion criteria. Any disagreement was resolved through discussion or with a third review author (not required), if necessary.

Eligibility criteria

We included women with singleton or multifetal pregnancies presenting with preeclampsia or superimposed preeclampsia from 34 weeks gestation onward. The definition of preeclampsia or superimposed preeclampsia was that used by the study at the time. All the definitions used would now be encompassed by the current International Society for the Study of Hypertension in Pregnancy (ISSHP) 2018 diagnostic criteria.[18]

Data extraction

We sought participant-level data from the authors of all eligible trials. The available data were extracted from trial databases (provided via a data-sharing agreement) according to prespecified variables by 2 of the review authors (A.B.G. and P.S.). The data were recoded into a common format, and the definitions of key characteristics, diagnoses (eg, preeclampsia), and outcomes were harmonized. A final dataset was then produced and rechecked for accuracy and completeness.

Assessment of risk of bias

Two review authors (A.B.G. and J.F.) independently assessed the included trials for risk of bias using the Cochrane risk-of-bias tool.[19]

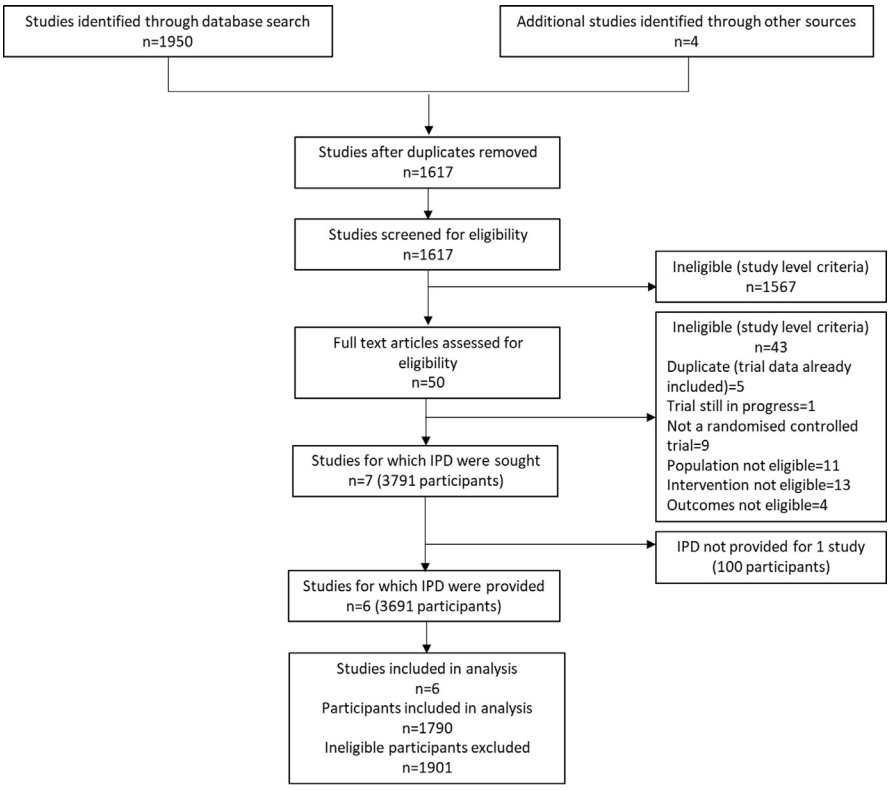
Outcomes

The primary maternal outcome was a composite of maternal mortality and severe maternal morbidity (adapted from a previously published composite derived by Delphi consensus).[20] The presence of severe maternal morbidity was defined as 1 or more of the following individual components: maternal death, eclampsia, stroke, pulmonary edema, HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, acute renal insufficiency, and placental abruption. The primary perinatal outcome was a composite of perinatal mortality or morbidity. This was defined as any 1 of perinatal death, neonatal death, or neonatal morbidity. The selection of components was guided by recent recommendations for core outcome sets in preeclampsia.[21] Neonatal morbidity was defined as 1 or more of respiratory disease (any one of respiratory distress syndrome, need for respiratory support, neonatal unit admission for respiratory disease or bronchopulmonary dysplasia), central nervous system complications (any 1 of intraventricular hemorrhage, intracerebral hemorrhage, periventricular leukomalacia, hypoxic ischemic encephalopathy, cerebral infarction, or convulsions), culture-proven sepsis, necrotizing enterocolitis, hypoglycemia requiring intravenous glucose or neonatal unit admission, or jaundice requiring neonatal unit admission. If data were missing (ie, not collected for a particular component) for either of the composite outcomes, we treated it as absent. The secondary maternal outcomes included severe postpartum hemorrhage, progression to severe hypertension, thromboembolic disease, hepatic dysfunction, onset of delivery, and admission to maternal intensive care unit. The secondary perinatal outcomes were gestational age at delivery, mode of delivery, birthweight, birthweight centile, baby sex, small for gestational age ($<$3rd centile or $<$10th centile), admission to neonatal unit, admission to neonatal intensive care unit, 5-minute Apgar score $<$7, and arterial pH $<$7.05.

Data synthesis

We analyzed all available data for baseline maternal characteristics at enrolment, related process outcomes (such as time from randomization to delivery) and the data for each prespecified outcome on an intention-to-treat basis. In each study, all the outcomes of interest were either reported completely with $<$5% missingness or not reported at all. Under these circumstances, multiple imputation is not feasible or recommended, and we therefore analyzed all the outcomes without imputation. For primary IPD meta-analyses, we used a 1-stage fixed-effect model. Standard errors, confidence intervals (CIs), and P values were adjusted for clustering within studies. In addition, we used robust standard errors to correct for clustering of twin pregnancies by the mother for the perinatal outcomes.[22] We set out to calculate the odds ratios using multilevel models as originally outlined in the statistical analysis plan. However, this multilevel model structure did not converge, as there were not sufficient datapoints at each of the levels. We therefore performed a multivariate

FIGURE 1
Flowchart summarizing search results



IPD, individual participant data.

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analysis, calculating risk ratios for binary outcomes and mean differences for continuous outcomes using a simpler fixed-effects model. We also calculated unadjusted risk differences. A fixed-effects, 1-stage analysis such as this is appropriate where there are small studies with rare event numbers. We gave a separate intercept for each trial but assumed the same treatment effect (ie, we used fixed effects for each trial).

The numbers needed to treat or harm with 95% CIs were calculated for outcomes where a significant difference between the management groups was found. The analysis was adjusted for study, gestational age at randomization (34^{+0}–34^{+6} weeks, 35^{+0}–35^{+6} weeks, 36^{+0}–36^{+6} weeks, 37^{+0}–37^{+6} weeks, 38^{+0}–38^{+6} weeks, 39^{+0}–39^{+6} weeks, 40^{+0} weeks and above), severity of systolic hypertension at study entry (<150 vs ≥ 150 mm Hg), parity (primiparous vs multiparous), and number of fetuses (singleton vs all other). The severity of systolic hypertension at study entry was chosen, because it is an objective marker of disease severity consistently available across studies, and there is a known dose–response relationship between increasing blood pressure and adverse pregnancy outcomes.[23–25] We calculated and used the average value (or proportion for categorical variables) across all studies, where these prespecified adjustment variables were missing. We did not use multiple imputation methods, as they are not recommended in this scenario. Subgroup analysis was conducted if there were at least 10 events in each subgroup; this was also done using a 1-stage, fixed-effects model. The prespecified subgroups were study, gestational age at randomization, parity, singleton vs multifetal pregnancy, previous cesarean delivery, prerandomization diabetes of any type, superimposed preeclampsia, and suspected fetal growth restriction at enrolment. Because many of the subgroups concerned the same adjustment variables used for our main analysis (including some additional subgroups of clinical relevance), our subgroup analysis was unadjusted to better delineate the effect of these variables. Heterogeneity was assessed using I^2 (the proportion of the total variance of the outcome that is between studies rather than between subjects within studies) as part of the subgroup analysis. We have also presented values for tau.[2] No additional analyses were undertaken. This IPD meta-analysis was prospectively registered with PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020206425).

Results

Study selection

We identified 1617 references after duplicates were removed (Figure 1). A total of 1567 references were excluded after title screening, and 43 were excluded after abstract and full-text screening. Seven trials (3791 participants) were considered eligible for inclusion at study-level. One trial (100 participants) was subsequently excluded, as the trial authors did not respond to our request for participant-level data despite several attempts.[26] The only published data available from this trial were a conference abstract, and therefore we were not able to include any aggregate data for this trial. Six trials[6–11] with participant-level data were available. Following data extraction and review by 2 authors, 1901 participants were deemed ineligible for inclusion in this IPD meta-analysis principally because of women being enrolled with conditions other than preeclampsia or before 34 weeks gestation, with the reasons given for exclusion in Table 1. The remaining 1790 participants from 6 trials were therefore included in our analysis.

Study characteristics

A summary of characteristics of included studies, including details of the interventions, can be found in Table 1 and Supplementary Tables S1 and S2. Two trials (GRIT and DIGITAT) enrolled

TABLE 1
Characteristics of included studies

Study	Setting	Total participants enrolled (n)	Trial participants (inclusion criteria)			Eligible for IPD (n)	Noneligible for IPD (n)
			Gestational age (wk)	Singleton or twin pregnancy	Diagnosis		
GRIT GRIT Study Group,[11] 2003	69 hospitals in 13 European countries	548 planned delivery n=296, expectant management=292	24^{+0} to 36^{+0}	Singleton or twin	Fetal compromise with an umbilical artery Doppler waveform recorded (including pregnancies complicated by preeclampsia)	15 planned delivery n=15, expectant management n=5	493 randomized before 34 wk; 40 no preeclampsia at study entry
HYPITAT Koopmans et al,[9] 2009	38 hospitals in The Netherlands	756 planned delivery n=377, expectant management=379	36^{+0} to 41^{+0}	Singleton	Gestational hypertension or preeclampsia without severe features[a]	246 planned delivery n=123, expectant management n=123	510 no preeclampsia at study entry
DIGITAT Boers et al,[10] 2010	52 hospitals in The Netherlands	650 planned delivery n=321, expectant management n=329	36^{+0} to 41^{+0}	Singleton	Suspected intrauterine growth restriction (including pregnancies complicated by preeclampsia)	45 planned delivery, n=18, expectant management n=27	605 no preeclampsia at study entry
Deliver or Deliberate Owens et al,[8] 2014	1 hospital in the United States	169 planned delivery n=97, expectant management n=86	34^{+0} to 36^{+6}	Singleton or twin	Preeclampsia (ACOG 2002 criteria) without any other maternal-fetal complications	165 planned delivery, n=93, expectant management n=72	4 randomized before 34 wk
HYPITAT II Broekhuijsen et al,[7] 2015	51 hospitals in The Netherlands	703 planned delivery n=352, expectant management, n=351	34^{+0} to 36^{+6}	Singleton or twin	Any hypertensive disorder of pregnancy without severe features[a]	420 planned delivery n=209, expectant management n=211	4 randomized before 34 wk; 283 no preeclampsia at study entry
PHOENIX Chappell et al,[6] 2019	46 hospitals in England and Wales	901 planned delivery n=450, expectant management n=451	34^{+0} to 36^{+6}	Singleton or twin	Preeclampsia (ISSHP 2014 criteria), not requiring immediate delivery	899 planned delivery, n=448, expectant management n=451	2 withdrew from trial

ACOG, American College of Obstetricians and Gynecologists; *IPD*, individual participant data; *ISSHP*, International Society for the Study of Hypertension in Pregnancy.

[a] Preeclampsia defined as a diastolic blood pressure of 90 mm Hg or higher measured on 2 occasions at least 6 hours apart, combined with proteinuria.

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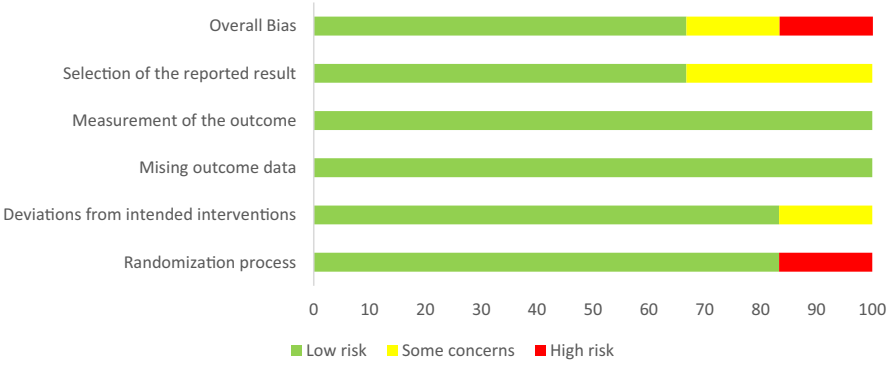
FIGURE 2
Risk of bias (using Cochrane RoB 2 tool) presented as percentage across all included studies



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women with suspected fetal growth restriction on ultrasound, including those with pregnancies complicated by preeclampsia, over a wide gestational age range. The HYPITAT and HYPITAT II trials enrolled women with any hypertensive disorder of pregnancy from 36^{+0} and 34^{+0} weeks gestation onward, respectively. The PHOENIX trial and Deliver or Deliberate trial focused specifically on women with preeclampsia (without severe features) between 34^{+0} and 36^{+6} weeks gestation. None of the trials enrolled women with severe features of preeclampsia or any other indications for immediate delivery. This was stated in each of their inclusion criteria (Table 1), with severe features defined in accordance with the relevant guidelines at the time (primarily American College of Obstetricians and Gynecologists or ISSHP criteria). These are consistent with current definitions.[27] For the purposes of this IPD meta-analysis, we selected only those participants who met our eligibility criteria as described in the section above.

Risk of bias of included studies

The results of our risk of bias assessment using the Cochrane Risk of Bias 2 tool can be found in Figures 2 and 3. The PHOENIX and HYPITAT trials were prospectively registered in a clinical trials registry (before enrolment of the first participants). The GRIT, DIGITAT, Deliver or Deliberate, and HYPITAT II trials were retrospectively registered. Four of the included trials were assessed as being at a low risk of bias. The HYPITAT II trial had some concerns because of minor discrepancies between the published protocol and final paper.

FIGURE 3
Risk of bias summary (using Cochrane RoB 2 tool) about each risk of bias domain for each included study

	Randomization process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
GRIT *GRIT Study Group* (2003)	+	+	+	+	+	+
HYPITAT I *Koopmans* (2009)	+	+	+	+	+	+
DIGITAT *Boers* (2010)	+	+	+	+	+	+
Deliver or Deliberate *Owens* (2014)	-	!	+	+	!	-
HYPITAT II *Broekhuijsen* (2015)	+	+	+	+	!	!
PHOENIX *Chappell* (2019)	+	+	+	+	+	+

Key
- High risk
- Some concerns
- Low risk

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The Deliver or Deliberate trial was judged to be at a high risk of bias. This was primarily because of limited reporting regarding the randomization process and an imbalance in the final analysis population suggesting postrandomization exclusions. Supplementary Tables S3 and S4 describe the missing data for each maternal and perinatal variable by study. Missing data were usually because of the outcome not being collected, with very few cases of missing data because of incomplete reporting or exclusion.

Synthesis of results

The baseline maternal characteristics at enrolment were similar across the planned delivery and expectant management groups (Table 2). Importantly, the proportion of women with suspected fetal growth restriction and severe hypertension at enrolment (Table 2) was balanced between the 2 management groups as expected with randomization. None of the trials enrolled women with severe features of preeclampsia. However, we acknowledge that some participants may have transiently had high blood pressure readings before enrolment. This alone would not be an indication for delivery.[18] The difference in median time between the 2 groups from randomization to delivery was 4.0 (95% CI, 3.0−4.0) days. One-stage meta-analysis found that planned delivery from 34 weeks gestation onward significantly reduced the risk of major maternal morbidity (2.6% vs 4.4%; adjusted risk ratio [aRR], 0.59; 95% CI, 0.36−0.98; P=.041) compared with expectant management (Table 3). This direction of effect was also consistent across the secondary maternal outcomes (Table 4), with a significant reduction in postrandomization severe hypertension (risk ratio [RR], 0.80; 95% CI, 0.73−0.87). The primary composite perinatal outcome of perinatal mortality (stillbirth or early neonatal death) or morbidity was increased by planned delivery (20.9% vs 17.1%; aRR, 1.22; 95% CI, 1.01−1.47; P=.040). This result was driven by a significant increase in neonatal respiratory disease (RR, 1.41; 95% CI, 1.05−1.90) (Table 5). Neonatal unit admission was also increased among infants born to mothers in the planned delivery arm (RR, 1.21; 95% CI, 1.08−1.36) (Table 6). However, infants in the planned delivery group were less likely to be born small for gestational age, both <3rd centile (RR, 0.74; 95% CI, 0.55−0.99) and <10th centile (RR, 0.82; 95% CI, 0.70−0.97). As expected, given the nature of the intervention, there was an adjusted mean difference of −0.61 weeks in the gestational age at delivery between infants in the planned delivery and expectant management groups and an adjusted mean difference of −127.28 g in birthweight between the 2 groups (Table 6). There was no significant difference in vaginal delivery between the planned delivery and expectant management groups. The observed difference in the primary perinatal outcome between the allocated groups was largely driven by a difference in respiratory distress syndrome, seen mainly in infants from trials conducted earlier in the time period (the HYPITAT II trial between 2009 and 2013 and the Deliver or Deliberate trial between 2002 and 2008). The individual components of the respiratory disease composite outcome by study are shown in Supplementary Table S5. Overall, there were small numbers of central nervous system complications (individual components of this composite outcome by study are shown in Supplementary Table S6), with babies from the earlier HYPITAT II and GRIT trials (conducted between 1993 and 2001) contributing to most of the cases. The subgroup analyses (Figures 4 and 5) were consistent with the main results. Higher degrees of heterogeneity were seen when analyzed by study and by twin or singleton pregnancy. Subgroup analysis was only undertaken if there were 10 or more events in each subgroup, which meant that the overall effect by study was different to that reported for the overall IPD meta-analysis because of the exclusion of certain trials from the subgroup analysis. A summary of findings and the numbers need to treat and harm are presented in supplementary tables S9 and S10.

Comment

Principal findings

In this IPD meta-analysis, we show that planned early delivery from 34 weeks gestation onward in women with preeclampsia significantly reduces adverse maternal outcomes and the number of infants born small for gestational age. This was balanced against an increase in the composite perinatal outcome driven by short-term neonatal respiratory

TABLE 2
Baseline maternal characteristics at enrolment

Characteristic	n	Planned delivery n = 901	n	Expectant management n = 889
Maternal age (y; mean [SD])	901	29.56 (6.32)	889	29.97 (6.12)
White European ethnicity	891	618 (69.4)	884	624 (70.6)
No previous births	891	564 (63.3)	884	555 (62.8)
Singleton pregnancy	901	866 (96.1)	889	843 (94.8)
Previous cesarean delivery	780	99 (12.7)	785	101 (12.9)
Prerandomization diabetes	780	94 (12.1)	785	88 (11.2)
Suspected fetal growth restriction	808	124 (15.3)	817	132 (16.2)
Systolic blood pressure≥160 mm Hg	810	227 (28.0)	818	221 (27.0)
Systolic blood pressure≥150 mm Hg	810	442 (54.6)	818	433 (52.9)
Diagnosis of superimposed preeclampsia	675	100 (14.8)	689	113 (16.4)

SD, standard deviation.

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TABLE 3
Primary maternal outcome

Outcome	Planned delivery n = 891	Expectant management n = 884	Effect size[a]
Primary composite maternal outcome n (%)	23 (2.6)	39 (4.4)	aRR,[b] 0.59; (0.36–0.98) *P* value=.041
			Unadjusted risk difference (%) −1.8% (−3.5 to −0.1)
Individual components			
Maternal death	0/891 (0.0)	1/884 (0.1)[c]	—
Eclampsia	3/891 (0.3)	6/884 (0.7)	RR, 0.50 (0.12–1.98)
Stroke	0/559 (0.0)	0/550 (0.0)	—
Pulmonary edema	1/798 (0.1)	4/812 (0.5)	RR, 0.25 (0.03–2.27)
HELLP syndrome	12/891 (1.3)	23/884 (2.6)	RR, 0.52 (0.26–1.03)
Renal insufficiency	4/768 (0.5)	6/761 (0.8)	RR, 0.66 (0.19–2.33)
Placental abruption	4/768 (0.5)	4/812 (0.5)	RR, 1.02 (0.26–4.05)

aRR, adjusted risk ratio; *HELLP*, hemolysis, elevated liver enzymes, low platelet count syndrome; *RR*, risk ratio.

[a] Effect sizes are RRs (95% CIs) unless stated otherwise; [b] aRR for study, gestational age at randomization, singleton pregnancy, parity, and severity of hypertension at study entry. Presented as unadjusted RR where the model failed to converge; [c] This death was considered unrelated to trial allocation by the original study authors.

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morbidity; there was no significant impact of gestational age on this primary outcome. These results indicate clinically important maternal benefits, and in particular, a reduction in severe hypertension and HELLP syndrome among women allocated to planned delivery. Importantly, the intervention did not increase the risk of cesarean delivery. Information on medical comorbidities was not consistently available across all studies. However, other than singleton or twin pregnancy subgroup analysis for the primary perinatal outcome, there was no significant test of interaction for any pre-enrolment characteristics such that we could not predefine a particular group of pregnant women in whom the impact of the intervention might be different. Most of the participants included in this analysis were classified as White European, which should be taken into account when considering the generalizability of these findings to other populations.

TABLE 4
Secondary maternal outcomes

Outcome	Planned delivery n = 891	Expectant management n = 884	Effect size[a]
Postrandomization severe hypertension	396/780 (50.8)	498/785 (63.4)	RR,[b] 0.80 (0.73– 0.87)
Hepatic dysfunction	72/891 (8.1)	96/884 (10.9)	aRR, 0.76 (0.57–1.01)
Thromboembolic disease	1/798 (0.1)	1/812 (0.1)	—
Severe postpartum hemorrhage	87/891 (9.8)	98/884 (11.1)	aRR, 0.88 (0.68–1.15)
Prelabor cesarean delivery	156/797 (19.6)	180/811 (22.2)	RR, 0.88 (0.73–1.07)
Intensive care unit admission	9/589 (1.5)	19/601 (3.2)	aRR, 0.48 (0.22–1.07)
Time from randomization to delivery (d), Median (IQR)	2.0 (1.0–3.0) n=890[c]	6.0 (3.0–10.0) n=883[c]	Difference (95% CI) 4.0 (3.0–4.0)

aRR, adjusted risk ratio; *CI*, confidence interval; *IQR*, interquartile range; *RR*, risk ratio.

[a] Effect sizes are RRs (95% CIs) unless stated otherwise; [b] aRR for study, gestational age at randomization, singleton pregnancy, parity, and severity of hypertension at study entry. Presented as unadjusted RR where model failed to converge; [c] One woman (from each group) excluded because of missing gestational age at delivery.

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The differences in the incidence of respiratory disease between the management groups was mainly seen among infants born to women from 2 trials, namely HYPITAT II[7] and Deliver or Deliberate,[8] conducted earlier in the time period considered for this meta-analysis. In HYPITAT II, only 8.6% of women randomized to planned delivery received antenatal corticosteroids. Steroid use was not reported in the Deliver or Deliberate trial, though planned delivery took place within 12 hours of randomization, leaving little time for optimal steroid administration. In comparison, 65% of the women in the PHOENIX trial[6] allocated to planned delivery received antenatal corticosteroids; this likely influences the much lower incidence of adverse respiratory outcomes among infants in this trial, with no difference between the 2 management groups. Although we acknowledge that our analysis was not specifically powered to address this question, it is likely that the difference in administration of steroids observed between different time epochs and trial settings explains our perinatal findings. This suggests that appropriately timed antenatal corticosteroid administration mitigates the short-term risk of respiratory complications for infants of women with preeclampsia, as previously demonstrated by a large systematic review.[28] Antenatal corticosteroids have also been shown to reduce infant

intraventricular hemorrhage,[28] which is a rare outcome in infants at this late preterm gestation, providing further potential benefit in ameliorating the risk of central nervous system complications at this gestational age. Although some authors have raised concerns over the association between maternal antenatal corticosteroid treatment and childhood behavioral disorders in term-born children (on the basis of a population-based study[29]), the most recent Cochrane systematic review of randomized controlled trials reported that antenatal corticosteroids probably lead to a reduction in developmental delay in childhood (RR, 0.51; 95% CI, 0.27−0.97).[28]

The rates of other serious neonatal complications such as sepsis and necrotizing enterocolitis were low, as expected in this population. The relatively high rates of neonatal admission across both groups highlights the additional care that this high-risk population of infants may require irrespective of the timing of delivery. In addition, infants born to mothers in the expectant management group were significantly more likely to be born small for gestational age. As low birthweight is a risk factor for long-term neurodevelopmental delay[30,31] and has been shown to be a more important predictor of long-term infant outcomes than gestational age at delivery,[32] avoidance of ongoing growth restriction may influence management choices. Use of ultrasound to accurately evaluate gestational age and presence of growth restriction should therefore be an integral part of assessment of a woman with preeclampsia. Although the average difference between the 2 groups was 4 days, the third quartile was 10 days. It remains difficult to identify the women (and infants) who are most likely to require delivery within the following 7 days using clinical risk factor or biomarker prognostication,[33] but for a progressive and unpredictable condition such as preeclampsia, this degree of pregnancy prolongation could be associated with a biologically plausible and clinical relevant difference in fetal growth restriction and neonatal outcomes. An increased awareness that expectant management increases the risk of a small for gestational age infant, most likely by perpetuating growth restriction within an adverse intrauterine environment, may lower the threshold for considering planned delivery from 34 weeks onward. These findings raise interesting questions regarding the influence of expectant management on fetal growth restriction and the impact that this may have on the infant, which should be addressed by future research.

TABLE 5
Primary perinatal outcome

Outcome	Planned delivery n = 936	Expectant management n = 935	Effect size[a]
Composite primary perinatal outcome	196 (20.9%)	160 (17.1%)	aRR,[b] 1.22 (1.01−1.47) *P*=.040
			Unadjusted risk difference (%) 3.83 (0.17−7.48)
Individual components	**Planned delivery**	**Expectant management**	**RR**
Stillbirth	0/936 (0.0)	0/935 (0.0)	—
Neonatal death	1/936 (0.1)	0/935 (0.0)	RR, 1.00 (1.00−1.00)
Respiratory disease	95/936 (10.1)	66/935 (7.1)	RR, 1.41 (1.05−1.90)
Central nervous system complications	11/936 (1.2)	4/935 (0.4)	RR, 2.65 (0.90−7.83)
Neonatal sepsis	3/489 (0.6)	2/502 (0.4)	RR, 1.54 (0.26−9.20)
Necrotizing enterocolitis	3/936 (0.3)	0/935 (0.0)	RR, 1.00 (1.00−1.00)
Hypoglycemia	86/692 (12.4)	86/708 (12.1)	RR, 1.03 (0.77−1.37)
Jaundice	19/612 (3.1)	13/625 (2.1)	RR, 1.56 (0.78−3.11)

aRR, adjusted risk ratio; *RR*, risk ratio.

[a] Effect sizes are RRs (95% CIs) unless stated otherwise; [b] aRR for study, gestational age at randomization, singleton pregnancy, parity, and severity of hypertension at study entry. Presented as unadjusted RR where model failed to converge.

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Comparison with existing literature

In the United States, current guidelines recommend planned early delivery in women with late preterm preeclampsia with severe features[34] but advise expectant management in women without severe features up to 37 weeks gestation. The guidelines acknowledge that this latter recommendation is based on limited and inconsistent evidence.[27-] Current United Kingdom[35] and international[18] guidelines provide similar recommendations but again note the uncertainty in clinical practice around thresholds for intervention and the limited evidence base. Many reviews, including a recent Cochrane review, have therefore called for evidence focusing on optimal timing of delivery in different types of pregnancy hypertensive disease. Our findings confirm clear maternal benefits associated with planned early delivery in women with preeclampsia from 34 weeks gestation onward and provide a greater understanding of the perinatal benefits and risks, including factors (such as antenatal steroid use) that mitigate these. Our analysis extends the current evidence base and quantifies the benefit−risk balance specific to women with preeclampsia in the late preterm period. The important lack of increased risk in operative delivery is in keeping with other recent clinical studies comparing induction of labor with expectant management[36−38]; women and clinicians may perceive similar rates of vaginal delivery in both groups as important to their decision-making. The perinatal results are consistent with interpretation by a systematic review evaluating planned early delivery for

TABLE 6
Secondary perinatal outcomes

Outcome	Planned delivery n=936	Expectant management n=935	Adjusted mean difference (CI)
Gestational age at delivery (wk; mean [SD])	36.2 (1.4) n=934	36.9 (1.5) n=934	−0.61 (−0.67 to −0.55)
Birthweight (g; mean [SD])	2561 (563.7) n=934	2681 (615.0) n=934	−127.28 (−171.0 to −83.5)
Birthweight centile (mean [SD])	41.0 (30.8) n=934	40.4 (33.2) n=933	−0.42 (−3.14 to 2.29)
			Effect size[a]
Small for gestational age (<10th centile)	198/934 (21.2)	241/933 (25.8)	RR,[b] 0.82 (0.70–0.97)
Small for gestational age (<3rd centile)	73/934 (7.8)	99/993 (10.6)	RR, 0.74 (0.55–0.99)
Neonatal unit admission	395/831 (47.5)	336/858 (39.2)	RR, 1.21 (1.08–1.36)
Neonatal intensive care unit admission	56/926 (6.0)	43/930 (4.6)	aRR, 1.20 (0.83–1.74)
5-min Apgar score<7	30/936 (3.2)	25/935 (2.7)	aRR, 1.20 (0.71–2.01)
Umbilical artery pH<7.05	17/926 (1.8)	19/930 (2.0)	aRR, 0.85 (0.45–1.61)
Vaginal delivery	377/713 (52.9)	349/702 (49.7)	RR, 1.06 (0.96–1.18)

aRR, adjuted risk ratio; *CI*, confidence interval; *RR*, risk ratio; *SD*, standard deviation.

[a] Effect sizes are RRs (95% CIs) unless stated otherwise; [b] aRR for study, gestational age at randomization, singleton pregnancy, parity, and severity of hypertension at study entry. Presented as unadjusted RR where the model failed to converge.

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suspected fetal compromise that highlighted an increased short-term risk of respiratory complications and neonatal unit admission.[39] However, the varying use of antenatal corticosteroids across the different trials included in our analysis should be considered when interpreting these results. Planned subgroup analysis showed that there was no difference in the primary perinatal outcome in the most recent trial,[6] where most of the women allocated to planned delivery received antenatal corticosteroids. Given that the universal administration of antenatal corticosteroids is not routinely recommended for women considered at risk of late preterm birth,[40] demonstrating benefit in certain clinical scenarios such as planned delivery for preeclampsia may guide clinical practice. Furthermore, we have demonstrated an increased risk of small for gestational age births associated with expectant management, a finding that is consistent with similar studies and is known to be associated with longer term impaired neurodevelopmental outcomes.[30,31] In addition, on the basis of the largest and most recent trial in this population,[6] clinicians and women should be aware that there is an average prolongation of pregnancy of around 3 days only with expectant management, with 74% progressing to severe preeclampsia (compared with 64% with planned delivery) and 55% requiring expedited delivery before 37 weeks gestation. The high proportion of women who were delivered early is in keeping with an expectant management strategy and highlights the rapidly progressive nature of preeclampsia often resulting in a constellation of maternal and fetal complications.

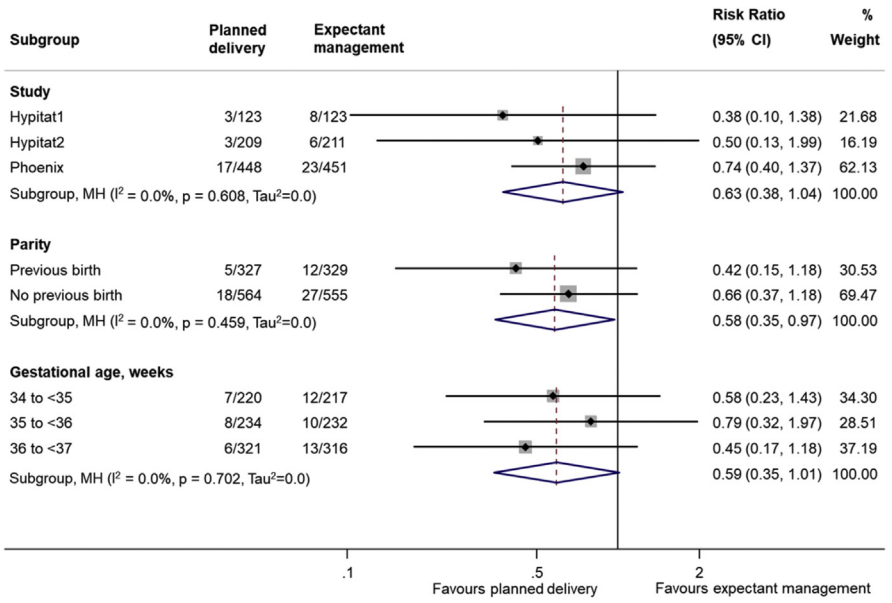
Data from this IPD meta-analysis (which included the trial discussed above) supported this finding with a difference in median time from randomization to delivery of only 4 days between the 2 management groups. This study therefore strengthens the current evidence supporting a policy of considering planned early delivery for maternal benefit in late preterm preeclampsia. Planned delivery has been shown to be cost-saving in the UK National Health Service setting compared with expectant management (£1478 per woman) when the total maternal and infant costs were considered, but the decision-making should reflect clinical and health economic factors together.

Strengths and limitations

Following guidance on the use of IPD meta-analysis,[41] we did not adopt an overly restrictive approach when selecting trials for inclusion, and this study is therefore strengthened by the inclusion of several large, well-conducted randomized clinical trials, most of which were assessed as being at a low risk of bias. For most outcomes, heterogeneity between studies was low, though some important differences have been highlighted above. Furthermore, the use of a 1-stage IPD meta-analysis approach allows the relative influence of multiple trial and participant characteristics on any intervention effect to be considered simultaneously.[41] We had full access to the trial data and were able to include all the eligible participants for most of the studies. We were able to include complete data for most of our outcomes of interest but were limited by differences in outcome reporting between trials such that data were not available for every variable. This low missingness for most of the variables and broad consistency between trials means that we have confidence in our results. The limitations include changes in clinical practice during the time period of the trials included such that external factors (such as uptake of antenatal corticosteroid use) may impact the main outcomes directly. Certain perinatal outcomes such as bronchopulmonary dysplasia, cerebral infarction, and intracerebral hemorrhage were not collected across a large proportion of included studies likely because of the rarity of these outcomes

and the availability of more objective measures. Ideally, all trials should include longer term follow-up of the women and infants, but retention within a study can be challenging and expensive to undertake. We were not able to report the indications for delivery, as this information was not consistently available across the included trials. However, given the randomized nature of the data, we would not expect significant differences between the 2 management groups at baseline. The PHOENIX trial reported indications for delivery for both the management groups. In the planned delivery group, 99% of women had allocation to planned delivery arm as their recorded indication for delivery, consistent with trial procedures. Women in the expectant management group were delivered more frequently for both maternal and fetal indications, with over 50% requiring expedited delivery, compared with the planned delivery group.

FIGURE 4
Primary maternal outcome: subgroup analysis (unadjusted)



Weights and between-subgroup heterogeneity test are from the MH model. Prespecified subgroup analysis only performed if there were ≥10 events in each subgroup, and subgroups without analysis therefore are shown in Supplementary table S7.

CI, confidence interval; *MH*, Mantel—Haenszel.

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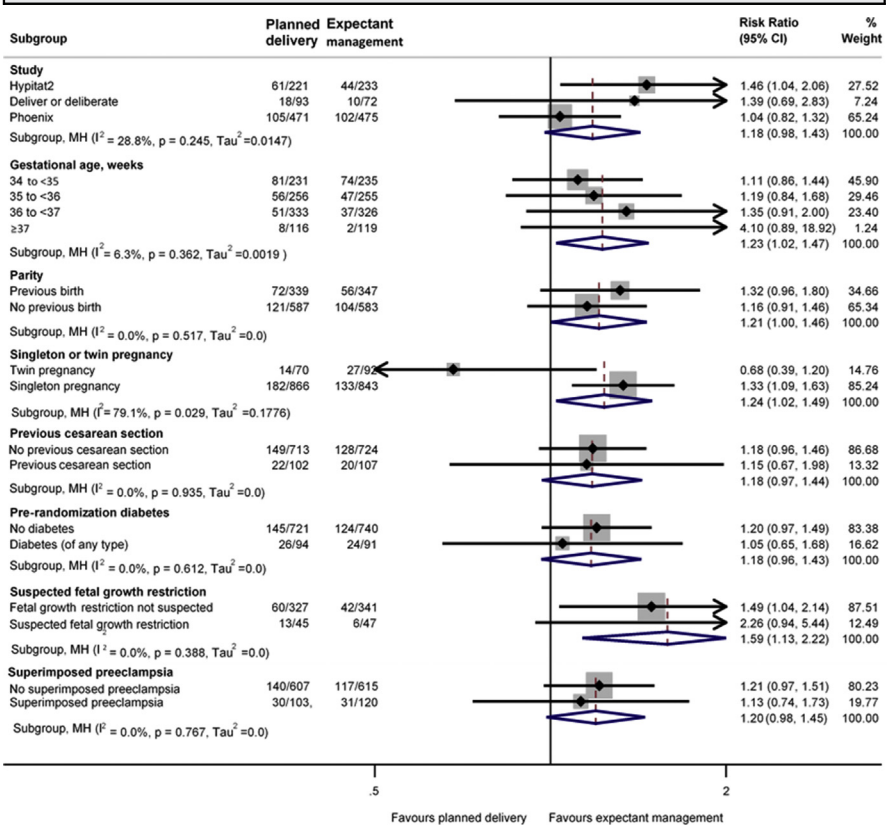
Clinical implications

Delivery is already known to improve maternal outcomes in preeclampsia. However, this review quantifies the effect, specific to gestation, on outcomes and addresses the balance between maternal and fetal effects. We also addressed the question specifically in women who have preeclampsia without severe features. By synthesizing and presenting the available data on this topic, we aim to provide as much information as possible on the balance of risks and benefits associated with each management strategy so that women and their caregivers can make fully informed decisions. For clinicians who already have a low threshold for planned delivery in women with late preterm preeclampsia, this meta-analysis provides new evidence that could support this approach. Other clinicians may consider that although maternal benefit of planned delivery is clear, there is a trade-off with short-term perinatal morbidity. However, this may be ameliorated by judicial use of antenatal corticosteroids.

Conclusions

This meta-analysis of IPD from 6 randomized controlled trials synthesizes the available evidence pertaining to timing of delivery in late preterm preeclampsia. We have clearly demonstrated that planned delivery in women with preeclampsia from 34 weeks onward provides maternal benefit with no increased risk of operative delivery compared with expectant management. Planned delivery reduces the likelihood of infants being born small for gestational age but increases short-term respiratory morbidity. The administration of antenatal corticosteroids was observed to reduce this risk such that perinatal morbidity was no different between the groups in the most recent trial; the potential benefits of antenatal corticosteroids should be discussed with women undergoing late preterm delivery. Further research is needed to identify the optimal methods of determining the women and infants who are at the greatest risk of adverse outcomes, enabling the stratification of surveillance and targeted intervention. A similar need for accurate prognostic strategies has been identified for planning delivery in pregnancies with suspected fetal compromise[39] and preterm prelabor rupture of membranes[42], as the challenges are common across these scenarios. Longer-term infant outcome data (including infants born with and without growth restriction) from large randomized controlled trials are also needed, as outcomes cannot be extrapolated from population-level databases comparing delivery at preterm gestations with term gestations in healthy pregnancies. There is also a need to establish the most clinically meaningful neonatal outcomes to measure when conducting preeclampsia trials, particularly those focused on timing of delivery. The impact of the intervention is likely to be very different in low-resource settings, where most of the maternal and perinatal disease

FIGURE 5
Primary perinatal outcome: subgroup analysis (unadjusted)



Weights and between-subgroup heterogeneity test are from the MH model. Prespecified subgroup analysis only performed if there were ≥10 events in each subgroup, and subgroups without analysis therefore are shown in Supplementary table S8.

CI, confidence interval; *MH*, Mantel—Haenszel.

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burden associated with preeclampsia lies.[43] Because antenatal stillbirth is much more common in these settings,[44,45] it is possible that early delivery in women with preeclampsia in low- and middle-income countries may reduce not just adverse maternal outcomes but fetal and perinatal deaths associated with severe maternal disease. However, this must also be balanced against the resource constraints in these environments. A multicenter randomized controlled trial evaluating this is currently underway[46] and may shed further light on this clinical dilemma in a different context. Our findings provide further information to guide women and clinicians in a high-income setting, who must consider the balance of benefits and risks associated with planned delivery for women and their infants with late preterm preeclampsia. In line with recent recommendations,[47] we recommend that clinicians discuss the trade-off with earlier delivery (better for maternal outcomes but with increased admissions to the neonatal unit) with women, fully supporting them to understand their options and consider both management strategies. ■

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SUPPLEMENTARY TABLE S1

Additional study characteristics

Study	Funding source	Conflict of interest	Study design	Enrolment dates	Intervention	Antenatal corticosteroid (ACS) use
GRIT *GRIT Study Group* (2003)	MRC, European Union Concerted Action, Princess Beatrix Foundation	Nil	Randomized controlled trial	November 1993-March 2001	Delivery initiated within 48h of randomization	Pre-randomization ACS given in 70% of immediate delivery group and 69% of expectant management group. Post-randomization ACS use not reported
HYPITAT *Koopmans* (2009)	ZonMw	Nil	Randomized controlled trial	October 2005-March 2008	Delivery initiated within 24h of randomization	Not reported
DIGITAT *Boers* (2010)	ZonMw	Nil	Randomized controlled trial	November 2004-November 2008	Delivery initiated within 48h of randomization	Not reported
Deliver or Deliberate *Owens* (2014)	Division of Maternal-Fetal Medicine in the Dept. of OBGYN at the University of Mississippi Medical Center	Nil	Randomized controlled trial	March 2002-June 2008	Delivery initiated within 12h of randomization	Not reported
HYPITAT II *Broekhuijsen* (2015)	ZonMw	Nil	Randomized controlled trial	March 1st 2009-Feb 21st 2013	Delivery initiated within 24h of randomization	Pre-randomization ACS given in 7.5% of immediate delivery group and 8% of expectant management group. Post-randomization ACS use 1% across both groups
PHOENIX *Chappell* (2019)	NIHR Health technology assessment programme	Nil	Randomized controlled trial	Sept 29th 2014-Dec 10th 2018	Delivery initiated within 48h of randomization	Post- randomization ACS given in 65% of immediate delivery group and 55% of expectant management group

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SUPPLEMENTARY TABLE S2

Additional study characteristics

Study	Short-term primary outcome	Short-term secondary outcomes
GRIT *GRIT Study Group* (2003)	Infant survival up to hospital discharge	Mode of delivery, surrogate outcomes for fetal morbidity: birthweight, sex, Apgar score <7 at 5 minutes, cord pH <7.0, ventilation >24hrs, necrotizing enterocolitis, neonatal convulsions, GMH/IVH, PVL/VM, stillbirth, neonatal death, death >28 days
HYPITAT *Koopmans* (2009)	Composite measure of poor maternal outcomes defined as: maternal mortality, maternal morbidity (eclampsia, HELLP syndrome, pulmonary oedema, thromboembolic disease, or placental abruption), progression to severe disease and major PPH up to maternal hospital discharge and 6 weeks after birth	Mode of delivery, neonatal mortality, and neonatal morbidity (composite outcome consisting of a 5 minute Apgar score <7, umbilical artery pH <7.05 or admission to a neonatal intensive care unit)
DIGITAT *Boers* (2010)	Composite measure of adverse neonatal outcome (defined as death before hospital discharge, 5 minute Apgar score <7, umbilical artery pH <7.05, or admission to the neonatal intensive care unit)	Operative delivery (vaginal instrumental delivery or caesarean section), length of stay in the NICU or neonatal ward, length of stay in the maternal hospital and maternal morbidity (PPH >1000ml, gestational hypertension or pre-eclampsia, pulmonary oedema, thromboembolism, or any other serious event)
Deliver or Deliberate *Owens* (2014)	Maternal mortality, maternal morbidity, and progression of PE with the appearance of severe features as defined by the American College of Obstetricians and Gynecologists (ACOG)	Onset of labor, progression to severe pre-eclampsia, postpartum complications (HELLP syndrome, eclampsia), total hospital length of stay (LOS) post delivery (days), total hospital LOS (days), birthweight, small for gestational age, arterial umbilical cord pH, NICU admission, asphyxia, respiratory distress syndrome, transient tachypnoea of the new-born, apnea, NICU LOS (days)
HYPITAT II *Broekhuijsen* (2015)	*Maternal: c*omposite of adverse maternal outcomes (thromboembolic disease, pulmonary oedema, eclampsia, HELLP syndrome, placental abruption, or maternal death) up to maternal final discharge from hospital and 6 weeks after birth. *Neonatal:* Respiratory distress syndrome (RDS), defined as need for supplementary oxygen for more than 24h combined with radiographic findings typical for RDS up to infant final discharge from hospital	Instrumental vaginal delivery, caesarean section, 5-minute Apgar score of less than 7, umbilical artery pH of less than 7.05, admission to a NICU, death before discharge, suspected or confirmed neonatal infection or sepsis, hypoglycemia necessitating intravenous glucose, transient tachypnoea of the new-born, meconium aspiration syndrome, pneumothorax or pneumomediastinum, necrotizing enterocolitis, IVH, PVL and convulsions
PHOENIX *Chappell* (2019)	*Maternal:* composite of maternal morbidity of fullPIERS[20] outcomes, with the addition of recorded systolic BP of at least 160mmHg post randomization, up to primary maternal hospital discharge *Perinatal:* composite of neonatal deaths within 7 days of delivery and perinatal deaths or neonatal unit admissions before infant primary hospital discharge	Individual components of the composite primary outcome, use of antihypertensive drugs, progression to severe pre-eclampsia (systolic BP of at least 160mmHg, platelet count <100, abnormal liver function enzymes - ALT or AST >70), time and mode of onset, confirmed thromboembolic disease, confirmed sepsis, primary and additional indications for delivery; and placental abruption. Stillbirth, NND within 7 days of delivery, NND before hospital discharge, admissions to NNU, number of nights in each category of care, total number of nights in hospital, BW, BW centile, BW less than 10th or 3rd centile, GA at delivery, Apgar score at 5 min after birth, umbilical arterial and venous pH at birth, need for supplementary oxygen before discharge, number of days required, need for respiratory support, other indications and main diagnoses resulting in NNU admission and health resource use outcomes

ALT, alanine aminotransferase; *AST*, aspartate transaminase; *BW*, birthweight; *GA*, gestational age; *GMH*, Germinal matrix hemorrhage; *HELLP syndrome*, Hemolysis, elevated liver enzymes, low platelet count syndrome; *IVH*, intraventricular hemorrhage; *NICU*, neonatal intensive care unit; *NND*, neonatal death; *NNU*, neonatal unit, *PPH*, post-partum hemorrhage; *PVL*, Periventricular leukomalacia; *VM*, ventriculomegaly.

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SUPPLEMENTARY TABLE S3

Missing maternal variables

	HYPITAT n=246	HYPITAT II n=420	DIGITAT n=45	Deliver or Deliberate n=165	GRIT n=15	PHOENIX n=899
Maternal death	0	0	0	0	15	0
Eclampsia	0	0	0	0	15	0
Stroke	246	420	0	0	15	0
Pulmonary oedema	0	0	0	165	15	0
HELLP syndrome	0	0	0	0	15	0
Renal insufficiency	246	0	0	0	15	0
Placental abruption	0	0	0	165	15	0
Post-randomization severe hypertension	0	0	45	165	15	0
Hepatic dysfunction	0	0	0	0	15	0
Thromboembolic disease	0	0	0	165	15	0
Severe postpartum hemorrhage	0	0	0	0	15	0
Pre-labor caesarean section	0	0	0	165	15	2[a]
Intensive care unit admission	0	420	0	165	15	0

HELLP syndrome, Hemolysis, elevated liver enzymes, low platelet count syndrome.

[a] Data missing/excluded. All other missing variables were not collected.

Beardmore-Gray. Timing of delivery in late preterm preeclampsia. Am J Obstet Gynecol 2022.

SUPPLEMENTARY TABLE S4

Missing perinatal variables

	HYPITAT n=246	HYPITAT II n=454	DIGITAT n=45	Deliver or Deliberate n=165	GRIT n=15	PHOENIX n=946
Stillbirth	0	0	0	0	0	0
Neonatal death	0	0	0	0	0	0
Respiratory distress syndrome	0	0	0	0	15	946
Need for respiratory support	0	454	0	0	0	0
Neonatal unit admission for respiratory disease	246	454	45	165	15	0
Bronchopulmonary dysplasia	246	454	45	0	15	946
Cerebral infarction	246	454	45	165	15	946
Hypoxic ischemic encephalopathy	246	0	45	165	15	0
Intra-cerebral hemorrhage	246	454	45	165	15	946
Intra-ventricular hemorrhage	0	0	0	0	0	0
Convulsions	0	0	0	165	0	0
Peri-ventricular leukomalacia	0	0	0	165	15	0
Neonatal sepsis	246	454	0	165	15	0
Necrotizing enterocolitis	0	0	0	0	0	0
Jaundice	0	454	0	165	15	0
Hypoglycemia	246	0	45	165	15	0
Gestational age at delivery	1[a]	0	0	0	0	2[a]
Mode of delivery	0	454	0	0	0	2[a]
Birthweight	0	1[a]	0	0	0	2[a]
Sex	0	0	0	0	0	2[a]
Neonatal unit admission	0	0	0	165	15	2[a]
Neonatal intensive care unit admission	0	0	0	0	15	0
5 -minute Apgar score less than 7	0	0	0	0	0	0
Arterial pH less than 7.05	0	0	0	0	15	0

[a] Data missing/excluded. All other missing variables were not collected.

Beardmore-Gray. Timing of delivery in late preterm preeclampsia. Am J Obstet Gynecol 2022.

SUPPLEMENTARY TABLE S5

Perinatal respiratory disease

	HYPITAT n=246		HYPITAT II n=454		DIGITAT n=45		Deliver or Deliberate n=165		GRIT n=15		PHOENIX n=946	
	PD[a] n=123	EM[a] n=123	PD n=221	EM n=223	PD n=18	EM n=27	PD n=93	EM n=72	PD n=10	EM n=5	PD n=471	EM n=475
Respiratory disease (composite)	**1**	**1**	**14**	**3**	**1**	**0**	**18**	**10**	**1**	**0**	**60**	**52**
Individual components:												
Respiratory distress syndrome	0	1	14	3	0	0	10	6	-	-	-	-
Need for respiratory support	1	0	-	-	1	0	12	6	1	0	40	41
Bronchopulmonary dysplasia	-	-	-	-	-	-	0	0	-	-	-	-
Neonatal unit admission for respiratory disease	-	-	-	-	-	-	-	-	-	-	47	39

[a] PD denotes planned delivery arm; EM denotes expectant management arm. Dash (-) indicates outcome not collected by study.

Beardmore-Gray. Timing of delivery in late preterm preeclampsia. Am J Obstet Gynecol 2022.

SUPPLEMENTARY TABLE S6

Perinatal central nervous system complications

	HYPITAT n=246		HYPITAT II n=454		DIGITAT n=45		Deliver or Deliberate n=165		GRIT n=15		PHOENIX n=946	
	PD[a] n=123	EM[a] n=123	PD n=221	EM n=223	PD n=18	EM n=27	PD n=93	EM n=72	PD n=10	EM n=5	PD n=471	EM n=475
Central nervous system complications (composite)	**0**	**1**	**6**	**3**	**0**	**0**	**0**	**0**	**3**	**0**	**2**	**0**
Individual components:												
Cerebral infarction	-	-	-	-	-	-	-	-	-	-	-	-
Hypoxic ischemic encephalopathy	-	-	0	0	-	-	-	-	-	-	0	0
Intracerebral hemorrhage	-	-	-	-	-	-	-	-	-	-	-	-
Intraventricular hemorrhage	0	0	2	0	0	0	0	0	3	0	2	0
Convulsions	0	1	2	1	0	0	-	-	0	0	0	0
Periventricular leukomalacia	0	0	4	2	0	0	-	-	-	-	0	0

[a] PD denotes planned delivery arm; EM denotes expectant management arm. Dash (-) indicates outcome not collected by study.

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SUPPLEMENTARY TABLE S7

Primary maternal outcome in excluded subgroups (descriptive only)

Subgroup	Planned delivery	Expectant management
Study		
DIGITAT	0/18	1/27
Deliver or deliberate	0/93	1/72
GRIT	No maternal data	No maternal data
Gestational age at randomization		
Gestational age $\geq$ 37 weeks	2/119	4/119
Singleton or twin pregnancy		
Twin pregnancy	1/35	1/46
Singleton pregnancy	22/856	38/838
Previous caesarean section		
No previous caesarean section	22/681	35/684
Previous caesarean section	1/99	2/101
Pre-randomization diabetes		
No diabetes	22/686	33/697
Diabetes (of any type)	1/94	4/88
Suspected fetal growth restriction		
Fetal growth restriction not suspected	20/683	37/685
Suspected fetal growth restriction	3/115	1/127
Superimposed pre-eclampsia		
No superimposed pre-eclampsia	18/575	29/576
Superimposed pre-eclampsia	2/100	1/113

Beardmore-Gray. Timing of delivery in late preterm preeclampsia. Am J Obstet Gynecol 2022.

SUPPLEMENTARY TABLE S8

Primary perinatal outcome in excluded subgroups (descriptive only)

Subgroup	Planned delivery	Expectant management
Study		
HYPITAT	5/123	2/123
DIGITAT	4/18	2/27
GRIT	3/10	0/5

Beardmore-Gray. Timing of delivery in late preterm preeclampsia. Am J Obstet Gynecol 2022.

SUPPLEMENTARY TABLE S9

Summary of findings

Planned delivery compared with expectant management for women with late preterm pre-eclampsia without severe features

Population: Pregnant women with a confirmed diagnosis of pre-eclampsia from 34 weeks' gestation onwards, not requiring immediate delivery

Setting: Multicenter trials across different high-income countries in Europe and U.S.A.

Intervention: Planned delivery within 48 hours of randomization

Comparison: Usual care — expectant management

Outcomes	Relative effect (95% CI)	Number of participants (studies)
Maternal[a]		
Eclampsia	RR 0.50 (0.12 to 1.98)	1,775 (5 studies)
HELLP syndrome	RR 0.52 (0.26 to 1.03)	1,775 (5 studies)
Renal insufficiency	RR 0.66 (0.19 to 2.33)	1,529 (4 studies)
Placental abruption	RR 1.02 (0.26 to 4.05)	1,610 (4 studies)
Perinatal[a]		
Respiratory disease	RR 1.41 (1.05 to 1.90)	1,871 (6 studies)
Hypoglycaemia	RR 1.03 (0.77 to 1.37)	1,400 (2 studies)
Jaundice	RR 1.56 (0.78 to 3.11)	1,237 (3 studies)

HELLP syndrome: Hemolysis, elevated liver enzymes, low platelet count syndrome.

[a] Outcomes selected as most prevalent

Beardmore-Gray. Timing of delivery in late preterm preeclampsia. Am J Obstet Gynecol 2022.

SUPPLEMENTARY TABLE S10

Numbers needed to treat and harm

Outcome	Number needed to treat/harm (95% CI)
Primary maternal	NNT 54.6 (28.3 to 816)
Primary perinatal	NNH 26.1 (13.5 to 363.5)

Beardmore-Gray. Timing of delivery in late preterm preeclampsia. Am J Obstet Gynecol 2022.

000 Planned delivery or expectant management in preeclampsia: an individual participant data meta-analysis

Alice Beardmore-Gray; Paul T. Seed; Jessica Fleminger; Eva Zwertbroek; Thomas Bernardes; Ben W. Mol; Cheryl Battersby; Corine Koopmans; Kim Broekhuijsen; Kim Boers; Michelle Y. Owens; Jim Thornton; Marcus Green; Andrew H. Shennan; Henk Groen; Lucy C. Chappell

Planned delivery from 34 weeks gestation onward in women with preeclampsia reduces adverse maternal outcomes with differing risks and benefits for the infant.

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RANDOMISED CONTROLLED TRIAL

Two-year follow-up of infant and maternal outcomes after planned early delivery or expectant management for late preterm pre-eclampsia (PHOENIX): A randomised controlled trial

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Funding information
National Institute for Health and Care Research (NIHR) Health Technology Assessment Programme.

Abstract

Objective: We evaluated the best time to initiate delivery in late preterm pre-eclampsia in order to optimise long-term infant and maternal outcomes.

Design: Parallel-group, non-masked, randomised controlled trial.

Setting: Forty-six maternity units in the UK.

Population: Women with pre-eclampsia between 34^{+0} and 36^{+6} weeks of gestation, without severe disease, were randomised to planned delivery or expectant management.

Main outcome measures: Infant neurodevelopmental outcome at 2 years of age, using the Parent Report of Children's Abilities – Revised (PARCA-R) composite score.

Results: Between 29 September 2014 and 10 December 2018, 901 women were enrolled in the trial, with 450 women allocated to planned delivery and 451 women allocated to expectant management. At the 2-year follow-up, the intention-to-treat analysis population included 276 women (290 infants) allocated to planned delivery and 251 women (256 infants) allocated to expectant management. The mean composite standardised PARCA-R scores were 89.5 (SD 18.2) in the planned delivery group and 91.9 (SD 18.4) in the expectant management group, with an adjusted mean difference of −2.4 points (95% CI −5.4 to 0.5 points).

Conclusions: In infants of women with late preterm pre-eclampsia, the average neurodevelopmental assessment at 2 years lies within the normal range, regardless of whether planned delivery or expectant management was pursued. With the lower than anticipated follow-up rate there was limited power to demonstrate that these scores did not differ, but the small between-group difference in PARCA-R scores is unlikely to be clinically important.

Alice Beardmore-Gray and Melanie Greenland contributed equally to this study.

Clinical Trial Information: Trial Registration Number: ISRCTN01879376 (ISRCTN registry, 25 November 20).

KEYWORDS
delivery, infant, neurodevelopment, pre-eclampsia, preterm

1 | INTRODUCTION

Pre-eclampsia complicates between 2% and 3% of pregnancies in high-income settings,[1] and is a leading cause of iatrogenic preterm birth.[2] It is a multisystem disorder characterised by placental and maternal vascular dysfunction and is associated with severe complications for both mother and infant.[3] Potential adverse consequences include maternal and perinatal death, maternal stroke, renal and hepatic injury and fetal growth restriction. Current management of pre-eclampsia in most high-income settings involves the close monitoring of maternal and fetal condition, with delivery recommended at 37 weeks of gestation, or sooner, if there is evidence of severe maternal or fetal compromise.[4,5] At 37 weeks of gestation, previous trials have shown that the initiation of delivery benefits the woman without any additional perinatal risk.[6]

In women with pre-eclampsia between 34^{+0} and 36^{+6} weeks of gestation, without severe features of the disease necessitating delivery, there is less evidence to guide the optimal timing of birth.[6] At this gestation, any maternal or perinatal benefit offered by early delivery must be balanced against the potential short- and long-term impacts of late prematurity to the infant. The PHOENIX trial showed that a policy of routine planned early delivery between 34^{+0} and 36^{+6} weeks of gestation significantly reduces short-term adverse maternal outcomes.[7] This was accompanied by an increase in neonatal unit admissions, but the indicators of short-term neonatal morbidity were similar between groups. Before making firm recommendations to guide clinical practice based upon these findings, it is important to fully evaluate the impact of planned delivery in this group on longer-term infant outcomes. Planned delivery may improve neurodevelopmental outcomes, as the disease process itself will be stopped, thereby limiting the continuing placental dysfunction associated with fetal growth restriction and other morbidities. However, the consequences of the intervention (planned delivery resulting in an earlier gestational age by 3–5 days, compared with expectant management) could also adversely impact neurodevelopmental outcomes. Thus, there remains a clinical dilemma about the best time to plan delivery, in order to optimise short- and long-term infant outcomes.

The aim of this follow-up study was to evaluate the primary infant outcomes of the PHOENIX trial at 2 years, comparing neurodevelopmental outcomes for infants of women with late preterm pre-eclampsia randomised to planned early delivery or to expectant management. Additionally, we evaluated the impact of the intervention on secondary maternal outcomes (health-related quality of life) and will report on the health economic evaluation separately.

2 | METHODS

2.1 | Study design and participants

The PHOENIX trial was a parallel-group, non-masked, multicentre randomised controlled trial across 46 maternity units in the UK. The published trial protocol and short-term co-primary outcomes described the trial methodology in detail,[7,8] and therefore a brief summary is provided here. There were no substantial changes to the published study design, methods or outcomes after the start of the trial. The trial was approved by the South Central – Hampshire B Research Ethics Committee (no. 13/SC/0645). We compared planned delivery with expectant management (usual care) in pregnant women presenting with pre-eclampsia between 34^{+0} and 36^{+6} weeks of gestation, without severe features of the disease (which would necessitate immediate delivery), aged 18 years or older, with a singleton or dichorionic diamniotic twin pregnancy and at least one viable fetus. Women with any other comorbidity or with a previous caesarean section or with any fetal position were eligible. The only exclusion criterion to participation was the clinician's decision to initiate delivery within the subsequent 48 h. After providing written informed consent, women were randomly assigned to planned delivery or expectant management via a secure web-based randomisation program provided by MedSciNet. A (non-deterministic) minimisation algorithm, including study centre, singleton or twin pregnancy, severity of hypertension in the 48 h before enrolment, parity, previous caesarean section and gestational age at randomisation, was used to ensure balance between the groups. The intervention could not be hidden from women, clinicians or data collectors because of the nature of the intervention.

2.2 | Interventions

Planned early delivery consisted of the initiation of delivery within 48 h of randomisation, to allow for the administration of antenatal corticosteroids if deemed necessary by clinicians. Induction of labour was commenced according to local protocol, with caesarean section undertaken only if an additional obstetric indication was present. Expectant management consisted of usual care, with close monitoring of the maternal and fetal condition, until either 37 completed weeks of pregnancy or the development of severe features necessitating delivery.

2.3 | Data collection

Baseline and short-term clinical outcome data were collected up until maternal and infant discharge from hospital

and recorded on the web-based trial database. Long-term outcomes were assessed at 6 months post-delivery and again when the infant was 2 years of age. Questionnaires were posted to all woman at these time points (or a link was sent electronically) and participants completed a paper copy or an online version captured by the MedSciNet study database. Health resource use and quality-of-life outcomes, including the EQ-5D-5L questionnaire, were also collected and are reported separately.

2.4 | Outcomes

2.4.1 | Infant outcomes

The primary long-term infant outcome was neurodevelopmental assessment at 2 years of age, using the Parent Report of Children's Abilities – Revised (PARCA-R) composite score.[9] Secondary long-term infant outcomes were the non-verbal and language PARCA-R subscale scores. The PARCA-R is a questionnaire completed by a parent (or caregiver), taking 15 min to complete, that assesses non-verbal and language development. It is recommended by the National Institute of Health and Clinical Excellence (NICE) as a practical and cost-effective method of identifying cognitive and language delay at 24 months in children born preterm.[10] Raw scores from the non-verbal subscale (range 0–34) and language subscale (0–124) are summed to produce an overall composite score. Non-verbal PARCA-R scores were prorated if up to four subscale questions were missing. During the trial the methodology to convert the overall composite score to an age- and sex-adjusted standard score and percentile ranking, relative to the norm, was published,[11] requiring the questionnaire to have been completed at 2 years corrected age (between 23 months and 16 days and 27 months and 15 days). A standardised score of between 85 and 114 would indicate development in the normal range, with scores between 70 and 84 indicating mild delay, scores between 55 and 69 indicating moderate delay and scores of 54 or less indicating severe delay.

2.4.2 | Maternal outcomes

Secondary long-term maternal outcomes included quality of maternal physical and mental health scored using the validated SF-12v2 Health Survey, a short-form generic measure of health status with eight health-related domains.[12] Scores from each of the eight health concepts can be used to generate a physical component summary scale score (PCS-12) and a mental component summary scale score (MCS-12), both with a mean of 50 and a standard deviation of 10, and with a higher score indicating better health. It has been validated in diverse populations, including women who are postpartum.[13–16]

For participants who completed the long-term follow-up, we have additionally reported the co-primary short-term outcome (a composite of maternal morbidity using fullPIERS outcomes and recorded systolic blood pressure of at least 160 mmHg post-randomisation) and the co-primary short-term perinatal outcome (a composite of neonatal deaths within 7 days of delivery and perinatal deaths or neonatal unit admissions).[17] Outcomes were selected before the development of a core outcome set for pre-eclampsia, which does not currently include any long-term outcomes.[18]

2.5 | Sample size

An initial loss to follow-up rate of 20% assumed that long-term outcomes would be available for approximately 690 infants.[8] This calculation was revised before follow-up was completed and analysis was undertaken, to take into account the higher than expected loss to follow-up rate of 40%. Based on this, it was anticipated that long-term outcomes would be available for approximately 568 infants in total (284 per group, assuming no difference in loss to follow-up between groups). With a one-sided significance level of 2.5%, under a non-inferiority hypothesis, a sample size of 284 in each group achieves 88% power to detect a non-inferiority margin of difference in the mean PARCA-R score of no fewer than four points (one-quarter of a standard deviation). A higher response rate would have enabled narrower confidence intervals and more certainty in our conclusions.

2.6 | Statistical analysis

Demographics and clinical characteristics at baseline and short-term infant and maternal outcomes are reported using descriptive statistics. The primary inferences for the 2-year infant outcomes were based on a non-inferiority hypothesis testing framework in both the intention-to-treat (ITT) and the per-protocol (PP) analysis populations. The primary inferences for the 6-month and 2-year maternal outcomes were based on a superiority hypothesis testing framework in the intention-to-treat analysis population. All analyses used the expectant management group as the reference group. There were no interim analyses planned.

2.6.1 | Infant outcomes

With the statistical analysis plan based on standardised scores, but with infant questionnaires being sent out at a chronological age of 2 years, a lower proportion than anticipated of PARCA-R questionnaires were completed during the time window allocated for standardising (at <23.5 and >27.5 months of age, corrected for prematurity). To correct for this, multiple imputation by chained equations was used to impute the PARCA-R standardised scores for those infants (approximately 74% of responders). Imputation models included the raw PARCA-R

scores, age-corrected for prematurity, sex, minimisation factors and any auxiliary variables associated with the outcome or the missingness of the outcome. Imputation models were developed separately for each outcome and each population. Pooled estimates were obtained from linear regression models, adjusted for minimisation factors as fixed effects and the correlation between multifetal pregnancies. Centre was not fitted as a random effect as planned, because of model non-convergence. Pooled adjusted means, adjusted mean differences and 95% confidence intervals are reported. The *p*-values for the composite score alone are reported, and are for one-sided 2.5% significance non-inferiority tests based on a margin of four standardised score points.

2.6.2 | Maternal outcomes

Mixed-effect linear regression models adjusted for minimisation factors were fitted for the maternal outcomes (PCS-12 and MCS-12), with centre fitted as a random effect. The adjusted mean values, the adjusted mean differences, the 95% confidence intervals and the corresponding *p*-values are reported. The means and standard deviations for subdomains are unadjusted.

2.6.3 | Subgroup analyses

Pre-specified subgroup analyses for the 2-year infant outcomes were performed on the multiply imputed data sets for the composite PARCA-R score. Pooled estimates were obtained from the same linear regression models used for the primary analysis, containing an interaction term between the subgroup and the study arm. Pooled adjusted means and 95% confidence intervals are reported.

2.6.4 | Sensitivity analyses

Sensitivity analyses were performed on the 2-year infant outcome, excluding infants outside of the time window for standardisation. Mixed-effect linear regression models were fitted, adjusting for correlation between twins, minimisation factors as fixed effects and centre as a random effect. The adjusted mean values, the adjusted mean differences and the 95% confidence intervals are reported.

2.7 | Role of the funding source

The study was funded by the UK's National Institute for Health and Care Research (NIHR) Health Technology Assessment Programme (12/25/03) following external peer review, and with involvement of public representative panel members. The funder of the study had no role in the study design, data collection, analysis, 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. The trial was prospectively registered with the ISRCTN registry (ISRCTN01879376).

2.8 | Patient and public involvement

We worked with representatives (including those with lived experience of pre-eclampsia) from Action on Pre-eclampsia (the patient support group) and Tommy's (a national baby charity) to ensure that the voices of pregnant women (and their wider families) informed and influenced every stage of the research process. Full details on the methodology and outcomes of this are reported in Table S8 (GRIPP2-SF checklist) of the supporting information.

3 | RESULTS

Between 29 September 2014 and 10 December 2018, 901 women were enrolled in the trial, with 450 women allocated to planned delivery and 451 women allocated to expectant management (Figure 1). The ITT analysis population for short-term maternal and perinatal outcomes included 448 women (471 infants) allocated to planned delivery (as two of the allocated women withdrew consent) and 451 women (475 infants) allocated to expectant management. Follow-up for the 2-year assessment continued until 31 December 2020. At the 2-year follow-up, the long-term ITT analysis population included 290 infants (62%) and 276 women allocated to planned delivery and 256 infants (54%) and 251 women allocated to expectant management. There were no serious adverse events reported at long-term follow-up.

3.1 | Characteristics of women responding to follow-up

Baseline maternal and pregnancy characteristics of women responding at 2 years were broadly similar across the two randomised groups (Table 1). The median gestational age at randomisation in both groups was 36 weeks, and the prevalence of suspected growth restriction was similar (19.8% in the planned delivery group and 23.1% in the expectant management group). The study centre at randomisation of the women responding at 2 years is shown in Table S1.

In women who completed the 2-year assessment, a higher proportion of infants in the planned delivery group had been delivered at 34 weeks of gestation (17.2% vs. 11.7%), as expected with the trial intervention (Table S2), and had been admitted to the neonatal unit (40.3% vs. 35.5%), driven by admissions where the primary indication was listed as prematurity. However, a higher proportion of infants in the expectant management group were born

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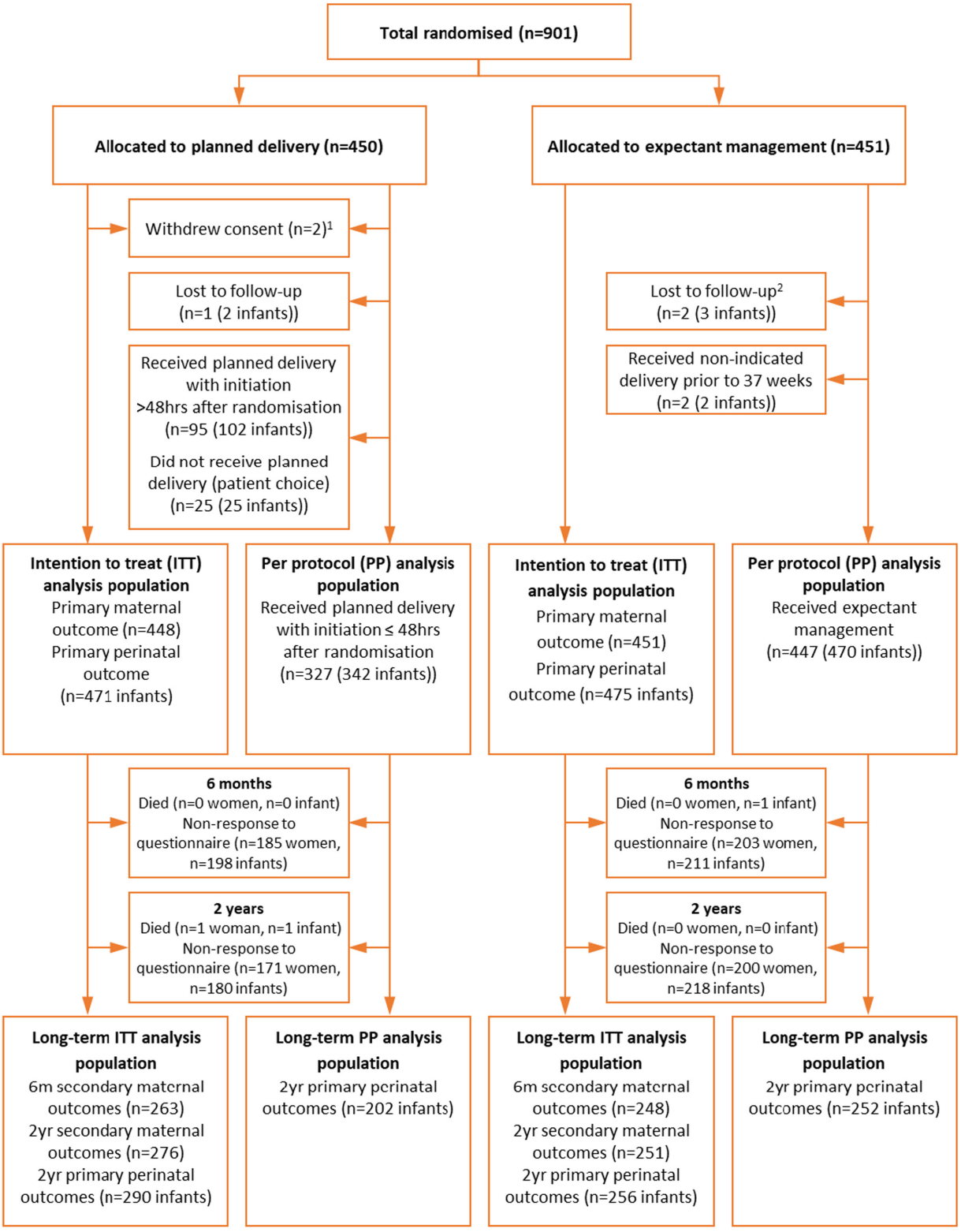

Notes:
1. These women withdrew from the trial and withdrew consent for data already collected to be used so are excluded from all analyses. One of these woman withdrew before initiation of delivery, the other withdrew after receiving planned delivery within 48 hours.
2. 1 woman in this group has documented delivery prior to 37 weeks (on electronic health records) but no further information available

FIGURE 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram of participants

small-for-gestational age (21.5% vs. 14.1% <10th centile; 5.1% vs. 2.8% <3rd centile), compared with those in the planned delivery group. Maternal mortality and morbidity were lower for responding women allocated to planned delivery, compared with those allocated to expectant management (65.2% vs. 75.5%) (Table S3).

TABLE 1 Maternal demographic and pregnancy characteristics

Baseline characteristics	Planned delivery (n = 276)	Expectant management (n = 251)
Age at randomisation (years), mean (SD)	31.1 (5.7)	31.4 (6.1)
Ethnicity, n (%)		
White	200 (72.5)	189 (75.3)
Black	23 (8.3)	21 (8.4)
Asian	42 (15.2)	22 (8.8)
Other	11 (4.0)	19 (7.6)
Deprivation index quintile 5 (most deprived), n (%)[a]	79 (30.6)	75 (31.0)
No previous pregnancies ≥24 weeks of gestation), n (%)[b]	166 (60.1)	159 (63.3)
Previous caesarean section, n (%)[b]	40 (14.5)	43 (17.1)
History of pre-eclampsia, n (%)	50 (18.1)	47 (18.7)
Body mass index at booking (kg/m^2), mean (SD)	30 (7.6)	29.2 (6.7)
Smoking at booking, n (%)	16 (5.8)	16 (6.4)
Systolic BP at booking (mmHg), mean (SD)	119.0 (13.6)	119.5 (13.2)
Diastolic BP at booking (mmHg), mean (SD)	72.8 (10.0)	73.3 (10.21)
Pre-existing chronic hypersion, n (%)	29 (10.5)	33 (13.1)
Pre-existing chronic renal disease, n (%)	3 (1.1)	2 (0.8)
Pre-pregnancy diabetes, n (%)	15 (5.4)	14 (5.6)
Gestational diabetes, n (%)	36 (13.0)	21 (8.4)
Aspirin prescribed during pregnancy, n (%)	114 (41.3)	101 (40.2)
LMWH prescribed during pregnancy, n (%)	69 (25.0)	66 (26.3)
Characteristics at randomisation		
Gestational age at randomisation (weeks), median (IQR)[b]	36 (35–36)	36 (35–36)
Singleton pregnancy, n (%)[b]	261 (94.6)	238 (94.8)
Highest systolic BP in previous 48 h (mmHg), mean (SD)	155 (14.8)	155.6 (16.1)
Highest diastolic BP in previous 48 h (mmHg), mean (SD)	95.8 (9.5)	95.8 (11.3)
Highest systolic BP in previous 48 h (mmHg), n (%)[b]		
≤149	100 (36.2)	88 (35.1)
150–159	69 (25.0)	65 (25.9)
≥160	107 (38.8)	98 (39.0)
Urinary protein/creatinine ratio ≥30 (mg/mmol), n (%)	253 (91.7)	228 (90.8)
Urinary protein/creatinine ratio (mg/mmol), median (IQR)	88 (43–185)	87 (43–197)
Fetal growth restriction ultrasound in previous 2 weeks, n (%)	222 (80.4)	212 (84.5)
Suspected fetal growth restriction on ultrasound, n (%)	44 (19.8)	49 (23.1)
Inpatient at time of randomisation, n (%)	217 (78.6)	210 (83.7)

Abbreviations: BP, blood pressure; LMWH, low molecular weight heparin.

[a]Deprivation quintiles calculated for participants in England only (not available for participants in Wales).

[b]Minimisation factors used to ensure balance at randomisation.

3.2 | Primary infant outcomes

Of the 546 infant questionnaires returned, and using imputed standardised scores for those who had a raw PARCA-R score outside of the age window for standardisation, the adjusted mean difference comparing planned delivery with expectant management for the composite PARCA-R score at 2-years follow-up was −2.4 (89.5 vs. 91.9, 95% CI −5.4 to 0.5, non-inferiority p = 0.1) in the ITT population (Figure 2). The confidence interval encompassed the four-point margin and so we could not conclude non-inferiority. Similar results were seen in the PP population: −1.9 (90.2 vs. 92.1, 95% CI −5.2 to 1.4, non-inferiority p = 0.1) (Figure 2). The adjusted means for both groups and populations were within the range of 85–114 (indicating normal neurodevelopment), as were the adjusted means for the subscale scores (Figure 2).

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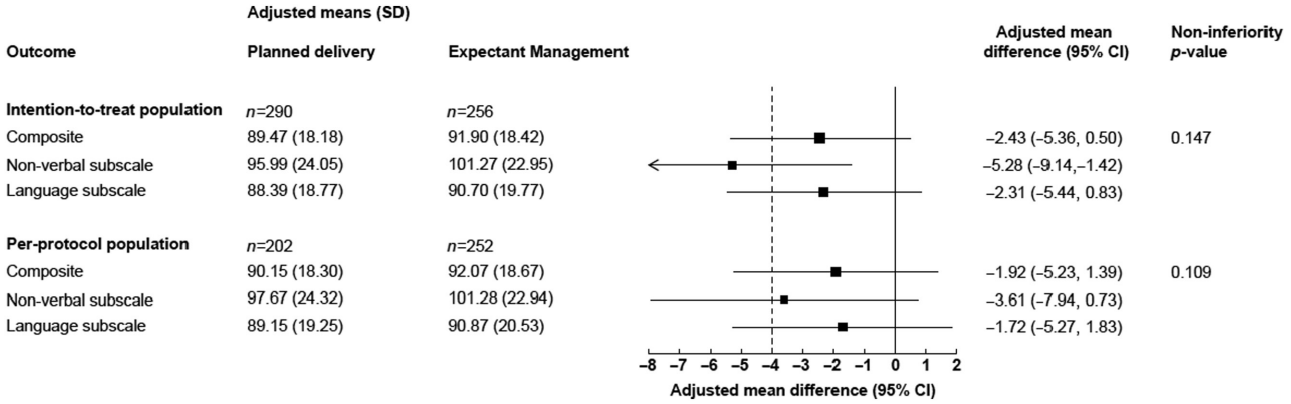

FIGURE 2 Primary infant long-term outcome non-inferiority comparison: imputed standardised Parent Report of Children's Abilities – Revised (PARCA-R) at 2 years follow-up. Standardised scores were imputed for responders who had raw PARCA-R scores outside of the time window used for standardisation. The *p*-values are for one-sided 2.5% significance non-inferiority tests based on a margin of four standardised score points. The dashed line shows the non-inferiority margin. The solid line shows the line of no difference. CI, confidence interval; SD, standard deviation

3.3 | Maternal outcomes

For maternal outcomes, there were no significant differences in physical component summary scale score (PCS-12) and mental component summary scale score (MCS-12) between women allocated to planned delivery and expectant management arms at 2 years (PCS-12 mean difference 0.29, 95% CI −1.29 to 1.87; MCS-12 mean difference 1.27, 95% CI −0.86 to 3.40) (Figure 3). Similar summary scores and subdomain scores were seen at 6 months and 2 years, indicating no evidence of a change of health status during follow-up.

3.4 | Sensitivity analyses (infant outcomes)

Sensitivity analyses including only infants assessed within a corrected age range of 23.5–27.5 months did not alter the findings (Tables S4 and S5).

3.5 | Subgroup analyses (infant outcomes)

Pre-specified analyses for the PARCA-R composite score did not suggest important clinical differences by subgroups for both ITT and PP populations (Figure S1).

3.6 | Women responding to follow-up

The baseline characteristics of responders and non-responders at the 2-year assessment are described in Tables S6 and S7. Maternal responders at the 2-year follow-up were more likely to be white, have a low deprivation index score and were less likely to currently smoke at the time of initial antenatal visit, compared with those who did not respond. Short-term infant outcomes between responders and non-responders at the 2-year follow-up were similar with regards to neonatal unit admission, birth of a small-for-gestational age (<10th centile) infant and short-term morbidity (Table S2).

4 | DISCUSSION

4.1 | Main findings

The mean standardised PARCA-R scores at 2 years for infants of mothers with late preterm pre-eclampsia randomised to planned early delivery or expectant management indicate that, on average, their neurodevelopment is within the normal range for both trial groups.[9] This provides reassuring data on the long-term outcomes of infants born late preterm, even when the additional complication of pre-eclampsia is present. Subgroup analysis by gestational age at randomisation showed that mean standardised scores remained within the normal range, even at earlier gestations (34^{+0}–34^{+6} weeks of gestation), where the severity of disease may also be worse. The confidence intervals for the adjusted mean difference of −2.4 points in the planned delivery arm compared with the expectant management arm were above the pre-specified threshold to be able to definitively confirm the non-inferiority of planned delivery. However, a mean difference of two points is unlikely to be clinically important at 2 years of age. No evidence of a difference was found in quality of maternal mental or physical health at 6 months and at 2 years between the two groups. Mean SF12-v2 scores were consistent with those previously reported in similar populations.[15,16]

4.2 | Strengths and limitations

This is the largest trial to date evaluating planned early delivery in late preterm pre-eclampsia and provides important information for clinicians and women faced with this clinical scenario. Long-term follow-up was identified as an important component of the research question and every possible strategy was employed to maximise the number of respondents. Similar trials attempting long-term follow-up of women and their infants report response rates varying from 14% to 61%,[19–21] demonstrating the challenge associated with this objective, particularly when the population of

	Planned delivery		Expectant management		Adjusted mean difference (95% CI)	*p*-value
	n	Mean (SD)	*n*	Mean (SD)		
Six months	*n*=263		*n*=248			
PCS-12	246	51.4 (9.9)	236	51.1 (9.8)	0.31 (–1.17, 1.79)	0.682
Physical functioning	256	87.8 (23.3)	241	87.8 (24.2)		
Role-Physical	256	87.9 (22.0)	244	86.5 (21.6)		
Bodily Pain	259	87.1 (21.8)	245	88.0 (19.3)		
General Health	262	65.0 (21.5)	244	66.1 (21.8)		
MCS-12	246	48.0 (11.9)	236	46.8 (11.9)	1.19 (–0.89, 3.27)	0.263
Energy/fatigue	261	56.5 (23.5)	244	57.2 (24.8)		
Social Functioning	261	83.4 (24.4)	242	79.3 (25.1)		
Role-Emotional	255	84.9 (23.5)	244	83.8 (23.9)		
Mental Health	258	70.4 (20.1)	243	69.2 (21.4)		
Two years	*n*=276		*n*=251			
PCS-12	264	50.9 (10.6)	240	50.6 (10.6)	0.29 (–1.29, 1.87)	0.717
Physical functioning	266	86.5 (22.8)	243	85.7 (25.1)		
Role-Physical	268	84.4 (23.4)	244	84.5 (22.8)		
Bodily Pain	271	85.3 (23.2)	246	86.0 (23.3)		
General Health	271	63.3 (23.0)	246	62.2 (24.4)		
MCS-12	264	46.1 (13.0)	240	44.9 (13.0)	1.27 (–0.86, 3.40)	0.242
Energy/fatigue	271	55.4 (25.0)	243	53.2 (26.0)		
Social Functioning	271	80.6 (25.1)	245	78.7 (28.2)		
Role-Emotional	269	82.5 (23.2)	245	80.5 (25.1)		
Mental Health	269	66.4 (21.0)	243	64.3 (22.2)		

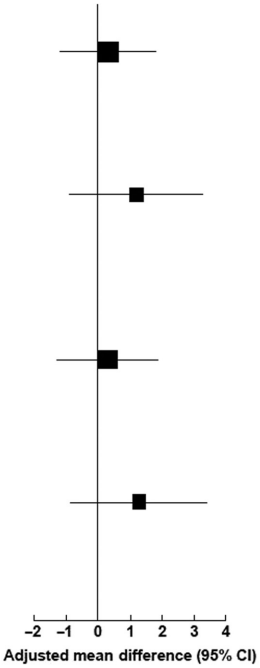

FIGURE 3 Maternal secondary long-term outcomes: SF-12 Health Survey Summary Scale at follow-up at 6 months and at 2 years. The solid line shows the line of no difference. CI, confidence interval; MCS-12, Mental Component Summary Scale Score; PCS-12, Physical Component Summary Scale Score; SD, standard deviation

interest is generally healthy and not under routine clinical follow-up (in contrast to infants born very preterm). Thus, the inclusion of long-term outcome data is a strength of this study and is likely to be of interest to women with pre-eclampsia and their clinicians.

The trial was limited by a higher loss to follow-up rate than expected, meaning that the extent and direction of bias in outcomes (between responders and non-responders) is uncertain. This was compounded by PARCA-R questionnaires being sent out at chronological rather than corrected age, meaning that imputation was needed to convert some raw scores into standardised scores. With a smaller sample size than expected for the long-term primary outcome, and the consequently reduced precision of our estimates, our ability to draw firm conclusions is limited. A longer follow-up period (e.g. up to 5 years) would have enabled us to provide further evidence on long-term infant outcomes, using measures such as intelligence quotient (IQ), and to identify whether any of the differences observed between the two groups resulted in any clinical meaningful differences at school age, but this runs the risk of greater attrition and increased expense.

4.3 | Interpretation

Infants born late preterm have been found to be at increased risk of neurodevelopmental delay and poor school performance in the long term,[22–26] but this is typically compared with healthy infants born at term.[27] Pre-eclampsia is a disease state associated with fetal growth restriction,[28] which itself is demonstrated to adversely impact childhood development.[29,30] In this scenario, it is possible that earlier delivery might improve long-term neonatal outcomes, compared with expectant management which is associated with increased risk of growth restriction.[7,20,31] In support of this, previous trials have shown that although infants of women with hypertensive disorders of pregnancy who underwent planned early delivery between 34^{+0} and 36^{+6} weeks of gestation had a small difference in neurodevelopmental outcomes at 2 years of age,[20] these differences did not persist at the 5-year follow-up.[21] At 5 years of age, other factors such as maternal education and birthweight appear to be more important predictors of long-term infant development than near-term gestational age at delivery.[21,26]

This trial provides strong evidence that planned early delivery reduces immediate adverse maternal outcomes with no evidence of differences in self-reported quality of maternal physical and mental health at 6 months and at 2 years between the intervention groups. However, the impact upon the infant remains unclear. Planned early delivery may increase the need for neonatal unit admission in the short term, primarily for an indication of prematurity (i.e. a routine admission without objective morbidity), but there is no evidence that it increases short-term neonatal morbidity. At 2 years, the mean PARCA-R scores for infants across both groups were within the normal range, which suggests no clinically important long-term harm to the infant, but as the confidence intervals for the mean difference between the groups crosses the pre-specified non-inferiority margin, uncertainty remains. Pre-eclampsia is an independent risk factor for

adverse infant neurodevelopmental outcomes,[26,32–34] and the mean PARCA-R scores in this trial were at the lower end of the normal range, consistent with previous studies. Infants in the planned early delivery group had lower PARCA-R scores compared with those in the expectant management group, but the mean difference of –2.4 points is unlikely to be clinically meaningful or to influence longer-term outcomes, such as school performance, particularly once other important predictors such as socio-economic status are taken into account.[26] In addition, the risks for an infant associated with late preterm birth must be balanced against those associated with continuing fetal growth restriction.

Future research must focus on how best to communicate these findings to women and translate them into clinical practice. The choice of clinically meaningful neonatal outcomes, particularly for infants born to mothers with pre-eclampsia, remains a challenge and an area where further work and consensus building is needed.[18] Furthermore, an intervention such as planned early delivery is likely to have a considerably different impact in different contexts where resources and disease burden are different. Most maternal and perinatal deaths associated with pre-eclampsia occur in low- and middle-income countries,[35] which have markedly higher stillbirth rates than those reported in high-income healthcare settings.[36] A multicentre randomised controlled trial evaluating the effect of planned delivery on adverse maternal outcomes and perinatal morbidity and mortality is currently underway.[37]

5 | CONCLUSION

Our results show that in women with late preterm pre-eclampsia, the average neurodevelopmental assessment of infants at 2 years lies within the normal range, regardless of the timing of delivery. The small between-group difference in PARCA-R scores is unlikely to be clinically important, but because of the lower than anticipated follow-up rate there was limited power to demonstrate that these scores did not differ. This follow-up provides further information for clinicians about the balance of risks of benefits of planned early delivery between 34^{+0} and 36^{+6} weeks of gestation to facilitate shared decision making.

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CONFLICT OF INTEREST

NM reports personal fees from Shire and Novartis, outside of the submitted work. All other authors report no conflicts of interests. Completed disclosure of interests form available to view online as supporting information.

AUTHOR CONTRIBUTIONS

LCC, RH, EJ, NM and 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. MG performed the study analysis. AP made a substantial contribution to the running of the trial. RH did the health economic analysis. AB-G, MG and LCC wrote the article. All authors reviewed, contributed to and approved the final version for publication.

ETHICAL APPROVAL

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

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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Reproductive Health

RESEARCH

Open Access

Planned early delivery for late preterm pre-eclampsia in a low- and middle-income setting: a feasibility study

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Abstract

Background: Pre-eclampsia is a leading cause of maternal and perinatal mortality and morbidity globally. Planned delivery between 34^{+0} and 36^{+6} weeks may reduce adverse pregnancy outcomes but is yet to be evaluated in a low and middle-income setting. Prior to designing a randomised controlled trial to evaluate this in India and Zambia, we carried out a 6-month feasibility study in order to better understand the proposed trial environment and guide development of our intervention.

Methods: We used mixed methods to understand the disease burden and current management of pre-eclampsia at our proposed trial sites and explore the acceptability of the intervention. We undertook a case notes review of women with pre-eclampsia who delivered at the proposed trial sites over a 3-month period, alongside facilitating focus group discussions with women and partners and conducting semi-structured interviews with healthcare providers. Descriptive statistics were used to analyse audit data. A thematic framework analysis was used for qualitative data.

Results: Case notes data (n = 326) showed that in our settings, 19.5% (n = 44) of women with pre-eclampsia delivering beyond 34 weeks experienced an adverse outcome. In women delivering between 34^{+0} and 36^{+6} weeks, there were similar numbers of antenatal stillbirths [n = 3 (3.3%)] and neonatal deaths [n = 3 (3.4%)]; median infant birthweight was 2.2 kg and 1.9 kg in Zambia and India respectively. Lived experience of women and healthcare providers was an important facilitator to the proposed intervention, highlighting the serious consequences of pre-eclampsia. A preference for spontaneous labour and limited neonatal resources were identified as potential barriers.

Conclusions: This study demonstrated a clear need to evaluate the intervention and highlighted several challenges relating to trial context that enabled us to adapt our protocol and design an acceptable intervention. Our study demonstrates the importance of assessing feasibility when developing complex interventions, particularly in a low-resource setting. Additionally, it provides a unique insight into the management of pre-eclampsia at our trial settings and an understanding of the knowledge, attitudes and beliefs underpinning the acceptability of planned early delivery.

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Plain language summary

Pre-eclampsia is a complication of pregnancy and is one of the major causes of pregnancy-related death and serious illness for women and babies around the world. Most of these deaths occur in lower income countries in Africa and Asia. Signs of pre-eclampsia include high blood pressure and protein in the urine. It is unpredictable and may affect different organs within the woman, leading to seizures, stroke and even death if not well managed. It can also affect the baby's growth and in severe cases lead to stillbirth. We know that birth of the baby (and placenta) is the only cure for pre-eclampsia. Currently, it is recommended by the World Health Organisation that all women with pre-eclampsia are offered planned early birth once they reach 37 weeks of pregnancy, unless they develop severe complications needing intervention sooner than this. However, research from higher income countries has shown that planned early birth from 34 weeks of pregnancy may reduce serious complications in the woman, without causing harm to the baby. We are designing a clinical trial to find out whether, in women with pre-eclampsia between 34 and 37 weeks of pregnancy, it is better to offer planned early birth or to offer close monitoring until either they reach 37 weeks, or a complication develops requiring emergency intervention. Before designing this trial, we carried out a study in order to establish whether the main trial would be possible, and acceptable to the local community, at our potential trial sites in India and Zambia.

Keywords: Pregnancy, Pre-eclampsia, Delivery, Low- and middle-income, Feasibility, Acceptability

Background

The disproportionate burden of pre-eclampsia in low and middle-income countries (LMIC), particularly in Sub-Saharan Africa and South Asia, is well described [1–3]. Hypertensive disorders are the second biggest cause of maternal mortality worldwide [2], and pre-eclampsia itself is responsible for 76,000 maternal deaths and 500,000 perinatal deaths every year [4].The vast majority of these (98%) occur in LMIC [1]. Despite this, there is a lack of research into interventions which could be implemented in these regions in order to improve pregnancy outcomes. One such intervention, planned early delivery, has been shown to reduce adverse maternal outcomes in a high-income setting [5, 6], but is yet to be evaluated in a LMIC setting. The proposed CRADLE-4 trial aims to establish whether planned early delivery in women with late preterm pre-eclampsia (between 34^{+0}- and 36^{+6}- weeks' gestation) is effective in reducing adverse pregnancy outcomes in India and Zambia. To our knowledge, it will be the first trial to evaluate timing of delivery in late preterm pre-eclampsia in LMIC. It is now widely recognised that conducting an assessment of feasibility is an essential step prior to the development and evaluation of a healthcare intervention as part of a larger-scale clinical trial [7, 8]. We therefore designed this initial feasibility study in order to understand the contextual factors likely to influence trial implementation and assess the perceived barriers and facilitators to the intervention. The findings were used to directly inform the design of the main trial protocol. We anticipate that the results of this study would not just optimise delivery of the trial itself, but also improve the external validity of any significant trial findings such that they are generalisable to similar settings and practicable to implement in a real-world environment.

Methods

Aims and objectives

The overall aim of this study was to explore the feasibility of planned early delivery in women with pre-eclampsia (not requiring immediate delivery) between 34^{+0}- and 36^{+6}-weeks'gestation in order to inform the design of the intervention and the main trial protocol. By assessing feasibility, we aimed to explore areas of uncertainty surrounding the main trial design. Specific study objectives were to confirm the need for the proposed intervention, obtain estimates to help with sample size calculation, explore potential outcome measures, understand the resource limitations likely to impact upon overall study design and to establish whether the proposed intervention would be acceptable to all stakeholders (pregnant women, their partners and relevant healthcare providers). In order to meet these objectives we set out to understand the disease burden associated with pre-eclampsia at the proposed trial sites, understand the current management of pregnancies complicated by pre-eclampsia at the proposed trial sites, and to explore the perceived risks and benefits of the intervention by women, their partners and healthcare providers involved in the delivery of maternal and new-born healthcare.

Ethical approval was provided by King's College London Research Ethics Committee (LRS-18/19-8818), University of Zambia Research Ethics Committee (014-11-18) and KLES Academy of Higher Education and Research Institutional Ethics Committee (KAHER/IEC/2019-20/D-2742).

Study design

CRADLE-4 Phase 1 study was designed as a mixed-methods [9] feasibility study which took place over a six-month period from 1st January 2019 to 30th June 2019. We chose to include qualitative research methods, which have gained increasing recognition for their important contribution to feasibility studies [10] and may be the most effective way of exploring key areas of uncertainty such as acceptability and local context. They are also increasingly used to address important questions about health and healthcare, particularly relevant in fields such as women's health where, for example, understanding women's experiences of childbirth is critical to the delivery of respectful maternity care [11]. In this study, we used a parallel approach [12], whereby quantitative and qualitative data collection and analysis were conducted separately and simultaneously and brought together at the interpretation stage [13]. This is a pragmatic approach to integration for such datasets [14] and allowed for qualitative data to complement and explain interesting findings from the quantitative data analysis. Analysis and interpretation of these integrated data was therefore exploratory, reflecting guidance for mixed methods feasibility studies [10].

Study settings

The study was conducted across four of the proposed sites for the interventional phase of the trial in India and Zambia. These are tertiary level hospitals (providing Comprehensive Emergency Obstetric and Newborn Care) situated in urban environments:

- University Teaching Hospital, Lusaka, Zambia
- Ndola Teaching Hospital, Ndola, Zambia
- KLE Academy of Higher Education and Research's, J N Medical College Hospital, Belgaum, Karnataka, India
- S Nijalingappa Medical College and Hanagal Shri Kumareshwar Hospital and Research Centre, Bagalkot, Karnataka, India

An additional site, Chipata first level hospital, was also used to facilitate two of the focus group discussions in Lusaka, Zambia.

Case notes review

We undertook a retrospective case notes review of all women with pre-eclampsia who delivered at the study sites between January and March 2019. Following discussion with local site teams and initial site visits, and noting the high prevalence of pre-eclampsia and maternal morbidity in these settings, a three month period was deemed adequate to provide a reliable estimate of the number of women who would be potentially eligible for the main trial. A retrospective assessment of pre-eclampsia cases at these facilities over the preceding year did not indicate any meaningful seasonal variation that might influence these results. We also collected key maternal and infant outcomes to inform selection of primary and secondary outcomes and undertake a power calculation for the main trial. Women's data were included if they had been diagnosed with pre-eclampsia and delivered at one of the participating sites. Relevant clinical notes were identified using ward registers with a record of diagnosis (e.g., pre-eclampsia) at discharge. The corresponding neonatal files were then located in order to record neonatal outcomes. Data were collected directly from case records by trained research assistants at each site. Study data were collected and managed using Research Electronic Data Capture Tools (REDCap). Whilst every effort was made to directly enter data onto REDCap, where internet connectivity made this impossible, data were entered onto paper case report forms (CRFs) and then inputted onto REDCap. Information was collected on baseline demographics, current pregnancy details, methods of gestational age determination, use of pre-eclampsia diagnostic criteria, clinical management of pre-eclampsia and gestation specific maternal and neonatal outcomes.

Focus group discussions

In order to assess acceptability of the intervention to women and their families, we facilitated separate focus group discussions for pregnant women and their male partners (or closest supporting relative such as mother or mother-in-law). In both India and Zambia, women are generally considered to have low-decision making power in their households, particularly in relation to decisions on healthcare and how to use cash earnings[15, 15]. We therefore identified male partners as being an important group to include in the feasibility study, recognising they may exert considerable influence over a woman's choice whether to participate in a research study or not. Participants were considered eligible if either they or their partner (or relative) were attending for routine antenatal care at any of the study sites. Individuals invited to take part were provided with written information detailing what their participation would involve (approximately one hour of audio-recorded focus group discussion) and written informed consent was obtained from all participants prior to initiation of the focus group discussion. Each focus group discussion was facilitated by a member of the local research team with previous experience in qualitative health research, using the local language preferred by participants (either Nyanja or Bemba in Zambia, or Kannada in India). Discussions took place in private spaces within the healthcare facility (e.g., seminar

room). Refreshments were provided and transport costs were reimbursed. A focus group discussion guide (Additional file 1) was used to explore key questions relating to participants' knowledge of pre-eclampsia, attitudes and beliefs towards planned early delivery and previous lived experience of hypertensive disorders of pregnancy. Each discussion was audio recorded, transcribed, translated, and subsequently analysed using NVivo qualitative data analysis software.

Key stakeholder interviews

Semi-structured interviews were used to explore the acceptability of the intervention to healthcare providers. A stratified, purposive, sampling strategy [17] was used to identify key stakeholders, with individuals selected based on their potential influence in the main trial, following discussion with each of the local site teams. We identified a cross-section of staff involved in the delivery of maternal and newborn care across study sites which included obstetricians, paediatricians, midwives, maternity nurses and neonatal nurses. These individuals were then invited (either by phone, e-mail, or in person) to take part in a semi-structured interview, lasting approximately 30 min. Following an invitation to participate, each individual was provided with written information about what their participation would involve, and if willing to take part they were asked to provide written informed consent. Interviews were conducted at times convenient for the participant and private office spaces were used. A topic guide (Additional file 2) was used to explore participants' understanding of pre-eclampsia, their clinical experience of the condition and the perceived risks and benefits of planned early delivery between 34^{+0}- and 36^{+6}-weeks' gestation in women with pre-eclampsia. The interviews were conducted in English (as this was the professional working language at each of the study sites), and discussions were audio recorded, transcribed, and subsequently analysed using NVivo qualitative data analysis software.

Data analysis

Descriptive analysis and summary statistics were used for the quantitative data generated from the case notes review. Qualitative data generated from the focus group discussions and stakeholder interviews were initially analysed separately and then combined. Triangulation of qualitative data (i.e., combining data from interviews and focus groups) in this way has been shown to enhance understanding of complex phenomena [13, 13]. Data were analysed using a thematic framework analysis appropriate to cross-disciplinary health research [18]. This adopts a deductive approach which enabled themes to be developed based on a combination of a priori research questions [19]. Thematic framework analysis is used to show presence and absence of patterns amongst different groups and does not rely on data saturation. Nevertheless, we adopted a pragmatic approach to data collection, continuing until we were satisfied enough data had been collected covering all major themes in the framework.

The thematic framework (Fig. 1) assessed three key domains, reflecting the study objectives: understanding disease burden of pre-eclampsia; current management of pre-eclampsia; and the acceptability of planned early delivery. Each of these were evaluated from a maternal perspective, an infant perspective, and a health system perspective.

The domains of disease burden and current management were chosen in order to explore the need for the intervention and understand the contextual factors likely to impact trial implementation. They were also considered to be important determinants of acceptability as they may influence the perceived risks and benefits that women and healthcare providers attribute to the intervention as a result of their experiences. Understanding these perceptions at an early stage of trial development was seen as an important step, not just in assessing the feasibility of the trial itself, but also the long-term feasibility of the intervention, should the main trial prove it to be effective.

Results

Medical records for 326 women with pre-eclampsia (and 342 infants) who delivered at one of the study sites between January and March 2019 were included in the case notes review. A total of eight focus group discussions (n = 59 participants) took place with the number of participants in each focus group ranging between six and ten. Five focus group discussions involved pregnant women attending for routine antenatal care (four in Zambia, n = 29 participants; one in India, n = 6 participants) and three separate focus groups were facilitated with their male partners (two in Zambia, n = 17 participants; one in India, n = 7 participants). A total of 29 healthcare providers were interviewed. This purposive sample included nine obstetricians (Zambia n = 6, India n = 3), six paediatricians (Zambia n = 2, India n = 4), six midwives (Zambia n = 6), two maternity nurses (India n = 2), five neonatal nurses (Zambia n = 3, India n = 2), and one healthcare assistant (India n = 1). An integrated summary of key qualitative and quantitative findings, presented according to the thematic framework, is shown below in Fig. 1. Key maternal data are shown in Table 1 and infant data in Table 2, grouped by gestational age (34^{+0}–36^{+6} and ≥ 37 weeks). Illustrative quotes drawn from qualitative data are found in Table 3. Supplementary case notes

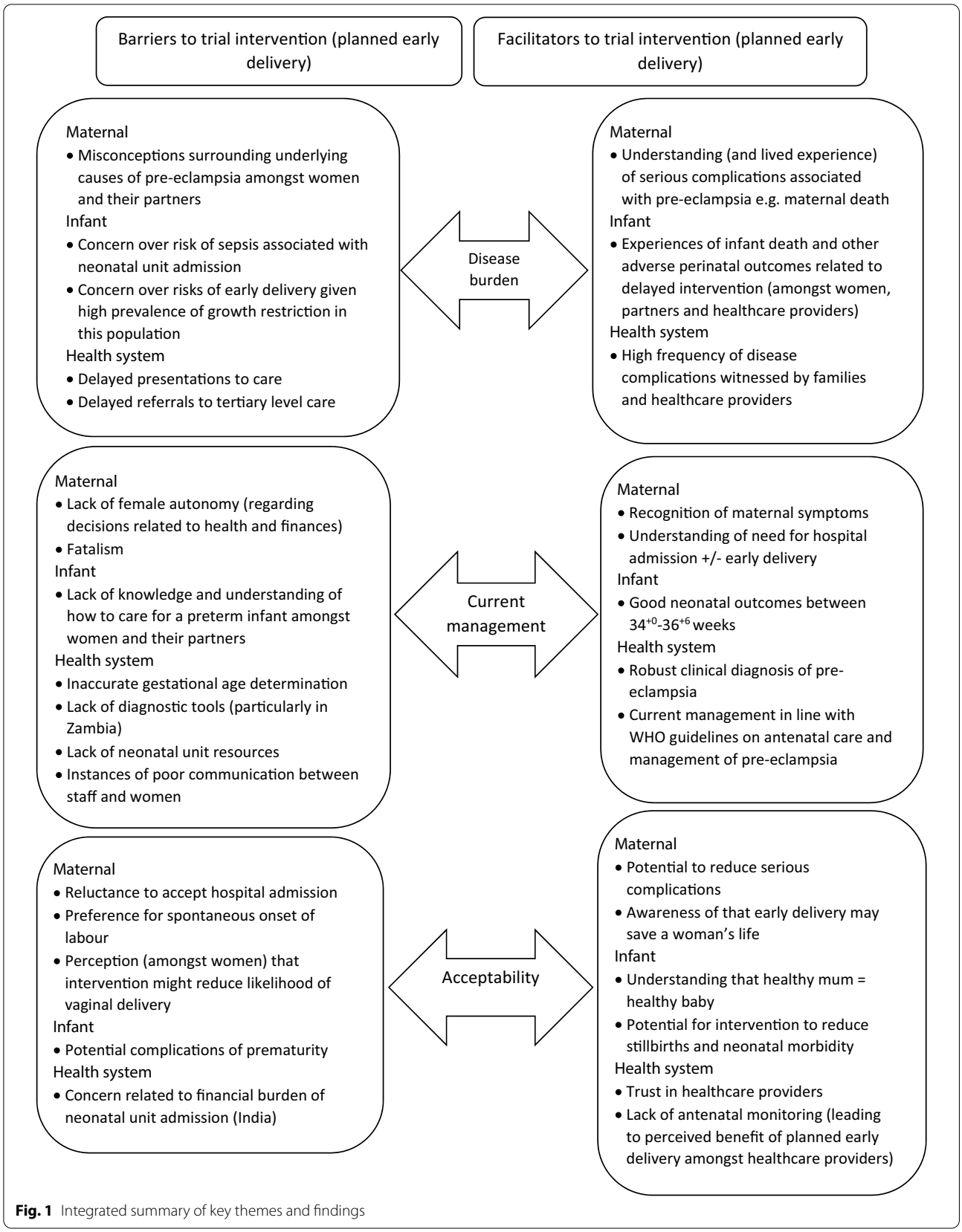

Fig. 1 Integrated summary of key themes and findings

Table 1 Case notes review—maternal data

	34–36^{+6} weeks N (%)		**≥ 37 weeks N (%)**	
	Zambian sites	**Indian sites**	**Zambian sites**	**Indian sites**
Total number of women	n = 69	n = 15	n = 98	n = 44
Maternal characteristics				
Mean (SD) age (years)	26.5 (7.0)	24.5 (3.2)	25.8 (5.9)	24.4. (4.2)
Primiparous	28 (40.5)	10 (66.7)	57 (58.2)	31 (70.5)
Singleton pregnancy	64 (92.8)	14 (93.3)	94 (95.9)	44 (100)
Ultrasound scan during pregnancy	44 (63.8)	8 (53.3)*	63 (64.3)	33 (75.0)*
At pre-eclampsia diagnosis				
SBP ≥ 140 or DBP ≥ 90 mmHg	68 (98.6)	11 (73.3)*	93 (94.9)	30 (68.2)*
≥ 1 + protein on urine dipstick	62 (89.9)	8 (53.3)	83 (84.7)	21 (47.7)
Quantitative assessment of proteinuria	0	0	0	0
Creatinine tested	18 (26.1)	15 (100)	23 (23.5)	42 (95.5)
Liver enzymes tested	24 (34.8)	15 (100)	24 (24.5)	42 (95.5)
Platelets tested	49 (71.0)	15 (100)	60 (61.2)	41 (93.2)
Pre-eclampsia management				
Given antihypertensives	61 (88.4)	15 (100)	88 (89.8)	35 (79.5)
> 1 antihypertensive agent	56 (81.6)	8 (53.3)	70 (71.4)	14 (31.8)
Received antenatal corticosteroids	42 (60.9)	4 (26.7)	9 (9.2)	1 (2.3)
Received magnesium sulfate	47 (68.1)	12 (80.0)	61 (62.2)	19 (43.2)
Admitted antenatally	66 (95.7)	15 (100)	90 (91.8)	44 (100)
Onset of labour:				
Spontaneous	22 (31.9)	3 (20.0)	43 (43.9)	24 (54.5)
Induced	25 (34.8)	4 (26.7)	28 (28.6)	5 (11.4)
Pre-labour caesarean section	22 (31.9)	8 (53.3)	27 (27.6)	15 (34.1)
Not documented	0	0	0	0
Composite of severe maternal mortality and morbidity (N women)	12 (17.4)	6 (40.0)	17 (17.3)	9 (20.5)
Individual components (non-exclusive events):				
Death	0	0	0	0
Stroke	0	0	0	0
Eclampsia	9 (13.0)	3 (20.0)	9 (9.2)	5 (11.4)
Hysterectomy	0	0	0	0
Placental abruption	0	3 (20.0)	1 (1.0)	0
Pulmonary oedema	0	0	0	0
Blood transfusion	3 (4.3)	2 (13.3)	7 (7.1)	4 (9.1)
Severe hypertension	60 (87.0)	13 (86.7)	68 (69.4)	31 (70.5)
Other maternal complications:	7 (10.1)	4 (26.7)	6 (6.1)	4 (9.1)
Documented primary indication for delivery by clinician (N = induced plus pre-labour CS)	n = 47	n = 12	n = 55	n = 20
Severe pre-eclampsia	34 (72.3)	9 (75.0)	40 (72.7)	15 (75.0)
Eclampsia	6 (12.8)	3 (25.0)	6 (10.9)	5 (25.0)
Other	6 (12.8)	0	9 (16.4)	0
Hospital length of stay	n = 69	n = 15	n = 98	n = 44
Median (IQR) pre-delivery length of stay (days)	1 (1–3)	1 (1–1)	1 (1–2)	1 (1–1)
Median (IQR) postnatal length of stay (days)	3 (2–5)	8 (7–11)	3 (2–4)	7 (5–9)

*Records of antenatal ultrasound or clinic visits not always available

Table 2 Case notes review—infant data

	34–36^{+6} weeks N (%)		**≥ 37 weeks N (%)**	
	Zambian sites	**Indian sites**	**Zambian sites**	**Indian sites**
Total number of infants (N)	n = 74	n = 16	n = 102	n = 44
Livebirths	72 (97.3)	15 (93.8)	99 (97.1)	41 (93.2)
Antepartum stillbirths	2 (2.7)	1 (6.3)	2 (2.0)	2 (4.5)
Intrapartum stillbirths	0	0	1 (1.0)	1 (2.3)
Neonatal deaths (% of livebirths)	2 (2.7)	1 (6.7)	2 (2.0)	1 (2.4)
No birth outcome reported	0	0	0	0
Mode of delivery:				
Spontaneous vaginal delivery	32 (43.2)	3 (18.75)	44 (43.1)	12 (27.2)
Assisted vaginal delivery	1 (1.4)	0	5 (4.0)	0
Caesarean section	41 (55.4)	13 (81.3)	52 (51.0)	32 (72.7)
Not documented	0	0	1 (1.0)	0
Median (IQR) gestation at delivery (days)	249 (243–252)	251 (245–255)	269 (266–280)	272 (266–282)
Median (IQR) birthweight (kg)	2.2 (1.9–2.7)	1.9 (1.8–2.3)	2.8 (2.3–3.3)	2.7 (2.5–3.0)
Median (IQR) birthweight centile*	16 (5–73)	5 (2–17)	18 (3–49)	11 (4–24)
Small for gestational age (birthweight < 10th centile)	28 (38.3)	10 (62.5)	37 (36.3)	22 (50.0)
Admission to neonatal unit N (% livebirths)	37 (50.0)	13 (86.7)	32 (32.3)	17 (41.5)
Primary indication for neonatal unit admission N (% livebirths):	n = 72	n = 15	n = 99	n = 41
Prematurity	13 (18.1)	0	3 (3.0)	0
Low birthweight	3 (4.2)	3 (20.0)	1 (1.0)	1 (2.4)
Respiratory distress	3 (4.2)	5 (33.3)	1 (1.0)	4 (9.8)
Birth Asphyxia/Cyanosis	5 (6.9)	0	7 (7.1)	2 (4.9)
Jaundice	0	5 (33.3)	0	8 (19.5)
Other	0	0	1 (1.0)	2 (4.8)
No clinical indication (healthy lodger)	7 (9.7)	0	14 (14.1)	0
Not documented	6 (8.3)	0	5 (5.1)	0
Respiratory support required (and type):	9 (12.5)	5 (33.3)	5 (5.1)	8 (19.5)
Oxygen	4 (5.6)	2 (13.3)	4 (4.0)	5 (12.1)
Continuous positive airway pressure	5 (6.9)	2 (13.3)	1 (1.0)	1 (2.4)
Intubation and ventilation	0	1 (6.7)	0	2 (4.9)
Antibiotics given (and indication):	9 (12.5)	3 (20.0)	6 (6.1)	6 (14.6)
Presumed sepsis	8 (11.1)	1 (6.7)	5 (5.1)	5 (12.2)
Prematurity	1 (1.2)	0	0	0
Confirmed infection	0	2 (13.3.)	1 (1.0)	1 (2.4)
Additional clinical outcomes:				
Neonatal hypoglycaemia	0	2 (13.3)	2 (2.0)	3 (7.3)
Neonatal seizures	0	1 (6.7)	0	2 (4.9)
Nasogastric feeding required	4 (5.6)	6 (40.0)	1 (1.0)	13 (31.7)
Hypoxic ischaemic encephalopathy	0	5 (33.3)	1 (1.0)	6 (14.6)
Necrotising enterocolitis	0	0	0	0
Outcome of NICU admission N (% admissions)	n = 37	n = 13	n = 32	n = 17
Discharged alive	28 (75.7)	12 (92.3)	30 (93.8)	13 (76.5)
Died	2 (5.4)	1 (7.7)	2 (6.3)	1 (5.9)
No outcome recorded	7 (18.9)	0	0	1 (5.9)
Left against medical advice	0	0	0	2 (5.9)
Hospital length of stay				
Median (IQR) length of stay (days)	4 (2–7)	6 (1–7)	3 (2–5)	6 (4–8)

Table 3 Illustrative quotes

	Pregnant women	Partners	Healthcare providers
Disease burden			
Maternal factors			
Facilitators	In my case, this condition started with high blood pressure and swelling of body parts. It affected me so much that I was admitted to intensive care unit (ICU). This condition is related to high blood pressure *(Zambia)*	Mother may have fits, haemorrhage (*India)*	I have seen eclampsia, I have seen HELLP syndrome, I have seen pulmonary edema. I have seen stroke, I have seen a massive IC bleed three weeks back. Because of the severe pre-eclampsia we lost the mother *(Obstetrician, India)*
Barriers	Is pre-eclampsia connected to sexually transmitted diseases? *(Zambia)*	It could be, maybe you are giving her too much pressure at home that's why that blood pressure keeps on going up *(Zambia)*	We need to sensitise them. Because mostly, you would ask the woman if at all she has heard of that condition. And she will be so surprised, asking how come it's high, that condition, or where the BP has come from *(Midwife, Zambia)*
Infant factors			
Facilitators	I also know one woman who had high BP and got fits. Her baby died but she is fine *(India)*	I have not seen but heard about it. In fact, it happened with one of my relatives. That mother's BP was very high and baby died inside the womb *(India)*	They could have…the baby could die whilst in utero because of the raised BP, and they could have a baby with severe asphyxia because of their condition *(Neonatal nurse, Zambia)*
Barriers	Baby will not put weight if it is born early *(India)*	Mother may have fits and stroke. Baby's growth will be restricted because of adverse effect of high BP *(India)*	And also the risk of sepsis is also very high. Because in our set-up, if the baby is shifted to the mother's side, her handling is more by the attendants. Improper handling. So they won't do hand washing and things. So the risk of sepsis is very high *(Paediatrician, India)*
Health system factors			
Facilitators	This is what I can say about the dangers of high blood pressure, my sister in-law passed on due to this condition and they only managed to save the child….. So I think from this example, we can see how dangerous this condition is *(Zambia)*	I know one woman who got seizures in pregnancy due to high BP. She was admitted to hospital. Baby died but mother survived *(India)*	Quite frequently, exactly. Yeah. Almost every week we have most attention from complication from pre-eclampsia. There are those that go for severe form, they go for dialysis. They have some renal injury as well, you know (*Junior doctor, Zambia)*
Barriers	If woman has high BP then she may not understand what to do!!! (*India)*	They delayed in bringing this lady to the hospital and by the time she was brought in, the placenta had burst and the baby died in the womb as a result *(Zambia)*	Sometimes the challenge is that despite being told antenatally, these mothers who experience headaches, they remain at home until that headache is very persistent that they even fail to sleep or do anything. That's when they come to the hospital. Sometimes it's late, yes *(Midwife, Zambia)*
Current management			
Maternal factors			
Facilitators	And also maybe the swelling of the body, usually it is the legs, the hands….*(Zambia)*	I have an in-law who had high blood pressure and swelling of the body whilst she was pregnant with twins. She underwent forced labor and that's how she was saved *(Zambia)*	First thing, I hope, first thing when they come, we give an IEC. That is heath talk. We talk to our women every day. So the health talk include danger signs in pregnancy, and what to prepare *(Midwife, Zambia)*

Table 3 (continued)

	Pregnant women	Partners	Healthcare providers
Barriers	Family member will decide whose life is important and who should be saved i.e. mother or baby *(India)*	Some children born early at 7th and 8th months will survive and some will not survive. My child did not survive. I feel it the destiny which decides the fate of each child. (He laughs in pain) Life and death is in the hands of god *(India)*	They are told at home no, you don't have to agree to induction. You don't have to agree to this. So they follow that. And they would rather follow what their parents or their relatives tell them not do it *(Midwife, Zambia)*
Infant factors			
Facilitators	At 34 weeks the baby is strong and big enough to be delivered. Overall, this will save the lives of both the mother and child. I once gave birth at 36 weeks and the baby weighed 3.8 kg *(Zambia)*	Both mother and baby will survive. Even the baby is small we can take care of baby so that it can have normal development *(India)*	I mean, as I said, between 34 and 37 weeks, babies are normal with none of these co-morbidities. Outcome will be good with monitoring *(Paediatrician, India)*
Barriers	Baby was very small so kept in the incubator. The cost of treatment was very high so could afford to keep baby in NICU for 4 days and then took the baby home against medical advice. In home they tried to take care of baby. They used Hot water bottle to keep baby warm. Baby survived for 21 or 27 days and then died *(India)*	Baby may require more care and medication. Apart from this, I do not know much (*India)*	Okay. So there are some things that I think…of course we are professional, but you may know them when you are in the shoes of the patient. So for example I think it is easy as a doctor to say give the baby medicine three times a day, but you don't know the actual struggle that the mother goes through to make those babies swallow that medicine *(Junior doctor, Zambia)*
Health system factors			
Facilitators	So I think they want to deliver you before you get to the stage were you might start fitting and the like *(Zambia)*	I tell people who had high BP to go to hospital early and deliver early by caesarean section or else mother will die *(India)*	Gestational hypertension means only the high BP. Then pre-eclampsia means they'll have all the categories. They have proteinuria, pedal enema, it may have abdominal wall oedema. They have them *(Community healthcare worker, India)*
Barriers	Just to add a few words, sometimes when we pregnant women go for antenatal clinics, they tell us medical terms that we can't understand (*Zambia)*	If it is indicated to deliver it is better to deliver and if you delay in such condition people will scold you (*India)*	Because the few vents, we have like four vents on the unit. And if I have six babies, obviously two babies won't be put on the vent, and then they actually end up dying *(Paediatrician, Zambia)*
Acceptability			
Maternal factors			
Facilitators	We would be able to save the life of the mother and the baby (*Zambia)*	On my own behalf, rather than losing my spouse I would say anyway, just do false labor (*Zambia)*	Okay. First of all we are going to preserve the mother's life, we are going to prevent her from tipping into severe PE. Yeah *(Midwife, Zambia)*
Barriers	Urban people cannot tolerate labour pain so they prefer to deliver by caesarean section *(India)*	Then on the disadvantages I think it's the actual forcing of labor before it's due. Like everything else that's forced, this in itself is a disadvantage. For example, in forced labor medicine is used to induce it, these medicines have side effects. God himself meant for pregnancy to last for 9 months before labor can start, but before that time you force it *(Zambia)*	So they tend not to understand the dangers of the condition that they have. So most of them request to go home, "sister, I want to be discharged" *(Midwife, Zambia)*

Table 3 (continued)

	Pregnant women	Partners	Healthcare providers
Infant factors			
Facilitators	Baby will have advantages. Baby will have less complications *(India)*	Delivering early is okay because by waiting, an expectant mother might die with the pregnancy or the child might die. The risks are just too many, so it's better to deliver this person and save both lives (*Zambia)*	Actually I'm treating pre-term, I am really comfortable. Rather than severe asphyxia. You can't do anything *(Paediatrician, India)*
Barriers	Maybe my worry is, I am not too sure if they are some conditions on developmental milestones that these children go through as a result of having been born too early *(Zambia)*	The baby might not have grown properly so it may have some problems *(India)*	So the thing is, when you deliver a baby at 34 weeks, obviously they are not yet mature. There are a few complications that the baby may suffer as a result of prematurity, for example physiological jaundice, their immunity's not yet as strong, they may have to undergo septic screenings *(Junior doctor, Zambia)*
Health system factors			
Facilitators	The Doctor has the authority to save you because they have been trained to do so. This is why in the first place we go to them (Doctors) because if you did not want to be saved, you would not have come *(Zambia)*	Doctors are god so whatever they suggest we will agree for that *(India)*	Because there are those who start antenatal from the clinics, and the follow-up is not that very good. There are times when the BPs are high at the clinic and they don't refer them, they refer them quite late at the hospital *(Midwife, Zambia)*
Barriers	If we have saving we will spend it if not we will ask any known person for help. If the patients are very poor they will sell their assets like Gold and bear the expenses of hospital in emergency to save mother and child (*India)*	We will borrow money from friends. If we have save money, we can use that. There are no insurance schemes right now to pay for expenses of pregnant woman (*India)*	One more challenge I would… many times the parents are not willing to keep the baby for such a long time. Because they feel that, I mean, the time spent, the amount and the revenues spent on these babies is not good *(Paediatrician, India)*

review data are presented in Additional file 3 (Tables 4, 5).

Disease burden

Maternal factors

Case notes review data highlighted the serious maternal and perinatal morbidity associated with pre-eclampsia across sites in both countries (Tables 1, 2). Notably, n = 12 (14.3%) women who delivered between 34^{+0} and 36^{+6} weeks in Zambia experienced eclampsia, compared to n = 14 (9.2%) delivering at term (≥ 37 weeks). Placental abruption, acute kidney injury, and HELLP syndrome were also frequently recorded clinical outcomes. Between 34^{+0} and 36^{+6} weeks, n = 60 (87%) women in Zambia and n = 13 (86.7%) women in India developed severe hypertension, which supports the finding that approximately three quarters of women at this gestation underwent clinician-initiated delivery for severe pre-eclampsia. Complementing this quantitative data, women, partners and healthcare providers all demonstrated a clear understanding of the complications linked to pre-eclampsia and were able to share examples of their own lived experience, either as healthcare providers managing these complications or as patients (or patient relatives) experiencing the disease itself (Table 3). Whilst healthcare providers were able to provide more detailed accounts using medical terms, women and their partners could identify links between raised blood pressure and serious complications such as death, stroke and eclampsia ("fits"). However, potential barriers to understanding were also highlighted. For example, misconceptions surrounding the underlying cause of pre-eclampsia were identified, with women and partners sometimes making connections between raised blood pressure and emotional states, and healthcare providers identifying a need to improve awareness around the condition.

Infant factors

Overall, there were a low number of infant deaths occurring after 34 weeks' gestation in our sample. Between 34^{+0} and 36^{+6} weeks, the proportion of antepartum stillbirths [n = 3, (3.3%)] was similar to the number of neonatal deaths [n = 3, (3.4%)]. Importantly, the proportion of neonatal deaths that occurred in infants born late preterm (34^{+0}–36^{+6} weeks) and term (≥ 37 weeks) was low in both groups [n = 3, (3.3%) and n = 3, (2.1%) respectively]. Furthermore, whilst respiratory distress was a more commonly documented indication for neonatal unit admission in infants born late preterm [n = 8, (16.0%) late preterm vs. n = 5, (10.2%) term], birth asphyxia was more common in those born at term [n = 5, (10.0%) late preterm vs. n = 9, (18.4%) term]. Additionally, women, partners and healthcare providers in both countries frequently mentioned instances of infant death, with examples of the baby dying "inside the womb" the most commonly reported infant complication of pre-eclampsia. Whilst recognising this important risk associated with continuing pregnancy, healthcare providers also expressed concern regarding the risks of early delivery. Interview participants mentioned high rates of hospital-acquired infection within neonatal units, however, these concerns were not borne out by the case notes review data which demonstrated only small numbers of confirmed infection amongst infants born after 34 weeks (n = 4, 4.0% of total neonatal unit admissions). There was also a perceived concern that higher rates of growth restriction amongst infants of women with pre-eclampsia would put these infants at greater risk of complications of prematurity. However, only n = 6 (12.0%) late preterm neonatal unit admissions were due to low birthweight.

Health system factors

Case notes review data demonstrated that in Zambia, approximately 1 in 5 women experienced a composite outcome of severe maternal mortality or morbidity (in India, this proportion was even higher with 2 in 5 women experiencing the composite outcome, though our sample size was smaller). Healthcare providers reported witnessing complications of pre-eclampsia on a weekly if not daily basis, and women and partners were both able to recall examples of friends and family (including their own partners in the case of male participants) affected by pre-eclampsia, often with severe consequences. Thus, pre-eclampsia was perceived as an important and frequent problem by pregnant women and their partners, and healthcare providers highlighted a clear need to optimise current management. Nevertheless, potential barriers to implementing a facility-based intervention (such as planned early delivery) were identified. These centred around delayed presentations to care related in part to lack of understanding amongst the local community, as well as delayed referrals from peripheral healthcare facilities to tertiary level care.

Current management

Maternal factors

Case notes review data showed that the majority of women diagnosed with pre-eclampsia met the diagnostic criteria of hypertension and proteinuria, as outlined by international guidelines [20, 20]. There was widespread use of antihypertensives and magnesium sulfate, suggesting appropriate management of those with severe disease. In accordance with World Health Organisation (WHO) guidelines on the management of pre-eclampsia, over 90% of women across both country sites were admitted to hospital once diagnosed and referred (although our

predominantly urban sample based in tertiary healthcare facilities may not necessarily be generalisable to other settings). Amongst healthcare providers there was a good understanding of both diagnosis and management of pre-eclampsia and particularly the need for early delivery (Table 3). This was supported by responses from women and partners who were able to recall many of the common signs and symptoms of pre-eclampsia in addition to recognising that medical interventions (such as induction of labour) may be required in order to save a woman's life. However, important themes identified from the focus group discussions at both Indian and Zambian sites also included a sense of fatalism and the idea that the outcome of a pregnancy would be "decided by God", rather than medical intervention. A lack of female autonomy related to making decisions regarding healthcare was also apparent in both countries, with partners and extended family members often given the power to decide whether to proceed with an intervention such as induction of labour or caesarean section.

Infant factors

Neonatal outcome data collected as part of the case notes review demonstrated good neonatal outcomes between 34^{+0} and 36^{+6} weeks. Median birthweight was above 1.8 kg (the threshold for neonatal unit admission according to local protocols) in both Indian and Zambian settings. Whilst a high proportion of livebirths were admitted to the neonatal unit [n = 37, (50.0%) in Zambia, n = 13 (86.7%) in India], the majority of these infants were discharged alive [n = 28 (75.7%) in Zambia, n = 12 (92.3%) in India] and only three neonatal deaths were recorded following neonatal unit admission [n = 2 (5.4%) in Zambia, n = 1 (7.7%) in India]. The same number [n = 3 (3.4%)] of neonatal deaths were recorded for neonates born ≥ 37 weeks. Small numbers of neonates born between 34^{+0} and 36^{+6} weeks required respiratory support [n = 9, (12.5%) of neonates in Zambia and n = 5 (33.3%) of neonates in India], but serious morbidity {such as necrotising enterocolitis [n = 0] or neonatal seizures [n = 1 (2%)]} was rare at this late preterm gestation. Qualitative data complemented these findings, particularly interviews with healthcare providers who expressed confidence that after 34 weeks' gestation, infants were likely to do well. Even amongst women and partners, there was recognition that hospitals and doctors were able to help small, premature babies and several women reported personal experiences of delivering their babies early, with positive outcomes. Nevertheless, some gaps in knowledge and understanding regarding the care of a preterm infant were identified during the focus group discussions. There was limited understanding of what a neonatal unit admission might involve and the type of support that could be provided to preterm infants, as well as examples of individuals who had attempted (sometimes unsuccessfully) to care for a preterm infant at home in order to avoid the cost of a neonatal unit admission.

Health system factors

Whilst maternal case notes data demonstrated robust clinical diagnosis of pre-eclampsia across the proposed trial sites and good adherence to WHO guidelines on the management of pre-eclampsia, it was also clear that resource limitations present a significant challenge in these settings. For example, only n = 5 [7.2%] women in Zambia and n = 5 [33.3%] women in India (see Additional file 3: Table 4) had an obstetric ultrasound scan before 20 weeks' gestation, making accurate gestational age determination harder. There was a clear disparity in the availability of laboratory investigations between the two countries noted. Whilst creatinine and liver enzyme testing appeared to be routinely available at the two Indian sites, only a quarter of women in Zambia had these tests performed. No women in either country had a quantitative (e.g., protein: creatinine ratio or 24 h urinary protein collection) assessment of proteinuria performed. Whilst neonatal outcomes were reassuring, interviews with healthcare providers also highlighted a number of concerns relating to a lack of neonatal resources, in particular ventilators and medications such as surfactant and anti-convulsants. A further challenge relating to women's willingness to accept care was identified during focus group discussions which revealed examples of poor communication between healthcare providers and women or families. These examples often related to a lack of explanation, or at times a didactic and paternalistic approach to delivering care and thus a breakdown of rapport between clinical staff and women.

Acceptability

Maternal factors

When considering the perceived risks and benefits of planned early delivery from a maternal perspective, the most important perceived benefit amongst healthcare providers, women and partners was the potential to save the woman's life and reduce the likelihood of life-threatening complications (Table 3). Whilst potential disadvantages were also identified (most notably there was a reluctance amongst women and their partners to accept early induction of labour), the benefit of preserving the woman's life was seen to outweigh any potential risks associated with a preterm delivery. Whilst some women and partners expressed concern that induced labour may increase the need for operative delivery, this fear was not supported by case notes review data which showed that

between 34^{+0} and 36^{+6} weeks, the majority of women who underwent induction of labour were able to deliver vaginally (Additional file 3: Table 4). Whilst healthcare providers expressed concerns regarding women's willingness to accept hospital admission based on a lack of understanding of the seriousness of the condition, most women and their partners felt that they would accept medical intervention if it meant saving the life of both the woman and their baby.

Infant factors

The perceived risks of early delivery to the infant identified by healthcare providers, women and partners was the impact of preterm delivery and the ways in which this may affect the infant's growth and development. However, overriding these concerns was a firm recognition of the mother-infant dyad and the idea that the best way to achieve a healthy infant was first to ensure the health of the mother. The consequences of waiting to deliver were clearly stated and included infant death due to stillbirth or severe birth asphyxia.

Health system factors

Considering the acceptability of planned early delivery from a health system perspective, the inherent challenges in delivering antenatal care and providing follow up for high-risk women in these settings acted as a facilitator towards the intervention as healthcare providers perceived a benefit to earlier intervention, given these challenges. Furthermore, whilst household decision making was often deferred to other family members (particularly male members of the household), women and partners demonstrated a high level of trust placed in medical professionals and ultimate decision-making authority provided to doctors. Countering this, was the perceived financial risk of a neonatal unit admission, which was highlighted as a particular issue in India, whereas care in Zambia was provided largely free of charge.

Discussion

Assessing the disease burden due to pre-eclampsia across our study sites demonstrated the high prevalence of adverse pregnancy outcomes associated with the condition in these settings. Combining case notes data with the powerful lived experiences of healthcare providers, women and their partners highlighted a strong desire for optimising current management and confirmed a need for evaluation of our proposed intervention (planned early delivery). Whilst it is not possible to draw firm conclusions based upon our relatively small sample, the infant data suggests there is no increased risk of neonatal mortality associated with late preterm delivery compared to term delivery in this high-risk population, and that prolonging pregnancy in this situation may be at least as risky to the infant as iatrogenic preterm delivery. In particular, there appears to be a higher risk of hypoxic brain injury secondary to severe maternal disease amongst infants born at term, compared to those born late preterm. Supporting this, a surprising finding was the positive attitude of paediatric doctors towards planned early delivery. Interview data showed that despite our concern that these individuals may perceive greater risk associated with the intervention, they felt more confident in managing late prematurity as compared to birth asphyxia following an emergency delivery for severe pre-eclampsia, and therefore attributed greater benefit to planned early delivery. Overall, neonatal outcome data provided reassuring evidence that the proposed trial sites have the facilities and skills to appropriately manage late prematurity. Data from the case notes review and stakeholder interviews identified key resource limitations which influenced the design of the interventional trial protocol. In particular, we were able to modify the eligibility criteria and refine our selection of maternal and perinatal outcomes, developing pragmatic, clinical definitions that would enable these variables to be measured reliably. Important facilitators assessed as part of current management included a strong recognition of the signs and symptoms of pre-eclampsia and an understanding of the need for hospital admission and early delivery. This reflects the fact that in our study settings, there is positive engagement with antenatal care [15, 16, 16] and good provision of the WHO recommended [23] 'Information, Education, Communication' sessions to women during these visits. Whilst healthcare providers, women and their partners did perceive some risk associated with planned early delivery (such as undergoing induction of labour or the costs of a preterm delivery), overall the intervention was found to be acceptable to the majority of stakeholders with clear perceived benefits identified (reducing the risk of death, serious complications and stillbirth) that were felt to outweigh any potential disadvantages. Our findings therefore suggest that, with appropriate modifications to suit the local context, the interventional phase of the trial would be feasible to deliver and acceptable both to those delivering the intervention (healthcare providers) and those receiving it (pregnant women with pre-eclampsia).

The mixed-methods design of this study enabled the integration of data from multiple sources. Qualitative data was used to explore and explain quantitative findings, with case notes review data also validating (or in some cases dispelling) key themes identified in analyses of focus group discussions and interviews. Case notes review data provided important findings relating to current management of pre-eclampsia as well as the

availability of specific resources and the incidence of severe morbidity. This enabled an objective assessment of feasibility, and rigorous case-finding and data collection provided a complete and realistic assessment over a three-month period. The acceptability of the intervention, and the perceived risks and benefits of planned early delivery, were assessed qualitatively and this enabled a methodical and thorough understanding of knowledge, attitudes and beliefs amongst local pregnant women and their partners. This sample of focus group participants was deliberately selected to be representative of the target study population for the main trial. Focus group data has therefore informed our recruitment strategy when designing the trial protocol and ensured engagement of local stakeholders from the outset. Our study was limited by challenges with documentation, for example, despite extensive efforts it was not always possible to locate antenatal and neonatal records and thus capture all outcomes. Additionally, further research may elucidate the role of sociodemographic influences on decision-making (e.g., around pregnancy interventions). The position of the research team facilitating focus group discussions as midwives and researchers was both a strength and a limitation. For example, as midwives they were able to build trust and rapport with colleagues and women; however, this role may also have created a power imbalance between facilitator and participants. Steps were taken to counter this, for example, acting as facilitators at healthcare facilities where they did not work clinically.

Our study findings enabled us to modify implementation of the main trial in order to suit the local context. For example, in order to address common misconceptions regarding the causes of pre-eclampsia and management of preterm birth, we developed brief educational videos to supplement trial recruitment materials. Recognising the involvement of male partners and learning from previous experiences of poor communication, discussions regarding trial participation would be encouraged to take place with both the woman and her partner present. Taking resource limitations into account, the CRADLE-4 trial inclusion criteria will utilise a broad definition of pre-eclampsia based on simple clinical parameters (hypertension and dipstick proteinuria) and gestational age determination based upon known last menstrual period (LMP) rather than first trimester ultrasound. However, the use of early (prior to 20 weeks) and late ultrasound will be encouraged, particularly when reliable data on LMP is not available. This is a pragmatic approach that would be transferable to similar settings. Furthermore, whilst it can be challenging to distinguish between growth restriction and early prematurity without accurate gestational age determination, we did not want to impose stringent criteria that could potentially exclude growth restricted fetuses (on the mistaken premise of prematurity before 34 weeks), who are in fact at the highest risk of intra-uterine death and potentially may benefit most from early delivery. Clinical outcomes were also adapted. The primary short-term maternal outcome used in the main trial will be based on the miniPIERS composite of adverse maternal outcomes [24], with the addition of severe hypertension. The miniPIERS composite had previously been selected for use in a prospective study of women with any hypertensive disorder of pregnancy in a low and middle-income setting [24]. We further modified the outcome definitions based upon our study findings. For example, we modified the definition of "blood transfusion" to include a request for transfusion even if blood products were unavailable at time of request or not received. Acknowledging the discrepancy in biochemistry testing between sites, we also plan to report a separate maternal mortality and morbidity composite of components detected by a clinical diagnosis only, as a secondary maternal outcome. Perinatal outcomes were also adapted via iterative discussion with site teams, building upon findings from stakeholder interviews with paediatric staff. For example, recognising that culture-proven sepsis is a difficult outcome to detect due to limited laboratory resources, a diagnosis of possible serious bacterial infection (based on WHO's Integrated Management of Childhood Illness guidelines [25]) was added as a secondary perinatal outcome.

Based upon the maternal and neonatal outcome data collected during the case notes review, we anticipate a maternal event rate composite outcome of severe maternal mortality or morbidity with severe hypertension) of 80% and a neonatal event rate (stillbirth or neonatal death of neonatal unit admission for > 48 h with morbidity) of 23% in the expectant management (usual care) group of the main trial, in women with late preterm pre-eclampsia. This informed our sample size calculation, which is detailed in the published trial protocol [26].

The Medical Research Council guidelines on developing and evaluating complex interventions recognise that interventions are often undermined by problems of acceptability, compliance, delivery of the intervention, recruitment, and retention [27]. The guidelines therefore advocate that initial feasibility studies are undertaken in order to address these potential issues when designing the main study protocol. Considering an intervention such as planned early delivery in

pre-eclampsia in India and Zambia, there are several behaviours required by those delivering the intervention (healthcare providers) and those receiving it (women) which are complex and need to be understood. Selecting meaningful maternal and perinatal outcomes, which can be reliably measured in a real-world setting, was also a potential challenge. Despite its importance, feasibility work is often poorly described and under-reported [7]. The CRADLE-4 feasibility study therefore serves as an important example of how the Medial Research Council Guidelines on developing and evaluating complex interventions can be put into practice and used to guide the development of a randomised trial design. Furthermore, there is currently inconsistent reporting of outcomes from randomised trials evaluating interventions for pre-eclampsia [28], leading to the potential omission of clinically important outcomes and difficulty in comparing and contrasting individual studies, thus limiting our ability to draw firm conclusions from the evidence available. Recent work has therefore focussed on the develop of a core outcome set for pre-eclampsia research [29]. The CRADLE-4 trial, informed by its feasibility phase, presents an opportunity to develop and validate these core outcomes, such that they may be shared and used in future pre-eclampsia trials taking place in similar settings.

Conclusion

Pre-eclampsia is a progressive and unpredictable disease and deciding when to recommend delivery presents a challenging scenario to clinicians around the world. The balance of risks and benefits must be carefully weighed depending on the gestational age of the pregnancy and the severity of the condition. When considering the specific gestational window between 34^{+0} and 36^{+6} weeks, it is clear that planned early delivery is likely to reduce adverse maternal outcomes, but further clarity is needed regarding impact on neonatal outcomes and other key maternal considerations such as mode of delivery. Our preliminary findings from this study suggest that whilst planned early delivery may involve an increased risk of neonatal unit admission with small numbers of babies requiring additional support with feeding and breathing, continuing with expectant management poses a significant risk of stillbirth and birth asphyxia. A larger scale randomised controlled trial is needed to fully evaluate which management strategy poses the least risk overall. This feasibility study has demonstrated that whilst contextual challenges related to the proposed trial environment need to be taken into consideration, such a trial is indeed feasible and the proposed intervention is acceptable to local stakeholders (healthcare providers, women and their partners). These preliminary findings have directly influenced the design of the interventional phase protocol, specifically the selection of outcome measures, with a view to contributing towards core outcome sets for similar trials taking place in low- or middle-income settings. Staff training and participant recruitment materials will address the gaps in knowledge identified during focus group discussions and interviews as well as fears and fixed beliefs surrounding early delivery. Co-creating a trial protocol with local stakeholders at this stage and taking into account the feasibility and acceptability of the intervention will be key in ensuring that any evidence generated as part of this research can be successfully implemented and sustained within routine clinical practice.

Abbreviations

LMIC: Low and middle-income countries; REDCap: Research electronic data capture tools; CRF: Case report form; NICU: Neonatal intensive care unit; HELLP syndrome: Haemolysis, elevated liver enzymes, low platelet count; WHO: World Health Organisation; LMP: Last menstrual period.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12978-021-01159-y.

Additional file 1. Focus group discussion guide example (women).

Additional file 2. Interview topic guide.

Additional file 3. Tables 4, 5 Case notes review data supplementary tables.

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Authors' contributions

The protocol was drafted by AB. NV, SAS, JS, LC and AS provided comments on the initial draft and on subsequent revisions. All authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analysed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate
Written informed consent was obtained from all focus group and interview participants. Ethical approval was provided by King's College London Research Ethics Committee (LRS-18/19-8818), University of Zambia Research Ethics Committee (014-11-18) and KLES Academy of Higher Education and Research Institutional Ethics Committee (KAHER/IEC/2019-20/D-2742).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Publisher's Note

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Understanding the language barriers to translating informed consent documents for maternal health trials in Zambia: a qualitative study

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ABSTRACT

Objective Providing comprehensible information is essential to the process of valid informed consent. Recruitment materials designed by sponsoring institutions in English-speaking, high-income countries are commonly translated for use in global health studies in other countries; however, key concepts are often missed, misunderstood or 'lost in translation'. The aim of this study was to explore the language barriers to informed consent, focusing on the challenges of translating recruitment materials for maternal health studies into Zambian languages.

Design We used a qualitative approach, which incorporated a multistakeholder workshop (11 participants), in-depth interviews with researchers and translators (8 participants) and two community-based focus groups with volunteers from community advisory boards (20 participants). Content analysis was used to identify terms commonly occurring in recruitment materials prior to the workshop. The framework analysis approach was used to analyse interview data, and a simple inductive thematic analysis approach was used to analyse focus group data.

Setting The study was based in Lusaka, Zambia.

Results The workshop highlighted difficulties in translating research terms and pregnancy-specific terms, as well as widespread concern that current templates are too long, use overly formal language and are designed with little input from local teams. Framework analysis of in-depth interviews identified barriers to participant understanding relating to design and development of recruitment materials, language, local context and communication styles. Focus group participants confirmed these findings and suggested potential solutions to ensure the language and content of recruitment materials can be better understood.

Conclusion Our findings demonstrate that the way in which recruitment materials are currently designed, translated and disseminated may not enable potential trial participants to fully understand the information provided. Instead of using overly complex institutional templates, recruitment materials should be created through an iterative and interactive process that provides truly comprehensible information in a format appropriate for its intended participants.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The use of a mix of qualitative data collection methods (interviews and focus groups) triangulated and enhanced the reliability of our findings and ensured representation of a broad range of perspectives.
⇒ Inclusion of additional stakeholders, such as members of ethical review boards, could have provided more information on the issue of informed consent, particularly regarding the ethical review process for recruitment materials.
⇒ The inclusion of community advisory board members strengthened our study by providing an important community voice; however, inclusion of a wider range of individuals from the community, including those more likely to be marginalised, and pregnant women in particular, could have ensured wider representation and added further to our findings.
⇒ The challenges described in this study are likely to be country and context specific. Our findings may inform other maternal health researchers working in Zambia, as well as outlining important principles which may apply to similar settings.

INTRODUCTION

Statement of the problem

Global health research typically involves partnerships between high-income and low or middle-income countries. These partnerships can sometimes perpetrate inherent structural inequalities or power dynamics,[1–5] whereby research methodology and institutional processes designed in a high-income country may be imposed on low-income partners without considering the relevance or acceptability to the local population. The process of informed consent, and ethical review of consent documents, are two of the domains which may be affected by this imbalance. This study evaluates an example within the context of a maternal health trial conducted in Lusaka, Zambia, specifically exploring how language barriers, and issues surrounding

translation of recruitment materials, may impact on informed consent.

Informed consent is fundamental to any research involving human beings. For consent to be valid, participants must have the capacity to consent, act voluntarily and be provided with sufficient comprehensible information. These principles are well described and upheld by international ethical and legal frameworks.[6 7] However, these frameworks are based on knowledge systems generated and perpetuated by dominant groups in high-income countries[1] and often imposed on other communities without considering local expertise. The participant information leaflets and consent forms (recruitment materials) used for enrolling participants into clinical trials conducted in low or middle-income countries are often designed by sponsoring institutions based in high-income countries[8] and are therefore more likely to meet the needs of trial sponsors and ethical review boards, rather than those of the intended participants. There is a focus on written documentation, complex medicolegal language and lengthy forms providing excessive information. These forms are then translated via a process of forward and back translation into the local language(s) of the country where the research is taking place. However, a 2014 review into participant comprehension found that the majority of trial participants across different African countries did not understand several key domains of informed consent such as voluntariness, confidentiality and the difference between taking part in research and seeking medical care.[9] This is attributed to a lack of conceptual equivalence,[10–13] arising from a lack of directly equivalent terms, as well as languages that are predominantly spoken and therefore do not have standardised written formats. Use of overly complex words and medical terminology further exacerbates this lack of understanding.[14] Studies have also highlighted a lack of universal tools for assessing understanding of trial participants[9 15–17] and this in itself presents a barrier to identifying areas for improvement. Several studies have highlighted linguistic factors as a significant barrier to comprehension, but there is very little literature exploring this particular issue. Maternal health is a key research priority which justifiably attracts large numbers of research studies. However, pregnant women are a vulnerable population and in many low or middle-income countries, including Zambia, vulnerability may be compounded by low levels of educational attainment and literacy.[18] By exploring the language barriers to cross-cultural adaptation of recruitment materials for a maternal health-related clinical trial, we aim to improve the quality of recruitment materials provided to future participants in maternal health studies in Zambia, and to contribute towards local efforts to strengthen research ethics capacity, which has been identified as a key priority by the Zambia National Health Research Policy and the Zambian National Health Regulatory Authority.[19]

Research objective

The overall aim of this study is to understand the language barriers to informed consent, and to demonstrate, via the example of translating maternal health research materials in Zambia, the importance of developing informed consent processes and providing participant information in a way that truly suits the needs of research participants.

METHODS

We used a qualitative study design incorporating a participatory workshop, in-depth interviews and focus group discussions. This study took place in three phases (table 1), based primarily in Lusaka, Zambia, alongside a timing of delivery in pre-eclampsia trial[20]; the research was led by the coordinator of this trial, a UK doctor. A Standards for Reporting Qualitative Research checklist is provided in the online supplemental materials.

Sampling strategy and data collection methods

The cross-sectional sample of recruitment materials used during phase 1 was obtained by inviting researchers working in Zambia to submit English language examples of recruitment materials they had previously developed (and subsequently translated) to inform individuals considering participation in their research studies (predominantly clinical trials). Researchers were identified via ongoing research being conducted at University Teaching Hospital, Lusaka, ongoing research conducted by the Department of Women and Children's Health at King's College London and via the Global Women's Research Society international conference. Researchers were asked to provide English language versions of participant information leaflets which were collated, read and analysed by the study lead (AB-G). All relevant examples of recruitment materials provided were included in the total sample of 13 documents. Summative content analysis (see the Data analysis section) was used to identify the most commonly occurring terms related to research and pregnancy (details shown in online supplemental table 1). These terms were organised into relevant themes such as pregnancy-specific terms, research concepts and confidentiality (online supplemental table 1). The workshop focused on how these different English terms could be translated for a Zambian population, and the potential difficulties that might be encountered when doing so. Through our discussion with workshop participants, we were able to identify which commonly occurring terms were most difficult to translate. Contemporaneous group notes were made on flip charts during this process. In addition, the independently performed back translations of participant information leaflets (translated as part of the timing of delivery in pre-eclampsia trial conducted in Zambia) were also discussed. These leaflets had been translated from English into Nyanja, and then back to English. The discussion focused on comparing and contrasting the original English versions with the back-translated versions.

Table 1 Study phases and participants

Phase	Activity	Participant summary
Phase 1 Lusaka 18 November 2019	Facilitated workshop with invited participants from a variety of professional backgrounds. We set out to explore how key maternal health research terms, identified from a cross-sectional sample of recruitment materials, from different research studies, might be translated from English into Nyanja and Bemba and how this process might alter their meaning, as part of an initial exploratory exercise to guide the subsequent two phases.	There were 11 participants including AB-G (study lead). Five participants were female, and six were male. Nine were Zambian, two were British. Four were obstetric researchers, three were research assistants and four were translators with a background in teaching and social science. Participants were invited based on their ongoing involvement with a clinical trial evaluating timing of delivery in pre-eclampsia.
Phase 2 13 May to 1 July 2021	In-depth interviews with key informants to understand in more detail the challenges involved with translating consent documents for a Zambian population.	A total of eight interviews took place. The age range of participants was 30–69, three were female and five were male. Most (six) had degrees, two had diplomas. Their occupations included language teacher (three participants), research coordinator (four participants) and one community engagement officer.
Phase 3 21 and 29 June 2021	Focus group discussions with local community advisory board members at primary health clinics to interrogate findings from phases 1 and 2 with individuals who would be representative of potential research participants.	A total of two focus group discussions (20 participants in total, 10 in each group) took place. The mean age of participants was 28 years, 12 were female and 6 were male (information not provided for two participants). Eight participants had attended tertiary-level education, with the remainder having attended secondary-level education.

Phase 2 in-depth interviews with key informants were significantly delayed due to the COVID-19 pandemic. An initial convenience sample of key informants was used, whereby individuals were invited to participate if they had prior experience of either translating recruitment materials or enrolling participants into research studies. As data collection continued, additional informants were invited to participate via snowball sampling. This comprised inviting other individuals, suggested by key informants, who were likely to have relevant insight and expertise, such as community engagement officers or research assistants. Interviews were conducted in English, the working language in Zambia, by the study lead (AB-G). A semi-structured interview guide was used (online supplemental table 2) and each interview was audio recorded and then transcribed. The interviews took place at times and locations convenient to the participants, primarily office spaces and meeting venues in Lusaka, Zambia. Phase 3 focus group discussions with community advisory board members were facilitated by three of the professional language teachers/translators who had participated in the in-depth interviews (phase 2) as key informants, supported by the study lead (AB-G). Focus group participants were invited by asking community advisory board members to participate if they wished. Community advisory board members were volunteers from the local community who were part of pre-existing community groups, linked to primary healthcare facilities in Lusaka, Zambia. Community advisory board members linked to Kanyama first-level hospital and Chawama first-level hospital were selected as these are two of the busiest primary healthcare facilities in Lusaka and both facilities had enrolled participants into the previously mentioned timing of delivery in pre-eclampsia trial. Invitations were sent out to community advisory board members via text message, and responding individuals were then invited to participate in a focus group discussion. Two initial focus groups were planned, as a purposeful sample, designed to interrogate findings from the workshop and key informant interviews. A focus group guide was developed following the phase 2 interviews and adapted from the interview topic guide (online supplemental table 2). Focus group discussions took place in outdoor meeting spaces attached to two first-level hospitals (Kanyama and Chawama) in Lusaka, and were audio recorded and transcribed. Focus groups were conducted in a mixture of English, Nyanja and Bemba and were translated at the time of transcription by a Zambian research assistant.

Ethical considerations

Written informed consent was sought from all participants before any interviews or focus group discussions were conducted and participation in the study was entirely voluntary. Electronic copies of interview and focus group transcripts were stored on a password-protected hard drive. Participants were anonymised and referred to by initials or numbers only.

Data analysis

Content analysis was used to analyse recruitment materials as a recognised method of rapidly identifying commonly occurring language. A summative approach was taken,

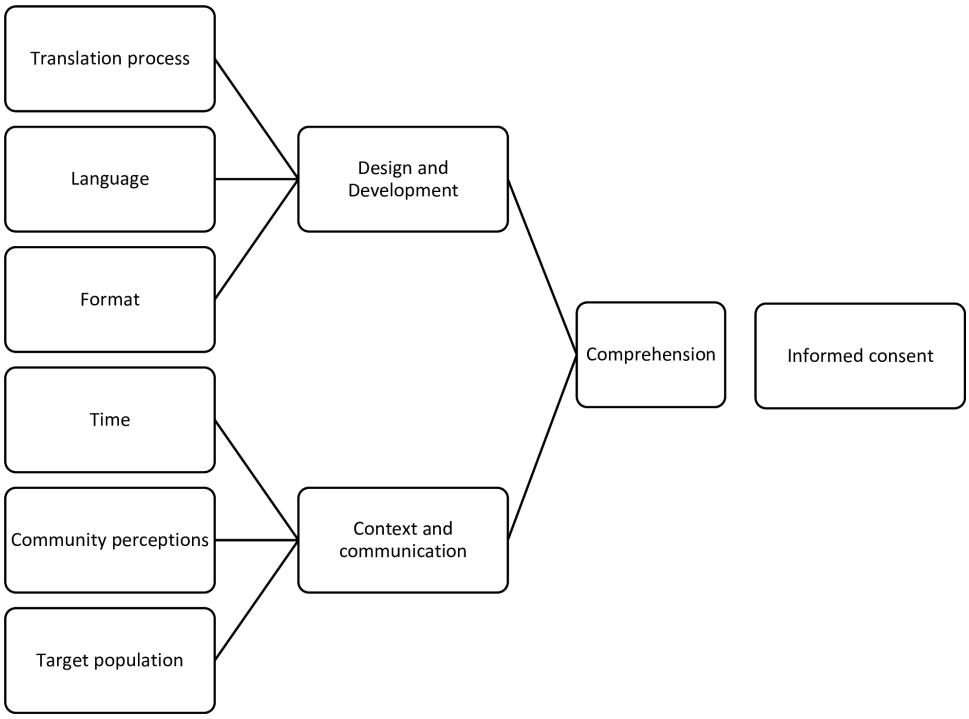

Figure 1 Thematic framework.

identifying the number of times that pregnancy-related phrases and research terms arose in the sample of recruitment materials.[21] During the phase 1 workshop (conducted in English), participants discussed the interpretation of these commonly occurring English terms, and explored how they might be translated into Nyanja and Bemba. Key outputs from the discussion notes were used to inform the design of phases 2 and 3. Interview transcripts from phase 2 were uploaded to NVivo V.12 for data coding. A framework analysis approach was used to analyse interview data.[22] The theory underpinning this framework was drawn from the conceptual framework for the process of obtaining informed consent outlined by Bhutta,[8] theories of reading and language proficiency[23] and models for translation and cross-cultural adaptation such as those outlined by Brislin[24] and Flaherty *et al*.[25] These theories were combined into one overarching framework (online supplemental figure 1[14 18 24 25]) which guided data analysis, and was developed further during the analysis process, informing the final thematic framework shown in figure 1. Focus group data were analysed using a simple inductive thematic analysis approach. The themes identified were compared and contrasted to findings from the interview data. By collecting data using different methods (workshop, interviews and focus group discussions) and from different sources (eg, research professionals and community members) we were able to triangulate our data[26] and test the validity of our findings from each phase, thereby enhancing the trustworthiness of our data. Focus group discussions with community members were chosen as a method of interrogating the findings from the workshop and interviews, and to seek differing perspectives and suggestions from individuals likely to represent potential research participants (as part of a local community linked to primary healthcare facilities involved in recruiting to clinical trials).

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.

Patient and public involvement

Patients and the public were not involved in the design or implementation of this study. However, the initial phase, a multidisciplinary workshop, incorporated individuals from a range of professional backgrounds including social scientists and language teachers in addition to clinicians and researchers. Subsequent phases involved professional translators and members of the public in the form of community advisory boards, with the overall findings and recommended actions reflecting their lived experience and perspectives.

RESULTS

Phase 1: initial workshop

During the phase 1 workshop, participating translators highlighted the lack of equivalent terms (in Nyanja or Bemba) for words such as ‘pre-eclampsia’, ‘proteinuria’ and ‘contractions’, as well as differing interpretations of words such as ‘research’, ‘benefits’ and ‘risks’. The word ‘consent’ itself was also raised as a term which could be interpreted differently depending on the context, with

Table 2 Examples of back translations

Original (English)	Back translation (from Nyanja translation)
We appreciate your time and are grateful for your help. However, there will not be any financial compensation for taking part in this study. By choosing to take part in this study you will be helping us to help other women like you in the future.	We are very thankful for giving us your time and all the help that you have rendered to us. Even if things are like this, there will be no funerals of any kind because you have taken part in this research study.
If you take part in the study we will collect some personal information. This will only be used by members of the research team if they need to contact you. This information will be kept confidential. This means that only members of the research team will have access to it, and it will not be shared with anybody else. The data will be protected according to UK Data Protection Laws.	I agree that my suggestions that I will give should be made use of in this lesson (the way my suggestions have been presented). I am aware that my suggestions will be kept following the best recommended practices of keeping secrets.
The CRADLE-4 Trial (Phase 1): the feasibility and acceptability of planned early delivery in pre-eclampsia in a low and middle-income setting.	Reviewing the advantages of early childhood delivery on the poor women and those at the centre of fending for their families. This is usually centred on the women with complications of swelling of feet and other body parts, excess proteins in the blood and urine and high blood pressure.
You have been invited to take part in this study because you have pre-eclampsia, but your condition does not require that your baby be delivered immediately.	Therefore, you are requested to take part in this study so as to help us get the facts regarding this matter.

some communities being less familiar with the concept of individualised consent than others. Important examples of discrepancies identified during discussion of the back translations are shown in table 2. This interactive workshop highlighted several concerns regarding current procedures for designing and translating research documents, and the lived experiences of the participants suggested this was a common and widespread issue. The group therefore proposed further exploration of the language barriers to adaptation of maternal health recruitment materials in Zambia via in-depth interviews, followed by community focus group discussions to develop locally driven solutions that may be generalisable to other researchers working in similar settings.

Phases 2 and 3: in-depth interviews and focus group discussions

The initial theoretical framework was modified throughout the coding process, with the final thematic framework used for data analysis shown in figure 1.

Design and development of recruitment materials

The interview participants working as research coordinators felt they were not given sufficient opportunity to contribute to the design of recruitment materials at an early stage, stating that they are often invited to review documents only after they have already been finalised and submitted to the ethics committee (table 3, quote D1). Information leaflets were criticised as being too long and wordy, with emphasis placed on the need to present key messages more succinctly using alternative methods such as flyers, community announcements and household visits. The translation process itself was identified as a significant issue, due to an overemphasis on literal word for word translations, rather than communicating the true meaning of the information. This issue was felt to be exacerbated by poor interactions between researchers and translators. The professional translators interviewed spoke of pressure to produce work within a tight timeframe, compounded by a lack of face-to-face meetings with researchers, meaning that research principles and scientific concepts were often not thoroughly understood by the individual translating the document (table 3, quote D2). Language itself was an important barrier, primarily due to a lack of equivalence—often there is simply no equivalent word in the local language for a particular English medical term. As a result, translators may try to explain the term using multiple words and phrases which ultimately distort or change the meaning (table 3, quote D3). Furthermore, a clear distinction was made between 'play' language and 'formal' language with some translators criticising the overuse of formal language in translated documents, rendering them incomprehensible to the intended recipients who use different, more colloquial versions. Finally, the presence of multiple languages in Zambia (72 in total) was identified as a further challenge, as most documents will be translated into just a few of these languages which will be understood to varying degrees by different individuals depending on their family background and where they live.

Focus group participants also felt that information in recruitment documents should be shortened and simplified and that lengthy information relating to the sponsoring institution and data protection was not necessary. Many participants felt that verbal explanations, audiovisual aids and flip charts could enhance information provision but agreed with interview participants that written documentation was an important component of the process that should not be eliminated. Participants

Table 3 Illustrative quotes

Design and development	
D1. 'What I noticed is that we just receive the consent, you can't change anything in the consent.'	Interview participant
D2. 'There are people, some people, would have sent work, you work on their consignment, you just send back. You've never met face to face. They have no time to sit with you.'	Interview participant
D3. 'Pre-eclampsia in our local language, we don't have it, it's not there, so a translator needs to have a rich vocabulary and full understanding for you to come up with the correct translation.'	Interview participant
D4. 'Here in Lusaka they don't use kubeleka, but instead they say (abala) so for this word, it will be difficult for the community to understand.'	Focus group participant
Context and communication	
C1. 'You will find that some people, when they find these women who maybe can't read on their own and they have to read for them, so you will find that most of the time, there is this issue of inadequate information being given and it will be like fast done.'	Interview participant
C2. 'You need to get consent from the husband and yet the pregnant woman is an adult, so they can consent on their own but they will not consent, they want consent from their husband or from their parents.'	Interview participant
C3. 'People need to understand, what is ultrasound, what is this machine, why are you doing this on me? What is its effect.'	Interview participant
C4. 'HIV, where you are doing blood draws so they would, from communities, they would, they would think you are selling their blood.'	Interview participant
C5. 'Looking at the community where we come from, the people that read this information trust me, most of them can't read, most of them can't even read the local language.'	Focus group participant

felt that greater emphasis needed to be placed on the voluntary nature of study participation, with statements such as 'you do not have to take part if you do not want to' given greater prominence and translated clearly and directly to ensure the meaning was clear. Participants also stated that language related to funding needed to be clarified, as direct translation of the English phrasing implied possible financial incentives could be provided by taking part. Participants also provided examples of different terms that may be used to explain pregnancy or birth depending on the context, and that while informal terms were sometimes considered less 'respectful', they were often better understood by their community (table 3, quote D4). There was tension between some translators who wished to preserve the formal, grammatically correct version of their language as taught in schools and focus group participants who preferred more colloquial terms. A suggested solution was using more informal terms in brackets so that both the official and colloquial terms could be presented and communicated effectively, depending on the user. Focus group participants also suggested creating a glossary of certain words at the start of any document, using local terms to explain in detail medical terms such as pre-eclampsia or proteinuria for the reader. Participants expressed specific preferences for different translations of particular words, examples of which are presented in online supplemental table 3. Throughout, more informal versions were preferred, and alternative terms suggested which were sometimes different from the versions originally provided by translators.

Context and communication

The way in which information is communicated to participants, as well as the context into which it is being delivered, was highlighted by both interview and focus group participants as an important area needing improvement. Some interview participants felt that potential participants are not given sufficient time to consider the information provided, with decisions often expected on the same day that a study is explained for the first time by research teams. Furthermore, some researchers described often needing to verbally explain recruitment materials to illiterate participants. They felt that this makes it difficult to standardise the information provided to potential participants and risks potential participants receiving insufficient or even inaccurate information (table 3, quote C1). When considering the context into which translated documents are being introduced, all of the interview participants raised the importance of the target population and the need to consider the levels of literacy, the languages used, the age and gender of potential participants (eg, many pregnant women require their husband's consent before participating in any study) and also the common misconceptions that may be prevalent within that community surrounding healthcare interventions or research studies (table 3, quotes C2–C4). Many interview participants highlighted the fact that use of inappropriate language or poorly designed forms will compound this issue, and risks both limiting the number of potential participants enrolled into a study and undermining the validity of the informed consent of those who do decide to take part.

Focus group participants raised similar concerns, recalling having previously been given brochures or leaflets to read, and not having the time or inclination to do so. Having more in-depth discussions, with audiovisual aids, and the opportunity for further discussions to ask questions at a later date were suggested as measures that may improve participant comprehension. Consistent with interview findings, focus group participants highlighted the importance of understanding the target community and in particular mentioned the fact that, in their experience, most individuals in their community could not read the local language (table 3, quote C5). They felt that simple information should be provided in ways that are easy to understand such as flip charts and pictures. However, the background and education of potential participants was also highlighted as an important factor to consider when choosing the most appropriate information format—with participants suggesting that in some communities, video consent may be deemed suspicious or inappropriate. Geographical region was also highlighted as important, with preferred terms changing depending on which area of the country the research is being conducted.

DISCUSSION

Our collaborative workshop highlighted the discrepancies between the original English versions of recruitment materials and translated copies, as well as the difficulty in finding equivalent terms to accurately convey the intended meaning of key research concepts and medical words such as 'pre-eclampsia'. We identified several barriers to participant comprehension and informed consent within in-depth interview data, including a lack of time available to translators, poor literacy and rushed interactions between researchers and potential participants. Researchers working in Zambia felt that the content and layout of recruitment materials were designed by 'the owners' in English-speaking countries and that they had little opportunity to influence the design or make their voices heard, with translations subsequently regarded as poor quality. In contrast to the grammatically correct, formal translations often used by professional translators, focus group participants expressed a clear preference for translated versions of recruitment materials to use more informal language, and that this should vary depending on the target population of a study. Furthermore, while workshop participants suggested audiovisual aids as a potential solution, interview and focus group participants felt that although they may be a helpful supplement, it was important to have hard copies of written information to refer back to and maintain trust.

Previous research on informed consent has focused primarily on identifying gaps in participants' understanding and evaluating community perceptions of research. Our findings correlate with those described by other studies, which found that there were widespread misconceptions regarding the purpose of research, the benefits and risks of taking part and the use of research samples such as blood samples.[27 28] If the content of research documents does not address peoples' fears and beliefs (for example around blood tests or ultrasound scans) and explain in detail what is expected of participants and why, participants may base their decision on whether to participate or not on misinformation. Previous studies highlighted a need to further investigate the language barriers to effective communication about research, as well as to develop pretested and standardised tools that can be used to explain research concepts in a way the local community can understand. However, ours is the first study, to our knowledge, which explores these barriers, with a focus on translating recruitment materials and a specific focus on maternal health terms. We therefore build on the issues raised by previous work, exploring the specific difficulties relating to language and conceptual equivalence in more detail, adding voices from a cross section of individuals in Zambia, directly involved in the design and implementation of maternal health research, as well as community representatives of target populations.

There has been a call to action within the global health community to redress the systemic imbalances that are perpetuated by Eurocentric institutions and practices.[29] However, there are very few worked examples that demonstrate how these inequities may cause harm to research participants, and even fewer examples that suggest ways of dismantling these practices.[30] This study provides a practical and tangible example of ways in which researchers and ethical review boards can begin the process of change right away. A recent scoping review highlighted the financial, administrative and regulatory barriers to good quality ethical review in low and middle-income countries[31]; our study provides relevant findings that may be used to address some of these concerns. A collaborative, multidisciplinary research programme in Kenya has successfully implemented a systematic approach to translating contextualised informed consent templates, drawing on community engagement processes within their research programme, which has received positive engagement from researchers and ethics committees.[32] We present our own summary of our recommended actions for institutions, researchers and translators in figure 2, which represents the perspectives of the Zambian participants in this study, and could be used to inform a similar approach in a Zambian setting.

Strengths and limitations

The initial research question and subsequent study design were influenced by the experiences of the study coordinator (AB-G) when translating recruitment materials for the feasibility study informing the main timing of delivery in pre-eclampsia trial,[20 33] which suggested the specific difficulties encountered during this process may represent a wider issue. This was explored further during the course of data collection and analysis, acknowledging the potential biases that may have been carried

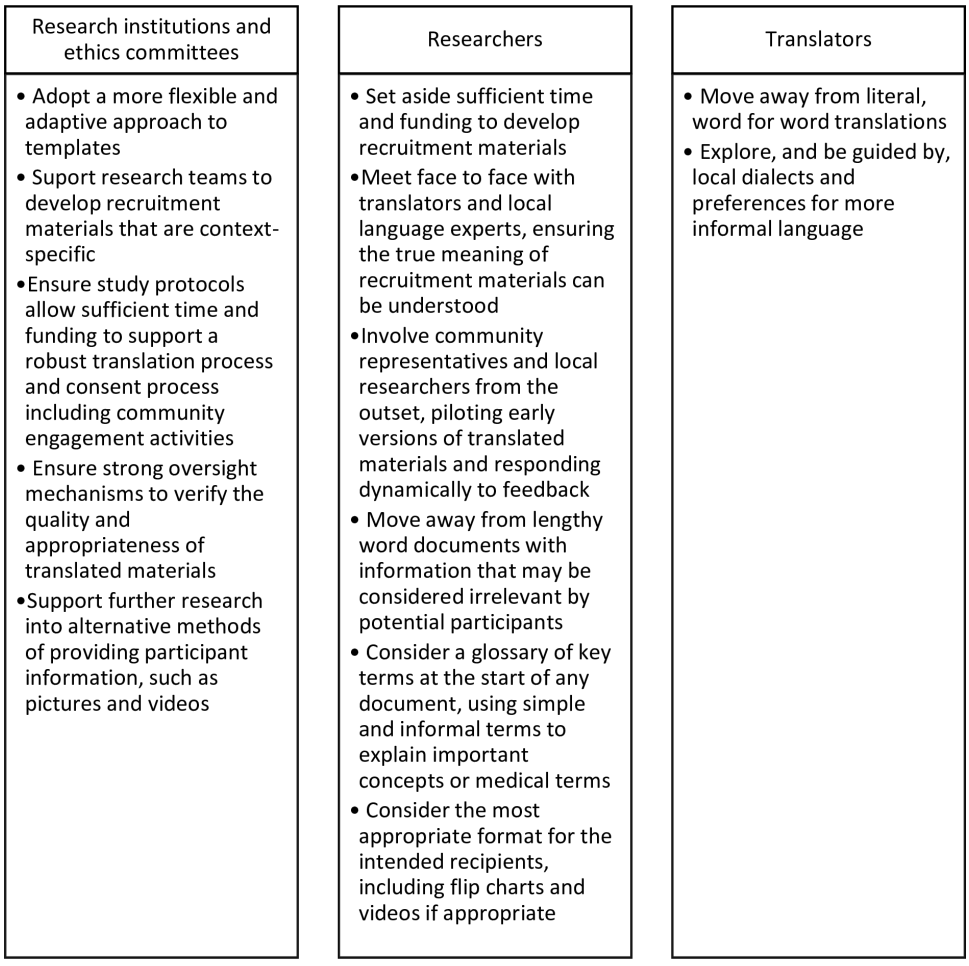

Figure 2 Summary of recommended actions.

forward from this initial experience. Collecting data from different sources helped counteract any inherent individual bias. For example, the assumption that participants might prefer information provided in alternative formats was dispelled by both interview and focus group participants who felt it was important to have a written, hard copy of any recruitment materials. In their position as a trial coordinator, it is possible that interview and focus group participants may have viewed them as possessing a certain level of authority, and this in turn may have influenced the responses of the participants. Steps taken to counteract this included a relaxed communication style during interviews and using local translators to help facilitate focus group discussions. In their position as a researcher based in Zambia during the time period that this study took place, the study lead was able to connect with and seek out key informants within the local research community and seek guidance from local experts working in social science research. Language teachers and translators represented an important group of participants for this research. While they had previous professional experiences of translating research materials, it was clear that the objective of this study was to learn from and understand their experiences, rather than engage them in a professional capacity, thus limiting the potential for any conflict of interest. The translators who performed the initial translations used for the back translations discussed at the workshop each worked as professional teachers of either Nyanja, Bemba or both, in the public education system in Zambia. Each translator had at least 5 years of experience of translating research documents for clinical trials. Although some of the discrepancies identified may be related to errors, rather than specific language barriers (for example, the addition of the word "funerals" in the first example provided in table 2), this highlights the importance of performing back translation (not always required by ethical review bodies), and allowing sufficient time for translators and researchers to meet face to face and discuss their work, an important process which, according to the translators interviewed, was frequently ignored by researchers. Focus group participants were recruited from local community advisory boards. These groups are local volunteers who are often consulted to gain community input and perspectives on healthcare interventions and research studies. While this meant they were well placed to participate in the focus group discussions facilitated as part of this study, participants outside of this well-established model may have provided a wider array of insights.

The views of both interview and focus group participants likely represent an urban population, though many interview participants had experience of a wide range of research studies conducted over different time periods and in different areas of the country. Interview and focus group participants had many experiences of research, given that they lived in Lusaka, the capital city, where many of the healthcare facilities have ongoing involvement in several research projects. A more remote setting in areas where participants are less familiar with research may have provided different findings. However, given the aim of this study was to specifically explore issues when translating, using and understanding participant information documents, the selected population was likely appropriate for the research objectives. Inclusion of ethical review board members, or study principal investigators, who are responsible for approving many of the recruitment materials used in global health studies, could have added an additional and important perspective on the issues explored in our study. Engaging these key stakeholders would be important in any future research and when implementing our recommended actions.

In this study, we focus on the example of translating recruitment materials for a maternal health-related clinical trial in Zambia. It is possible that the specific challenges described by participants in this study may not necessarily apply to other study designs or contexts, thereby limiting the generalisability of our findings. However, by sharing the key learning points identified from this qualitative study, it may prompt any individual involved in translating or using participant information in similar settings to critically review the language they use, and whether it is appropriate and comprehensible to its intended audience.

CONCLUSIONS

Our study has identified that current methods of designing and translating recruitment materials for potential research participants in maternal health studies in Zambia may not always facilitate true understanding, and therefore may not serve the needs of their intended recipients. This problem requires researchers and ethics committees to re-evaluate their current practice and move away from viewing translation as merely a tick box exercise required to gain ethical approval, but a collaborative and dynamic process that can be adapted to suit the needs of the communities, countries and languages in which the research is taking place.

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Contributors AB-G, AS and LC were involved in the study conception and in securing funding for the study. AB-G, MS, BV, SC, LC, JS and AS designed the study protocol and secured ethical approval for the study. AB-G coordinated the study supported by BV and SC. AB-G did the study analysis with input from MS and JS. AB-G wrote the original manuscript draft. All authors reviewed, contributed to and approved the final version of the manuscript. AB-G (guarantor) accepts full responsibility for the work and the conduct of the study, had full access to the data, and controlled the decision to publish.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by King's College London (MRSP-20/21-22350) and University of Zambia Biomedical Research Ethics Committee (1517-2020). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The dataset will be available to appropriate academic parties on request from the corresponding author in accordance with the data sharing policies of King's College London, with input from the coauthor group where applicable.

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Planned delivery or expectant management for late preterm pre-eclampsia in low-income and middle-income countries (CRADLE-4): a multicentre, open-label, randomised controlled trial

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Summary

Background Pre-eclampsia is a leading cause of maternal and perinatal mortality. Evidence regarding interventions in a low-income or middle-income setting is scarce. We aimed to evaluate whether planned delivery between 34^{+0} and 36^{+6} weeks' gestation can reduce maternal mortality and morbidity without increasing perinatal complications in India and Zambia.

Methods In this parallel-group, multicentre, open-label, randomised controlled trial, we compared planned delivery versus expectant management in women with pre-eclampsia from 34^{+0} to 36^{+6} weeks' gestation. Participants were recruited from nine hospitals and referral facilities in India and Zambia and randomly assigned to planned delivery or expectant management in a 1:1 ratio by a secure web-based randomisation facility hosted by MedSciNet. Randomisation was stratified by centre and minimised by parity, single-fetus pregnancy or multi-fetal pregnancy, and gestational age. The primary maternal outcome was a composite of maternal mortality or morbidity with a superiority hypothesis. The primary perinatal outcome was a composite of one or more of: stillbirth, neonatal death, or neonatal unit admission of more than 48 h with a non-inferiority hypothesis (margin of 10% difference). Analyses were by intention to treat, with an additional per-protocol analysis for the perinatal outcome. The trial was prospectively registered with ISRCTN, 10672137. The trial is closed to recruitment and all follow-up has been completed.

Findings Between Dec 19, 2019, and March 31, 2022, 565 women were enrolled. 284 women (282 women and 301 babies analysed) were allocated to planned delivery and 281 women (280 women and 300 babies analysed) were allocated to expectant management. The incidence of the primary maternal outcome was not significantly different in the planned delivery group (154 [55%]) compared with the expectant management group (168 [60%]; adjusted risk ratio [RR] 0·91, 95% CI 0·79 to 1·05). The incidence of the primary perinatal outcome by intention to treat was non-inferior in the planned delivery group (58 [19%]) compared with the expectant management group (67 [22%]; adjusted risk difference –3·39%, 90% CI –8·67 to 1·90; non-inferiority p<0·0001). The results from the per-protocol analysis were similar. There was a significant reduction in severe maternal hypertension (adjusted RR 0·83, 95% CI 0·70 to 0·99) and stillbirth (0·25, 0·07 to 0·87) associated with planned delivery. There were 12 serious adverse events in the planned delivery group and 21 in the expectant management group.

Interpretation Clinicians can safely offer planned delivery to women with late preterm pre-eclampsia, in a low-income or middle-income country. Planned delivery reduces stillbirth, with no increase in neonatal unit admissions or neonatal morbidity and reduces the risk of severe maternal hypertension. Planned delivery from 34 weeks' gestation should therefore be considered as an intervention to reduce pre-eclampsia associated mortality and morbidity in these settings.

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Introduction

810 women have been reported to die every day from preventable causes related to pregnancy and childbirth. 94% of these deaths occur in low-income countries (LICs) and lower-middle-income countries (LMICs).[1] In particular, women living in sub-Saharan Africa and south Asia have a disproportionately high risk of death.[1] Hypertensive disorders of pregnancy are a leading cause of maternal death, with pre-eclampsia representing the most serious of these disorders. Pre-eclampsia complicates around 3–5% of pregnancies[2] and is estimated to cause at least 42 000 maternal deaths[2] and

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Research in context

Evidence before this study

A Cochrane Review published in 2017 that compared planned delivery with expectant management for hypertensive disorders from 34 weeks' gestation to term found that planned delivery was associated with lower maternal mortality and morbidity, but there was insufficient information to draw any conclusions about the effect on the baby. The authors of this review highlighted the need for an individual participant data meta-analysis to better delineate the effect of planned delivery in different types of hypertensive disorders in pregnancy. In 2022, some of the present authors published an individual participant data meta-analysis (IPDMA) comparing planned delivery with expectant management in pre-eclampsia from 34 weeks' gestation onwards, building on a previous IPDMA that assessed all hypertensive disorders of pregnancy together. We did an electronic search of the Cochrane Central Register of Controlled Trials, PubMed, MEDLINE, and ClinicalTrials.gov, to review the available evidence on timing of delivery in late preterm pre-eclampsia. We used the search terms "pre-eclampsia" OR "preeclampsia" AND "delivery" OR "birth" with the limits "human" and "randomised controlled trial". We did not restrict our search by language. Cluster randomised trials or studies with quasi-randomised design were excluded, as were trials published before the year 2000. The final search date was Dec 18, 2021. Six trials that compared planned delivery with expectant management in women with pre-eclampsia from 34 weeks' gestation onward were eligible for inclusion in this IPDMA. Most were assessed as being at low risk of bias. Using one-stage IPD meta-analysis of 1790 participants from these six trials, we found that planned delivery from 34 week's gestation onward significantly reduced the risk of maternal morbidity (adjusted risk ratio [RR] 0·59, 95% CI 0·36–0·98) compared with expectant management. The primary composite perinatal outcome was increased by planned delivery (1·22, 1·01–1·47), driven by short-term neonatal respiratory morbidity. However, infants in the expectant management group were more likely to be born small for their gestational age (RR 0·74, 95% CI 0·55–0·99). All these trials took place in a high-income setting.

Added value of this study

The CRADLE-4 trial addresses a key gap in the current evidence around the effect of planned delivery in late preterm pre-eclampsia in low-income or lower-middle-income countries. These countries bear the highest burden of pre-eclampsia-related mortality and morbidity, and it is therefore essential that any interventions targeted at reducing these adverse outcomes are evaluated in the environments where they are most needed. We have shown that, in line with current evidence, planned delivery reduces severe maternal hypertension and other serious complications such as eclampsia and placental abruption. Although our study did not show a significant reduction in the maternal composite outcome, almost all outcomes for the woman favoured planned delivery, with the remaining outcomes showing no difference. The intervention did not increase operative delivery, and length of stay in hospital for the woman was shorter, consistent with findings from previous studies. We found that planned delivery significantly reduced stillbirth, driven by a large difference in antepartum stillbirth (none in the planned delivery group *vs* ten in the expectant management group). This is a novel, and important finding. Previous studies done in high-income countries with very low rates of perinatal mortality have not been able to show perinatal benefit associated with planned delivery. Furthermore, our results show that babies born at late preterm gestations do not have high rates of morbidity, even in settings where neonatal care might be less advanced; this might be due, in part, to the availability of antenatal corticosteroids and kangaroo mother care. Neonatal outcomes were similar between the two management groups, with no significant differences in respiratory outcomes or other important markers of neonatal morbidity such as jaundice or hypoxic ischaemic encephalopathy.

Implications of all the available evidence

Our findings, alongside evidence from randomised controlled trials done in high-income countries, support initiating delivery in pre-eclampsia from 34 weeks' gestation for maternal benefit. Importantly, we have shown that this can be offered without harm to the baby, showing non-inferiority of planned delivery compared with expectant management for our primary perinatal outcome. We provide new evidence showing benefit and safety for the baby, even in settings with variable resource availability. We have shown that in low-income or lower-middle-income settings, planned delivery reduces stillbirth, and should therefore be considered for improving both perinatal and maternal outcomes.

500 000 perinatal deaths, including 200 000 stillbirths,[3] every year. Pre-eclampsia is typically defined as new onset hypertension after 20 weeks' gestation with evidence of one or more of proteinuria, maternal organ dysfunction, or uteroplacental insufficiency.[4] Pre-eclampsia can lead to severe consequences for both the woman and infant, including eclampsia, maternal death, and stillbirth. The clinical course is progressive and difficult to predict, with delivery the only curative treatment. Early detection and timely delivery reduce complications for the woman.[5–7] The timing of delivery must consider the risks or benefits of preterm birth for the infant. WHO recommends delivery at 37 weeks' gestation for all women with pre-eclampsia irrespective of disease severity.[8] Before 34 weeks, expectant management is considered preferable due to the neonatal risks associated with early preterm birth, with delivery only recommended for severe maternal or fetal compromise.[8,9] Between 34 and 37 weeks

of pregnancy, the optimal timing of delivery is less clear. 2019 evidence from high-income settings has shown maternal benefit associated with planned delivery during this gestation period, with an increase in neonatal unit admissions (compared with expectant management) but no increase in neonatal morbidity.[7] Fetal death is rare at late preterm gestations in high-income settings, with none reported in a 2022 meta-analysis.[10] On the basis of our literature search, no published studies to date have reported a comparison of planned delivery versus expectant management for late preterm pre-eclampsia in a LIC or LMIC, despite the overwhelming proportion of maternal and perinatal mortality occurring in these settings. The potential risks and benefits of late preterm delivery for the infant in a low resource setting with varying levels of antenatal, intrapartum, and neonatal care available are likely to be different to those in a high-income setting, and therefore this intervention requires careful evaluation. The aim of this trial was to evaluate whether planned delivery between 34 and 37 weeks' gestation, in women with pre-eclampsia without an indication for immediate delivery, could reduce adverse pregnancy outcomes, compared with usual care (expectant management), in sites across India and Zambia.

Methods

Study design

This was a multicentre, open-label, randomised controlled trial with individual randomisation, across nine sites in India and Zambia, which are currently classified as a lower-middle-income country and a low-income country, respectively. The four sites in India were tertiary level urban referral hospitals based in the state of Karnataka. The five sites in Zambia were tertiary level urban referral hospitals based in the Lusaka, Central, and Copperbelt provinces, including their referring health-care facilities, which serve a mixed urban and rural population. A full site listing is shown in the appendix (p 1). Ethical approval was obtained from King's College London (reference numbers HR-19/20-13535), the University of Zambia (UNZA-301/2019), BVV Sangha's S Nijalingappa Medical College (SNMCIEC/1.1 /2019-2020), and the Women's and Children's Health Research Unit, Karnataka Lingayat Education Society Academy of Higher Education and Research (KAHER/IEC/2019-20/D-251119016).

Before designing the protocol for the interventional phase of the trial, some of the present authors did a 6-month feasibility and acceptability study, seeking to understand the barriers and facilitators to our proposed intervention across the trial sites, including the acceptability of the intervention to pregnant women and their supporting relatives.[11] This study directly informed trial design, enabling us to develop pragmatic methods of diagnosing pre-eclampsia (in accordance with ISSHP recommendations for low resource settings),[4] identifying gestational age, and defining clinical outcomes suitable for the local context.

Participants

A pregnant woman of any age was eligible if she had a clinical diagnosis of pre-eclampsia and a gestational age between 34^{+0} and 36^{+6} weeks, as confirmed by a doctor, with a single-fetus pregnancy or multi-fetal pregnancy and at least one viable fetus. Women with any other co-morbidity (including pre-existing hypertension, diabetes, and HIV) or having had a previous caesarean section, or with the fetus in any presentation, were eligible. Women were excluded if a decision had already been made to initiate delivery within the next 48 h, as recommended for pre-eclampsia with severe features. Site research teams sought written consent from eligible women after providing a full verbal and written description of the trial in her preferred language, supplemented by three short video clips when these were available. A full version of the published study protocol is available online.[11] There were no substantial changes to the published study design, methods, or outcomes after the start of the trial.

Randomisation and masking

Baseline participant details were entered onto the trial database by local research assistants. Participants were randomly assigned to planned delivery or expectant management in a 1:1 ratio by a secure web-based randomisation facility hosted by MedSciNet. Randomisation was stratified by centre and minimised by parity, single-fetus pregnancy or multi-fetal pregnancy, and gestational age (34^{+0} to 34^{+6}, 35^{+0} to 35^{+6}, 36^{+0} to 36^{+6}). MedSciNet wrote the randomisation programme and held the allocation code. The randomised allocation was generated by the web-based programme (using a tablet computer or other internet-enabled device) and then directly communicated to the woman and her clinical team. Due to the nature of the intervention, masking of clinicians and participants was not possible.

Procedures

See Online for appendix

The intervention consisted of initiation of delivery within 48 h of randomisation (48 h was given to enable corticosteroid administration to accelerate fetal lung maturation if necessary). Expectant management comprised usual care, with delivery at 37 weeks' gestation or sooner if clinically indicated, in accordance with WHO guidelines. Expectant management included both inpatient and outpatient monitoring depending on local capacity, clinical judgement, and the woman's preferences. Use of antenatal corticosteroids was left to the discretion of the clinical team, in line with local guidance. Method of induction, mode of delivery, intrapartum care, and postnatal care followed local clinical practice at each trial site. Outcomes were recorded on the web-based trial database contemporaneously by site research teams up until maternal and infant primary discharge from hospital. Each participant record was cross-checked by the trial co-ordinator and any queries resolved with local site teams with

retrospective case-note review if required. The end of the intervention phase was defined by the date when the last participating woman and infant were discharged from hospital, or 42 days after the final participant was recruited (whichever occurred sooner).

Outcomes

There was one primary maternal outcome and one primary perinatal outcome. The primary maternal outcome was a composite of maternal multi-organ pre-eclampsia-associated morbidity based on miniPIERS outcomes (including maternal death, CNS, cardio-respiratory, haematological, hepatic, renal variables, and placental abruption, listed in full in our trial protocol)[12] modified to suit our trial environment,[11,12,13] with the addition of recorded systolic blood pressure of at least 160 mm Hg after randomisation (on any occasion). The primary perinatal outcome was a composite of neonatal death, antenatal or intrapartum stillbirth, or neonatal unit admission of more than 48 h due to neonatal morbidity (as defined by a clinical indication for admission to the neonatal unit according to local site guidelines). Data for every participant was checked by the trial coordinator. Secondary maternal outcomes comprised individual components of the composite primary outcome (miniPIERS outcomes or recorded systolic blood pressure of ≥160 mm Hg), miniPIERS outcomes detected by clinical diagnosis only, onset of labour, need for antihypertensives before delivery, primary indication for delivery, and process outcomes such as length of stay and time from randomisation to initiation of delivery. Secondary perinatal outcomes comprised individual components of the composite outcome, any admission to the neonatal unit, number of nights in each category of care, total number of nights in hospital, birthweight, birthweight centile, birthweight less than tenth or third centile, gestational age at delivery, Apgar score at 5 min after birth, need for respiratory support, need for supplemental oxygen, confirmed diagnosis of sepsis, antibiotics given for possible serious bacterial infection, hypoxic ischaemic encephalopathy (all grades), and respiratory distress syndrome. Research teams undertook standard assessments of safety, with reporting of adverse events and serious adverse events as specified in the trial protocol and following the usual governance procedures for a clinical trial.

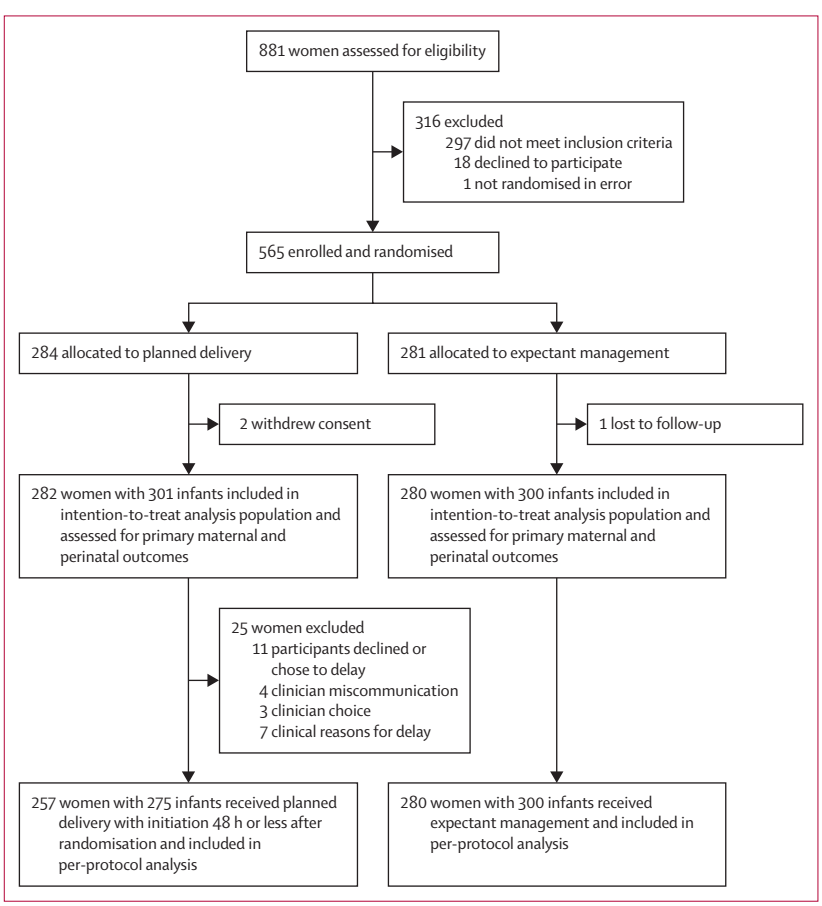

Figure: **Trial profile**

Statistical analysis

Assuming an anticipated composite adverse maternal outcome incidence of 80% in the expectant management group, on the basis of data from the CRADLE-4 feasibility study,[11] a sample size of 558 women would provide 90% power to detect a 15% relative risk reduction of the primary maternal outcome in the planned delivery group with a two-sided 5% significance level. With an anticipated 10% loss to follow-up, the overall inflated target for recruitment was 620 women. Assuming a composite adverse perinatal outcome incidence of 24%, based on data from the CRADLE-4 feasibility study,[11] complete data on 480 women would be required for 90% power to exclude a difference against planned delivery of 10% or more (based on a non-inferiority analysis using a one-sided 5% significance test and 90% CI). This estimate was in line with the planned sample size and overall recruitment target. 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-compliance. The primary analysis for all perinatal outcomes was by both intention to treat and per protocol since the hypothesis under examination for these outcomes was non-inferiority. All outcomes were analysed adjusting for minimisation factors at randomisation, which were gestational age at randomisation, twin pregnancy, and parity. Binary outcomes were analysed using log binomial regression models with results presented as adjusted risk ratios (RRs) with associated CIs. Continuous outcomes were analysed using linear regression models with results presented as differences in means with associated CIs. 95% CIs are presented for all primary outcomes and their main components. 99% CIs are presented for secondary outcomes, in order to minimise the risk of a type I error.

	Planned delivery (n=282)	Expectant management (n=281)
Maternal age, years	*28·53 (6·66)*	*28·07 (6·32)*
Ethnicity		
Black African	204 (72%)	202 (71·9%)
Asian Indian	78 (28%)	79 (28·1%)
Educational level		
None	6 (2%)	4 (1·4%)
Primary	76 (27%)	70 (24·9%)
Secondary	159 (56%)	157 (55·9%)
Tertiary	41 (15%)	50 (17·8%)
No previous births*	110 (39%)	106 (37·7%)
One or more previous birth (≥24 weeks)	172 (61%)	175 (62·3%)
Previous caesarean section	53/172 (31%)	42/175 (24·0%)
High blood pressure in a previous pregnancy		
No	140/184 (76%)	120/186 (64·5%)
Yes	37/184 (20%)	51/186 (27·4%)
Unknown	7/184 (3%)	15/186 (8·1%)
BMI, kg/m²	26·9 (5·8)	27·5 (6·1)
First trimester weight recorded	50 (18%)	61 (21·7%)
Any tobacco use	0	0
Pre-existing chronic hypertension	18 (6%)	29 (10·3%)
Pre-existing chronic renal disease	0	0
HIV positive	12 (4%)	12 (4·3%)
Pre-pregnancy diabetes	2 (1%)	2 (0·7%)
Gestational diabetes	3 (1%)	6 (2·1%)
Aspirin prescribed during pregnancy	5 (2%)	15 (5·3%)
Gestational age determination method		
Last menstrual period	122 (43%)	142 (50·5%)
Early scan (before 24 weeks)	102 (36%)	96 (34·2%)
Late scan (at or after 24 weeks)	58 (21%)	43 (15·3%)
Median gestational age, weeks	35·7 (34·9–36·4)	35·6 (34·9–36·3)

(Table 1 continues in next column)

(Continued from previous column)

	Planned delivery (n=282)	Expectant management (n=281)
Gestational age category*		
34 to <35 weeks	81 (29%)	78 (27·8%)
35 to <36 weeks	83 (29%)	90 (32·0%)
36 to <37 weeks	118 (42%)	113 (40·2%)
Single fetus pregnancy*	263 (93%)	261 (92·9%)
Highest systolic blood pressure leading to pre-eclampsia diagnosis, mm Hg	158·2 (13·9)	157·7 (13·9)
Highest diastolic blood pressure leading to pre-eclampsia diagnosis, mm Hg	103·3 (9·6)	103·0 (9·5)
Severity of systolic hypertension at diagnosis		
≤149 mm Hg	70 (25%)	80 (28·5%)
150–159 mm Hg	97 (34%)	76 (27·0%)
≥160 mm Hg	115 (41%)	125 (44·5%)
Proteinuria at diagnosis (dipstick)		
1+	120 (43%)	114 (40·6%)
2+	126 (45%)	121 (43·1%)
3+	28 (10%)	38 (13·5%)
4+	8 (3%)	8 (2·8%)

Data are mean (SD), n (%), or median (IQR). *Minimisation factors used to ensure balance at randomisation.

Table 1: **Baseline maternal characteristics at enrolment**

For all perinatal outcomes, all infants (single-fetus pregnancy or multiple-fetal pregnancy) were treated separately, adjusting standard errors for clustering by mother.[14] Prespecified subgroup analyses were done for primary outcomes based on gestational age at randomisation (test for trend), single-fetus versus multi-fetal pregnancy, country, and region (with a region being tertiary centre and referring health-care facilities). To allow for clinical and logistical delays, we did a prespecified sensitivity analysis on the primary outcomes excluding women and infants randomly assigned to the planned delivery group for whom initiation of delivery was more than 96 h post randomisation. Data analyses were done with STATA version 17. An independent data monitoring committee reviewed trial progress and conduct, including all reported serious adverse events, at regular intervals throughout the study. No formal interim analysis was planned, and guidance for early cessation of the trial followed the Haybittle-Peto principle that overwhelming evidence is needed in favour of one treatment option, such that randomisation would no longer be ethical. The trial was prospectively registered with the ISRCTN registry (ISRCTN10672137).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Dec 19, 2019, and March 31, 2022, 881 women were screened, and 584 women were found to be eligible, of whom 565 were enrolled (figure), across four referral sites in India and five referral sites and their linked primary health-care facilities in Zambia (appendix p 1). 284 women were allocated to planned delivery and 281 to expectant management (figure). For the intention-to-treat analysis, data from 282 women and 301 babies in the planned delivery group and 280 women and 300 babies in the expectant management group were included. Follow-up to maternal and infant discharge continued until May 12, 2022. Two women allocated to planned delivery withdrew consent, and one woman was lost to follow-up in the expectant management group (figure). Baseline maternal characteristics appeared

balanced between the two groups (table 1). A high proportion of women in each group had their pregnancy dated using the self-reported date of their last menstrual period (122 [43%] in the planned delivery group and 142 [51%] in the expectant management group). Only five (2%) women in the planned delivery group and 15 (5%) women in the expectant management group were prescribed aspirin at any stage during their pregnancy.

The proportion of women with the primary maternal outcome (table 2) was lower in the planned delivery group (154 [55%]) compared with the expectant management group (168 [60%]), but the difference was not statistically significant (adjusted RR 0·91, 95% CI 0·79 to 1·05). Planned delivery was associated with a similar incidence of the primary perinatal outcome compared with the expectant management group (58 [19%] in the planned delivery group *vs* 67 [22%] in the expectant management group; adjusted RR 0·88, 95% CI 0·64 to 1·21; table 2). The risk difference was less than 10% (–3·39%, 90% CI –8·67 to 1·90, p value for non-inferiority <0·0001); hence we can conclude non-inferiority of planned delivery compared with expectant management. The per-protocol analysis produced similar findings (adjusted RR 0·88, 95% CI 0·64 to 1·23, non-inferiority risk difference –3·22%, 90% CI –8·61 to 2·18).

Prespecified analysis of individual components of the primary maternal and perinatal composite outcomes showed a significant reduction in post-randomisation severe hypertension in women allocated to planned delivery (adjusted RR 0·83, 95% CI 0·70–0·99), with a reduction in the same direction, which was not statistically significant, seen in the maternal morbidity and mortality component (0·92, 0·68–1·25). We identified a significant reduction in stillbirth associated with planned delivery (0·25, 0·07–0·87), with no significant differences observed in neonatal death (seven [2%] in the planned delivery group *vs* five [2%] in the expectant management group) or neonatal unit admission for more than 48 h (adjusted RR 1·00, 95% CI 0·71–1·41) between the two groups. The reduction in stillbirth was driven by a marked difference in antepartum stillbirths, with none occurring in the planned delivery group and ten occurring in the expectant management group. The number needed to treat for planned delivery to prevent one antepartum stillbirth was 33 (95% CI 18–193).

The prespecified analysis of selected individual components of the maternal morbidity composite did not show significant differences in the proportion of women in the planned delivery group who had eclampsia (adjusted RR 0·50, 99% CI 0·08 to 3·07), placental abruption (0·38, 0·07 to 2·15), and postpartum haemorrhage requiring transfusion or hysterectomy (0·69, 0·20 to 2·40; table 3), although event rates for these clinical endpoints were lower in the planned delivery group. Other secondary descriptive maternal outcomes show that there was one (<1%) maternal death and four (1%) women admitted to the intensive care unit in the planned delivery group, compared with three (1%) maternal deaths and ten (4%) women admitted to the intensive care unit in the expectant management group (table 3, appendix p 2). The majority (264 [99%] of 266) of women allocated to planned delivery had trial allocation documented as their primary indication for delivery. Women allocated to expectant management were most frequently delivered due to reaching 37 weeks' gestation (81 [34%] of 240), severe maternal symptoms (71 [30%] of 240), and fetal compromise (33 [14%] of 240). The mean time from randomisation to initiation of delivery was 2·37 days (SD 6·06) for women in the planned delivery group, compared with 5·54 days (SD 7·55) for women in the expectant management group. A high proportion of women across both groups received antenatal corticosteroids (168 [60%] in the planned delivery group *vs* 148 [53%] in the expectant management group), with rates of antihypertensive use (275 [98%] *vs* 274 [98%]) and magnesium sulphate administration (81 [29%] *vs* 96 [34%]) also similar between the two groups. The mean length of stay for women allocated to planned delivery (6·38 days, SD 4·75) was significantly lower compared with those

	Planned delivery (n=282)	Expectant management (n=280)	Risk ratio* (95% CI), p for superiority	Risk difference* (90% CI, p for non-inferiority)
Primary maternal outcome				
Intention to treat	154/282 (55%)	168/280 (60%)	0·91 (0·79–1·05), p=0·182	..
Individual components				
Post-randomisation severe hypertension	123/282 (44%)	146/280 (52%)	0·83 (0·70–0·99), p=0·035	..
Maternal morbidity and mortality	61/282 (22%)	66/280 (24%)	0·92 (0·68–1·25), p=0·601	..
Maternal morbidity and mortality detected by clinical diagnosis only†	14/282 (5%)	24/280 (9%)	0·58 (0·31–1·09), p=0·091	..
Primary perinatal outcome				
Intention to treat	58/301 (19%)	67/300 (22%)	0·88 (0·64–1·21), p=0·441	–3·39% (–8·67 to 1·90), p<0·0001
Per protocol	52/275 (19%)	67/300 (22%)	0·88 (0·64–1·23), p=0·456	–3·22% (–8·61 to 2·18), p<0·0001
Individual components				
Stillbirth	3/301 (1%)	12/300 (4%)	0·25 (0·07–0·87), p=0·029	..
Neonatal death‡	7/301 (2%)	5/300 (2%)	..	..
Neonatal unit admission for >48 h	51/301 (17%)	52/300 (18%)	1·00 (0·71–1·41), p=0·994	..

Data are n (%) unless otherwise specified. *Analysis adjusted for gestational age at randomisation, twin pregnancy, and parity. †Any one of: maternal death, hepatic haematoma, rupture, Glasgow coma score <13, stroke, cortical blindness, reversible ischaemic neurological deficit, retinal detachment, postpartum haemorrhage requiring transfusion or hysterectomy, placental abruption, myocardial ischaemia or infarction, eclampsia, requiring >50% oxygen for greater than 1 h, severe breathing difficulty, or pulmonary oedema. ‡Excluding deaths due to congenital anomalies, risk ratio not calculated due to pooled event rate <5% (as per statistical analysis plan for this variable).

Table 2: **Primary maternal and perinatal outcome**

allocated to expectant management (8·19 days, SD 5·07; adjusted mean difference –1·81, 99% CI –2·88 to –0·74). The proportion of vaginal deliveries was similar between the two groups (adjusted RR 0·95, 99% CI 0·74 to 1·24; table 4). Secondary perinatal outcomes showed the median gestational age at delivery was 252 days compared with 255 days for babies born to women in the planned delivery group and expectant management group, respectively (table 4). Median infant birthweight in the planned delivery group was 2340 g (IQR 2000 to 2700) and 2300 g (IQR 2000 to 2700) in the expectant management group. Birthweight centile was significantly higher in those with planned delivery (median difference 4·4, 99% CI 0·5 to 8·8), with fewer infants born less than the tenth centile, although this difference was not significant (adjusted RR 0·85, 99% CI 0·64 to 1·13). Proportions of overall neonatal unit admission were similar between the two groups (119 [40%] of 298 in the planned delivery group *vs* 124 [43%] of 288 in the expectant management group), with only four infants (two in each group) requiring acute-level (invasive ventilation) care. Overall, no statistically significant differences in short-term neonatal complications were observed between the two management groups. Markers of respiratory morbidity such as the proportion of infants needing respiratory support (24 [8%] *vs* 24 [8%], adjusted RR 0·98, 99% CI 0·49 to 1·99), supplemental oxygen (43 [14%] *vs* 55 [19%], 0·77, 0·48 to 1·24), or with respiratory distress syndrome (28 [9%] *vs* 29 [10%]) were similar between the two groups, and lower in the planned delivery group. Rates of other secondary perinatal outcomes were also similar (appendix p 4). Mean number of nights in hospital was 4·68 days (SD 4·70) and 5·18 days (SD 5·50) for infants in the planned delivery group and expectant management group, respectively (table 4).

There was a total of 33 serious adverse events (affecting 32 pregnancies) during the trial (appendix p 6). The events comprised four maternal deaths (one in the planned delivery group compared with three in the expectant management group); 14 neonatal deaths (eight in the planned delivery group compared with six in the expectant management group), which included two linked to congenital anomalies; and 15 stillbirths (three in the planned delivery group compared with 12 in the expectant management group). None of these serious adverse events were deemed to be unexpected or related to the intervention.

In the prespecified subgroup analyses (unpowered), we found no significant interaction between the incidence of the primary maternal or perinatal outcome and gestational age at randomisation, single-fetus or multifetal pregnancy, country, or region (appendix p 9). A prespecified sensitivity analysis excluding women or infants randomly allocated to the planned delivery group with initiation of delivery after 96 h did not alter our findings in any way (appendix p 8).

	Planned delivery	Expectant management	Effect measure* (99% CI)	p value
Eclampsia	3/282 (1%)	6/280 (2%)	aRR 0·50 (0·08 to 3·07)	0·329
Placental abruption	3/282 (1%)	8/280 (3%)	aRR 0·38 (0·07 to 2·15)	0·152
Postpartum haemorrhage requiring transfusion or hysterectomy	7/282 (3%)	10/280 (4%)	aRR 0·69 (0·20 to 2·40)	0·449
Platelet count <50 × 10⁹ per L without blood transfusion	5/238 (2%)	4/250 (2%)	aRR 1·31 (0·24 to 7·27)	0·681
Hepatic dysfunction†	30/171 (18%)	32/179 (18%)	..	..
Acute renal insufficiency†	5/176 (3%)	5/190 (3%)	..	..
Maternal death	1/282 (<1%)	3/280 (1%)	..	..
Maximum systolic blood pressure post-randomisation, mm Hg	158·32 (14·01)	160·46 (15·94)	..	..
Onset of labour				
Induced	139/282 (49%)	104/280 (37%)	..	..
Pre-labour caesarean section	127/282 (45%)	136/280 (49%)	..	..
Spontaneous	16/282 (6%)	38/280 (14%)	..	..
PROM and augmentation	0/282	2/280 (1%)	..	..
Need for anti-hypertensives before delivery	275/282 (98%)	274/280 (98%)	..	..
Any antenatal corticosteroids	168/282 (60%)	148/280 (53%)	..	..
Complete course received	106/282 (38%)	106/280 (38%)	..	..
Primary indication for delivery‡ (non-exclusive)				
Trial allocation to planned delivery arm	264/266 (99%)	0/240	..	..
Reaching 37 weeks' gestation	3/266 (1%)	81/240 (34%)	..	..
Severe maternal symptoms	4/266 (2%)	71/240 (30%)	..	..
Fetal compromise on ultrasound	5/266 (2%)	13/240 (5%)	..	..
Fetal compromise on cardiotocography	1/266 (<1%)	16/240 (7%)	..	..
Fetal compromise on intermittent auscultation	4/266 (2%)	33/240 (14%)	..	..
Maternal haematological abnormality	0/266	3/240 (1%)	..	..
Maternal biochemical abnormality	0/266	8/240 (3%)	..	..
Maternal hypertension not controlled by maximal therapy	4/266 (2%)	30/240 (13%)	..	..
Intrauterine fetal death	0/266	6/240 (3%)	..	..
Other	1/266 (<1%)	10/240 (4%)	..	..
Process outcomes				
Time from randomisation to initiation of delivery, days	2·37 (6·06)	5·54 (7·55)	MD –3·18 (–4·63 to –1·72)	<0·0001
Time from randomisation to delivery, days	3·01 (6·06)	5·89 (7·59)	MD –2·88 (–4·34 to –1·42)	<0·0001
Length of stay, days	6·38 (4·75)	8·19 (5·07)	MD –1·81 (–2·88 to –0·74)	<0·0001

Data are n (%) or mean (SD) unless otherwise specified. aRR=adjusted risk ratio. MD=mean difference. PROM=pre-labour rupture of membranes. *Risk ratios are adjusted for gestational age at randomisation (34 weeks, 35 weeks, or 36 weeks), parity (multiparous *vs* primiparous), and multifetal pregnancy. †Not tested due to missing data >20% in both groups. ‡Excluding women who went into spontaneous labour.

***Table 3*: Secondary maternal outcomes**

	Planned delivery	Expectant management	Effect measure*(99% CI)	p value
Stillbirth				
Antepartum stillbirth	0/301	10/300 (3%)	..	..
Intrapartum stillbirth	3/301 (1%)	2/300 (1%)	..	..
Gestation at birth, days	252 (246 to 257), n=301	255 (248 to 259), n=300	MedD −3·0 (−4·0 to −1·0)	<0·0001
Gestation at birth				
34 to <35 weeks	58/301 (19%)	30/300 (10%)	..	..
35 to <36 weeks	78/301 (26%)	82/300 (27%)	..	..
36 to <37 weeks	123/301 (41%)	88/300 (29%)	..	..
≥37 weeks	42/301 (14%)	100/300 (33%)	..	..
Vaginal birth	115/301 (38%)	119/300 (40%)	aRR 0·95 (0·74 to 1·24)	0·650
Birthweight, g	2340 (2000 to 2700), n=301	2300 (2000 to 2700), n=300	..	..
Birthweight centile†	22·8 (7·7 to 55·8), n=301	16·9 (3·8 to 41·9), n=300	MedD 4·4 (0·5 to 8·8)	0·003
Small-for-gestational age (<10th centile)†	97/301 (32%)	115/300 (38%)	aRR 0·85 (0·64 to 1·13)	0·137
Small-for-gestational age (<3rd centile)†	35/301 (12%)	64/300 (21%)	..	..
Apgar score at 5 min	9·0 (8·0 to 9·0), n=298	9·0 (8·0 to 9·0), n=288	MedD 0·0 (0·0 to 0·0)	0·178
Need for resuscitation	36/298 (12%)	45/288 (16%)	aRR 0·78 (0·46 to 1·33)	0·227
Any admission to neonatal unit	119/298 (40%)	124/288 (43%)	aRR 0·97 (0·77 to 1·24)	0·784
Number of nights in neonatal unit	3·63 (4·58), n=119	4·15 (5·15), n=124	MD −0·53 (−2·21 to 1·15)	0·412
Number of nights in each level of care‡				
Acute care	7·50 (6·36), n=2	1·50 (0·71), n=2	..	..
Subacute care	4·68 (4·44), n=90	4·91 (5·25), n=104	..	..
Kangaroo mother care	4·68 (3·31), n=41	4·48 (3·66), n=42	..	..
Normal care	3·15 (1·98), n=243	3·37 (2·61), n=234	..	..
Total number of nights in hospital	4·68 (4·70), n=298	5·18 (5·50), n=288	..	..
Need for respiratory support	24/298 (8%)	24/288 (8%)	aRR 0·98 (0·49 to 1·99)	0·949
Endotracheal ventilation	2/298 (1%)	2/288 (1%)	..	..
Continuous positive airways pressure	23/298 (8%)	24/288 (8%)	..	..
Need for supplemental oxygen	43/298 (14%)	55/288 (19%)	aRR 0·77 (0·48 to 1·24)	0·157
Confirmed diagnosis of sepsis§	1/298 (<1%)	1/288 (<1%)	..	..
Antibiotics for possible serious bacterial infection	35/298 (12%)	34/288 (12%)	..	..
Hypoxic ischaemic encephalopathy	14/298 (5%)	14/288 (5%)	..	..
Respiratory distress syndrome	28/298 (9%)	29/288 (10%)	..	..

Data are n (%); mean (SD), n; or median (IQR), n. aRR=adjusted risk ratio. MedD=median difference. *Risk ratios are adjusted for gestational age at randomisation (34 weeks, 35 weeks, or 36 weeks), parity (multiparous *vs* primiparous), and multifetal pregnancy. Median differences are unadjusted. †Calculated using intergrowth centiles. ‡Fetuses might have received more than one level of care, including normal care on the postnatal ward. §Positive blood cultures.

***Table 4*: Secondary perinatal outcomes**

Discussion

In this randomised controlled trial of planned delivery versus expectant management for women with late preterm pre-eclampsia in India and Zambia, we showed that planned delivery significantly reduces severe maternal hypertension, with an important but non-significant reduction in maternal morbidity and mortality. For the fetus or infant, we found that planned delivery did not increase perinatal mortality or morbidity, and significantly reduced the risk of stillbirth, particularly for those in the antenatal period. Secondary maternal and perinatal outcomes were consistent with our main findings, showing fewer short-term maternal complications with no difference in short-term neonatal complications. Overall, best estimates of these secondary treatment effects were in the direction favouring planned delivery, with no indication of harm to the fetus or infant. Planned delivery did not increase rates of operative delivery and was associated with a significant reduction in maternal hospital stay and equivalent neonatal hospital stay.

To our knowledge, this trial is the first to be published evaluating optimal timing of delivery in pre-eclampsia between 34^{+0} and 36^{+6} weeks' gestation in LICs and LMICs and is strengthened by its relevance to settings where the vast burden of pre-eclampsia-related morbidity and mortality exists. The inclusion of two different countries with different health-care systems and populations adds to the potential applicability of our results. Reassuringly, the proportion of infants requiring neonatal unit stay, respiratory interventions, or with neonatal morbidity was not increased by the intervention,

suggesting planned delivery can be safely implemented in countries with less neonatal resources. Our trial sites incorporated tertiary level hospitals and their local network of primary level health-care facilities, serving a mixed urban and rural population, in accordance with national referral pathways. Therefore, we anticipate our findings would apply to women across different geographical contexts. Our low loss to follow-up rate (one participant) and low rate of missing data, alongside robust in-country oversight from the trial coordinator, provides confidence in the quality and completeness of our data.

A 2021 trial[15] evaluating therapeutic hypothermia for moderate and severe neonatal encephalopathy, an intervention that has been proven to work in a high-income setting, has shown that such interventions might have a different effect in a low-resource setting. These results highlight the importance of generating evidence from LICs and LMICs before implementing interventions, and the importance of gaining a thorough understanding of the trial environment. The varied disease phenotypes in different populations and settings might also provide new insights into the efficacy of interventions. Our trial was done in settings with variable resource availability, shown by monthly site audits highlighting differences in access to blood pressure monitors, urinalysis sticks, laboratory reagents, and neonatal unit equipment between sites, with rural health-care facilities often not having these key resources. The 6-month feasibility and acceptability study that preceded the interventional phase of the trial enabled us to design a pragmatic protocol and analysis plan, suited to the context, which strengthened our engagement with local health-care partners, the consent process, and our ability to screen and enrol the target number of participants; it also enabled accurate detection of clinical outcomes and adaptation of definitions where necessary. This initial phase enhanced our successful delivery of the trial despite the challenges of working in these settings and, more broadly, the COVID-19 pandemic. However, a larger sample size might have enabled identification of a statistically significant reduction in adverse maternal outcomes, associated with planned delivery, as seen in studies across high-income settings. The planned delivery group had a lower proportion of babies with the primary perinatal outcome, despite a lower than anticipated event rate in the expectant management group. There was no evidence of harm to the infant, which supports our conclusion that planned delivery can be safely recommended. Although there were fewer serious adverse events in the planned delivery group compared with the expectant management group, the high number of serious adverse events overall shows the unacceptably high levels of maternal and perinatal mortality in these settings.

A further challenge during the trial was reaching women with late preterm pre-eclampsia before they developed severe features of the disease. Delays in detection, diagnosis, and referral across local sites meant it was sometimes difficult for site research teams to reach these women at an earlier stage in their disease and could partly explain the smaller than anticipated difference in maternal outcomes between the two groups. Additionally, the small mean difference in time from randomisation to initiation of delivery between the two groups highlights the rapidly progressive and unpredictable nature of pre-eclampsia, particularly in these settings, such that women allocated to expectant management frequently deteriorated and required delivery before 37 weeks' gestation. This narrow time difference between the groups, which is similar to that found in other studies,[7,10] could also explain the absence of a statistically significant difference in overall maternal outcomes between the two groups. Importantly, other clinical outcomes such as postpartum haemorrhage or operative delivery were not increased in the planned delivery group, indicating no additional harm to the woman associated with the intervention.

The PHOENIX trial[7] compared planned delivery with expectant management for pre-eclampsia between 34^{+0} and 36^{+6} weeks' gestation and was done in a high-income setting. This trial was the largest reported study to date, and found that planned delivery significantly reduced adverse maternal outcomes but increased the primary perinatal outcome of neonatal unit admission. Overall, the prevalence of serious adverse outcomes in this setting was rare. When incorporated into a larger individual participant data meta-analysis (IPDMA),[10] combining data from six randomised controlled trials that evaluated planned delivery from 34 weeks' gestation onwards, these findings remained consistent, with the results of this IPDMA showing a significant reduction in adverse maternal outcomes associated with planned delivery from 34 weeks' gestation, but an increase in short-term neonatal complications, primarily respiratory distress syndrome. These findings might in part be explained by the wide variation in antenatal corticosteroid use observed in these trials, with those studies done later in the observed period showing greater antenatal corticosteroid use, and no difference in respiratory morbidity between management groups. The high rates of antenatal corticosteroid use in our CRADLE-4 trial show that this intervention is widely available even in lower-resource settings and might partly explain the similar neonatal outcomes observed in both management groups. Although use of antenatal corticosteroids beyond 34 weeks requires further evaluation,[16] the recently published ACTION-I trial showed that antenatal dexamethasone for women in low-resource countries at risk of preterm birth significantly reduced the risk of neonatal death or stillbirth, with no increase in the incidence of possible maternal bacterial infection.[17] The CRADLE-4 trial fills a crucial knowledge gap in the evidence relating to timing of delivery, with none of these previous studies evaluating the intervention in an LIC or

LMIC. Our findings are consistent with current evidence and supported by a clear biological rationale; planned delivery is well established to provide maternal benefit in the context of pre-eclampsia,[6] and is associated with higher rates of vaginal delivery, as shown in a 2019 trial[7] and 2022 meta-analysis.[10] The significant reduction in severe maternal hypertension observed with planned delivery in this trial is likely to be of clinical benefit, since we know that severe hypertension is associated with an increased risk of adverse maternal outcomes.[18]

In contrast to previous studies, we have shown that planned delivery between 34⁺⁰ and 36⁺⁶ weeks' gestation for pre-eclampsia in an LIC or LMIC does not increase harm compared with expectant management, but also significantly reduces the risk of stillbirth, with no increase in short-term neonatal complications or neonatal death. In the recently published IPDMA[10] comparing planned delivery with expectant management in late preterm pre-eclampsia in high-income settings, there were no stillbirths. In the CRADLE-4 trial, 15 women (2·7%) had a stillborn child. This difference highlights the context in which we evaluated planned delivery, and the high rates of pre-eclampsia-associated perinatal mortality that occur in settings with fragile health-care systems and limited resources. An estimated 2·6 million stillbirths occur every year, 98% of which are in LICs or LMICs,[3] with extensive psychological, physical, and economic consequences.[19] The number needed to treat to prevent one stillbirth in our trial was 33, considerably lower than the 554 needed to treat[20] to prevent one stillbirth via post-dates induction of labour in the UK; clinicians and women might therefore feel there is sufficient rationale to offer planned delivery to women with pre-eclampsia from 34 weeks' gestation onwards. Despite often limited neonatal unit resources, we have shown that in pre-eclampsia after 34 weeks' gestation, delivery offers clinical benefit to both the infant and the woman. Our secondary perinatal outcomes provide reassuring evidence to support this finding, showing low rates of neonatal complications overall and no difference in neonatal unit admissions or length of stay between the two groups. Supporting a policy of planned delivery, we found a reduction in the proportion of infants born small for gestational age in the planned delivery group, with similar birthweights in each group. These results are consistent with a similar intervention for infants with suspected intrauterine growth restriction,[21] which found, at 2 years of age, that normal birthweight (increased with planned delivery) increased the chance of a normal neurodevelopmental score.[22] 2-year follow-up of infants in the PHOENIX trial showed that neurodevelopmental scores were within the normal range for infants in both management groups,[23] consistent with 2-year and 5-year follow-up of infants in the HYPITAT-II trial which found no significant differences at 5 years of age between infants in the planned delivery and expectant management groups.[24,25]

A formal health-care resource use analysis will be published separately, alongside qualitative data exploring women's experiences of participating in the trial; however, the process outcomes presented here such as length of stay and level of neonatal care required would suggest that planned delivery might be cost-saving for the health-care system, consistent with the cost savings for a high-income setting reported by the PHOENIX trial.[7,26]

These findings have important implications for health-care professionals working in LICs and LMICs, and for women who develop pre-eclampsia. Given the strong body of evidence to support planned delivery from 34 weeks' gestation for maternal benefit, combined with the new findings from this trial showing both infant safety and a reduction in the risk of stillbirth, we conclude that clinicians can safely offer planned early birth to women with late preterm pre-eclampsia, even without severe features, in an LIC or LMIC, from 34 weeks' gestation onwards.

Further research must focus on identifying local barriers and facilitators to implementation, engaging communities to raise awareness of pre-eclampsia, and understanding the social and economic factors that might influence a woman's decision to seek antenatal care as well as the wider determinants of the health-care system and its ability to provide safe, timely, and good quality care. This research should include accurate gestational age determination and precise diagnosis of pre-eclampsia. We anticipate that our findings will be incorporated into national and international guidance on timing of delivery in pre-eclampsia, as supported by a policy lab focused on implementation strategies, which indicated positive engagement and commitment from key stakeholders. Context matters: we have shown that even in low resource settings, planned delivery can be safely and effectively implemented, and is recommended to reduce adverse pregnancy outcomes in late preterm pre-eclampsia, particularly stillbirth. This intervention should form part of a concerted global effort to end all maternal and perinatal deaths from preventable causes.

CRADLE-4 study group members

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Contributors

NV, BV, SC, UC, MBB, SG, JS, LCC, and AHS were involved in the study conception and in securing funding for the study. PTS supervised and did the study analyses with input from AB-G. PTS and AB-G directly accessed and verified the underlying data reported in this manuscript. AHS was chief investigator and was responsible for all aspects of the study. LCC, BV, SC, and SG were co-investigators and were responsible for trial oversight. VS, ABK, UC, GK, LL, SB, and KD made substantial contributions to the running of the trial. AB-G developed the trial protocol, coordinated the trial, curated the data, had input into the data analyses, and wrote the original manuscript draft. AB-G and PTS accessed and verified the data. All authors reviewed, contributed to, and approved the final version of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

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

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Trials

STUDY PROTOCOL Open Access

Planned early delivery versus expectant management to reduce adverse pregnancy outcomes in pre-eclampsia in a low- and middle-income setting: study protocol for a randomised controlled trial (CRADLE-4 Trial)

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Abstract

Background: Pre-eclampsia is a pregnancy complication characterised by high blood pressure and multi-organ dysfunction in the mother. It is a leading contributor to maternal and perinatal mortality, with 99% of these deaths occurring in low- and middle-income countries (LMIC). Whilst clear guidelines exist for management of early-onset (< 34 weeks) and term (≥ 37 weeks) disease, the optimal timing of delivery in pre-eclampsia between 34^{+0} and 36^{+6} weeks is less clear. In a high-income setting, delivery may improve maternal outcomes without detriment to the baby, but this intervention is yet to be evaluated in LMIC.

Methods: The CRADLE-4 Trial is a non-masked, randomised controlled trial comparing planned early delivery (initiation of delivery within 48 h of randomisation) with routine care (expectant management) in women with pre-eclampsia between 34^{+0} and 36^{+6} weeks' gestation in India and Zambia. The primary objective is to establish whether a policy of planned early delivery can reduce adverse maternal outcomes, without increasing severe neonatal morbidity.

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Discussion: The World Health Organization recommends delivery for all women with pre-eclampsia from 37 weeks onwards, based on evidence showing clear maternal benefit without increased neonatal risk. Before 34 weeks, watchful waiting is preferred, with delivery recommended only when there is severe maternal or fetal compromise, due to the neonatal risks associated with early preterm delivery. Currently, there is a lack of guidance for clinicians managing women with pre-eclampsia between 34^{+0} and 36^{+6} weeks. Early delivery benefits the mother but may increase the need for neonatal unit admission in the infant (albeit without serious morbidity at this gestation). On the other hand, waiting to deliver may increase the risk of stillbirth, fetal growth restriction and hypoxic brain injury in the neonate as a result of severe maternal complications. This is especially true for LMIC where there is a higher prevalence of adverse events. The balance of risks and benefits therefore needs to be carefully assessed before making firm recommendations. This is the first trial evaluating the optimal timing of delivery in pre-eclampsia in LMIC, where resources and disease burden are considerably different.

Trial registration: ISRCTN 10672137. Registered on 28 November 2019.

Keywords: Pre-eclampsia, Hypertension, Pregnancy, Perinatal, Global health, Low- and middle-income countries

Background

Pre-eclampsia is a pregnancy-specific disorder which complicates 2–8% of pregnancies worldwide [1] and up to 12% of pregnancies in low- and middle-income countries [2]. Pre-eclampsia is responsible for 76,000 maternal deaths and 500,000 perinatal deaths each year [2] with the overwhelming majority (99%) of these occurring in Sub-Saharan Africa and South Asia [3].

Pre-eclampsia is a multi-system disorder. It arises due to inadequate perfusion of the uteroplacental unit, leading to hypoxic placental tissue and endothelial dysfunction. The resulting systemic vascular inflammation leads to widespread organ involvement in the mother as well as growth restriction and even stillbirth in the fetus [1]. Its clinical course is difficult to predict, and the development of symptoms is usually an indicator of end-stage organ damage. The only definitive management of pre-eclampsia is delivery of the dysfunctional placental unit—thereby ending the pregnancy. Given the progressive and unpredictable nature of the condition, timely intervention and delivery is key.

Delivery at 37 weeks onwards is recommended by the World Health Organization for all women with pre-eclampsia irrespective of disease severity [4]. Prior to 34 weeks (which is an important milestone for fetal lung maturity), expectant management is preferable due to the neonatal risks associated with early preterm birth [4]. Therefore, delivery before 34 weeks' gestation is usually only initiated if there are signs of severe maternal or fetal compromise.

Guidance on the optimal timing of delivery in late preterm pre-eclampsia (between 34^{+0} and 36^{+6} weeks' gestation) is less clear and is likely to be context dependent. In different settings, the risks and benefits of delivery may vary according to the prevalence and character of serious adverse events and the facilities available to manage them.

Currently, a policy of close surveillance is pursued until either 37 weeks' gestation is reached (at which point delivery is recommended) or an indication for immediate delivery (evidence of severe maternal or fetal compromise) develops. It is likely that planned early delivery would benefit the mother as this is the cure to the disease process; however, this must be balanced against any potential risks associated with late preterm delivery to the neonate.

In high-income settings, previous randomised controlled trials have shown that planned early delivery between 34^{+0} and 36^{+6} weeks' gestation in pre-eclampsia reduces the risk of severe complications in the woman [5–7]. An increase in neonatal unit admissions amongst infants in the planned delivery group has been reported, though serious neonatal morbidity remains uncommon at this gestation [5]. Planned early delivery has only been shown to increase respiratory distress syndrome in the neonate when the study population included women with gestational hypertension with a longer time to delivery interval in the usual care arm [6]. This and the fact that antenatal corticosteroid use was less prevalent in this study may explain the difference in neonatal respiratory morbidity between the two arms.

This question is yet to be evaluated in a low- and middle-income setting. Planned early delivery at this gestation may increase risk to the neonate given the lack of neonatal intensive care facilities. In addition, the availability of antenatal corticosteroids and indeed their impact on neonatal outcomes is yet to be fully evaluated in low- and middle-income countries [8, 9]. However, in settings where the disease burden and incidence of serious complications (in particular eclampsia, renal insufficiency, abruption and stillbirth) are related, in part, to inadequate surveillance and delayed intervention, planned early delivery may in fact confer even greater benefit for the woman and the infant to that seen in a

high-income setting. Severe disease in this setting implies time to delivery intervals will be shorter, and the benefit of removing maternal harm relatively greater than the risk of immaturity. Given the disproportionate number of maternal and perinatal deaths occurring in low- and middle-income countries, it is imperative that interventions designed to reduce mortality and morbidity are developed and tested within these settings, where their impact may be considerably different.

There is therefore a need to compare a policy of planned early delivery to expectant management for late preterm pre-eclampsia in low- and middle-income settings. This trial aims to establish whether planned early delivery in women with pre-eclampsia between 34^{+0} and 36^{+6} weeks' gestation can reduce adverse pregnancy outcomes in India and Zambia.

Methods/design

Trial objectives

The aim of this trial is to establish whether planned early delivery in pre-eclampsia between 34^{+0} and 36^{+6} weeks can reduce adverse pregnancy outcomes compared to expectant management in a low- and middle-income setting.

Primary objectives

The primary objectives of the study are:

1. To evaluate whether planned early delivery for women with pre-eclampsia between 34^{+0} and 36^{+6} weeks of gestation can reduce maternal mortality and morbidity based on a composite of outcomes during pregnancy and delivery, until primary hospital discharge.
2. To evaluate the impact of the intervention on short-term neonatal outcomes. These will be assessed based on a composite of stillbirth, neonatal death and neonatal unit admission for > 48 h due to neonatal morbidity, until primary hospital discharge.

Secondary objectives

The secondary objectives of the study are:

1. To evaluate the impact of the intervention on individual components of the primary outcomes and other secondary short-term outcomes for the mother and baby.
2. To evaluate the impact of the intervention on health resource use and cost.
3. To assess how the intervention influences the experiences of women.
4. To evaluate how the effectiveness of the intervention and its implementation is influenced by external factors (specifically resource availability and health system factors).

Trial design

This will be a pragmatic, multicentre, randomised controlled trial of planned delivery versus expectant management in 872 women with pre-eclampsia between 34^{+0} and 36^{+6} weeks of gestation inclusive.

Study setting

The trial will be conducted in five tertiary hospitals across India and Zambia, including their referring district healthcare facilities (sites listed on http://www.isrctn.com/ISRCTN10672137). An initial 6-month feasibility study was conducted across the proposed trial sites. This was a mixed-methods study consisting of semi-structured interviews with a cross-section of healthcare providers, focus group discussions with pregnant women and their relatives and a retrospective case notes audit evaluating gestation-specific maternal and neonatal outcomes in women with pre-eclampsia. The results of this feasibility study directly informed the development of the interventional phase protocol.

Recruitment is anticipated to take 22 months based on an assumption that approximately 45 participants will be recruited per month (across all sites), with some allowance for unforeseen events and centres recruiting slower than expected. Daily visits by the research team to the relevant clinical areas at each healthcare facility will ensure that all potentially eligible participants are screened. In addition to this, key personnel at each of the referring healthcare facilities will be provided with a basic mobile phone and airtime in order to facilitate referrals of potentially eligible participants. The development of culturally appropriate trial materials for both participants and key members of their household will help to engage and inform potential participants. Dissemination of trial posters and flowcharts will ensure that clinical staff are well informed and aware of trial procedures. If necessary, additional strategies to boost trial recruitment (such as additional sites or small financial incentives for clinical staff will be considered).

Selection and withdrawal of participants

Inclusion criteria

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

- Able to give valid written, informed consent
- Viable ongoing pregnancy at time of recruitment
- Clinical diagnosis of pre-eclampsia confirmed by the obstetric team: must fulfil minimum criteria of hypertension and proteinuria after 20 weeks'

gestation. Hypertension will be defined as a systolic blood pressure of ≥ 140 mmHg and/or a diastolic blood pressure of ≥ 90 mmHg (or on anti-hypertensive drug at enrolment). Proteinuria will be defined as a 'positive' (≥ 1 + protein) urine dipstick result [10].
- Gestational age between 34^{+0} and 36^{+6} confirmed by a doctor (as determined by known last menstrual period date validated by early or late ultrasound scan if available)

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

Exclusion criteria

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 (in the relevant local language) to women who meet the inclusion criteria (as above). Additionally, participant information videos in local languages have been developed to aid comprehension amongst both trial participants and their relatives. 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 member of the research team.

Study periods

A woman's participation in the study may be from 34 weeks' gestation until primary discharge of the woman and her baby after birth (Fig. 1). Long-term follow-up will be considered by obtaining permission to contact participants later, but only after further ethical approval and governance has been ascertained. Both the maternal and neonatal short-term outcomes will be collected quickly as the time period from randomisation to outcome collection will not exceed 14 weeks (participants will be followed up until primary discharge of mother and baby post-delivery) and in many cases will be less. Outcome collection will end 42 days after the final participant has been recruited (or sooner if primary discharge of mother and baby occurs before this endpoint).

Withdrawal of participants

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. For a woman allocated to the expectant management group, if clinical needs dictate delivery prior to 37 weeks' gestation based on local criteria, 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 be monitored by her attending clinician, this will not constitute withdrawal from the study.

Assessment of outcomes

Outcomes will be recorded on the web-based database after a review of case notes by trained members of the

Procedure	Screening	Randomisation	Delivery	Post-natal hospital discharge
Assessment of eligibility	x			
Informed Consent	x	x		
Baseline Data collection		x		
Decision regarding timing of delivery		x	x	
Data collection until discharge from hospital			x	x

Fig. 1 Schedule of participant enrolment, interventions and assessment in the trial (SPIRIT figure)

research team. This will be done contemporaneously and completed no later than 24 h after the mother and baby have been discharged. Confirmation of maternal and neonatal outcome data will be undertaken with an additional sign-off by the site's principal investigator for each participant and constant communication with the relevant clinical teams.

Co-primary outcomes

Primary short-term maternal outcome

Primary short-term maternal outcome will include maternal mortality and morbidity based on the miniPIERS composite [11] (see Table 1 for full list) of adverse maternal outcomes (with the addition of severe hypertension) during pregnancy and delivery until primary hospital discharge.

Primary short-term perinatal outcome

Primary short-term perinatal outcome will include composite of one or more of antenatal/intrapartum stillbirth or neonatal death (but not deaths due to congenital anomalies) or neonatal unit admissions > 48 h due to neonatal morbidity (necessitating admission to the neonatal unit according to local guidelines) until primary hospital discharge.

Secondary outcomes

Secondary maternal outcomes will include assessment of:

- Individual components of the primary outcome
- Mode of onset of birth (spontaneous, induced or pre-labour caesarean section)
- Primary indication for delivery in both arms

Table 1 Full definitions of individual components of the primary short-term maternal outcome

Outcome	Definition
Mortality	Maternal death occurring before primary discharge from hospital
Hepatic dysfunction	Elevated liver enzymes (alanine transaminase or aspartate transaminase ≥ 70 IU/L)
Hepatic hematoma or rupture	Blood collection under the hepatic capsule as confirmed by ultrasound or laparotomy
Glasgow coma score < 13	Based on GCS scoring system [12]
Stroke	Acute neurological event with deficits lasting longer than 48 h
Cortical blindness	Loss of visual acuity in the presence of intact pupillary response to light
Reversible ischaemic neurologic deficit (RIND)	Cerebral ischaemia lasting longer than 24 h but less than 48 h revealed through clinical examination
Retinal detachment	Separation of the inner layers of the retina from the underlying retinal pigment epithelium (RPE; choroid) and is diagnosed by ophthalmological exam
Acute renal insufficiency	For women with an underlying history of renal disease: defined as creatinine > 200 μM; for patients with no underlying renal disease: defined as creatinine > 150 μM
Dialysis	Including haemodialysis and peritoneal dialysis
Postpartum haemorrhage (PPH) requiring transfusion or hysterectomy	Occurrence of PPH that required transfusion or hysterectomy
Placental abruption	Any occurrence of abruption diagnosed clinically or based on placental pathology report
Platelet count < 50,000 without blood transfusion	Measurement of platelet count recorded as less than 50,000 without patient being given a blood transfusion
Transfusion of blood products	Includes transfusion of any units of blood products: fresh frozen plasma (FFP), platelets, red blood cells (RBCs), cryoprecipitate (cryo) or whole blood. Includes request for transfusion even if products unavailable at time of request.
Positive inotropic support	The use of vasopressors to maintain a systolic blood pressure > 90 mmHg or mean arterial pressure > 70 mmHg
Myocardial ischaemia/infarction	ECG changes (ST segment elevation or depression) with ischaemic symptoms with or without typical enzyme changes
Eclampsia	Any episode of seizure antepartum, intrapartum or before postpartum discharge as follow-up beyond discharge is not possible
Require > 50% oxygen for greater than 1 h	Oxygen given at greater than 50% concentration based on local criteria for longer than 1 h
Intubation other than for Caesarean section	Intubation may be by endotracheal tube insertion or continuous positive airway pressure
Severe breathing difficulty	Suspected pulmonary oedema where X-ray confirmation is unavailable may be diagnosed by presence of chest pain or dyspnoea, crackles in the lungs and SaO_2 < 90%
Pulmonary oedema	Clinical diagnosis with X-ray confirmation or requirement of diuretic treatment and SaO_2 < 95%
Severe hypertension	Systolic blood pressure of ≥ 160 mmHg between randomisation and post-delivery discharge

- Intensive care unit admission
- Length of stay in hospital (prior to delivery and after delivery)
- Time from randomisation to delivery (process outcome)
- Use of magnesium sulfate
- Use of antenatal corticosteroids for fetal lung maturity
- Use of anti-hypertensive medications

Secondary perinatal outcomes will include assessment of:

- Individual components of the primary outcome
- Mode of delivery (vaginal vs. all others)
- Gestational age at delivery
- Birthweight
- Birthweight centile
- Admissions to neonatal unit (and primary indication)
- Total number of nights in hospital and number of nights in each level of care for babies admitted
- Sepsis—with evidence of confirmed infection
- Course of antibiotics given for possible serious bacterial infection (according to the World Health Organization's Integrated Management of Childhood Illness (IMCI) guidelines) [13]
- Apgar score at 5 and 10 min post birth
- Need for neonatal resuscitation
- Hypoxic ischaemic encephalopathy and grade
- Neonatal seizures requiring anti-convulsants
- Respiratory distress syndrome
- Supplementary oxygen and duration required
- Use of continuous positive airway pressure ventilation and duration required
- Invasive ventilation support and duration required
- Administration of surfactant
- Hypoglycaemia (< 2.6 mmol) requiring intervention
- Hypothermia (temperature < 36.5 °C)
- Neonatal jaundice requiring phototherapy
- Necrotising enterocolitis (diagnosed at surgery or resulting in death)
- Nasogastric feeding required and indication
- Exclusively breast-fed at discharge from hospital

Trial procedures

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, in her preferred language). The local research team at each site are fluent in English and the relevant local languages spoken by the majority of the population across the trial sites (Bemba and Nyanja at the Zambian sites, Kannada at the Indian sites). The participant information leaflet will be read aloud to women who are unable to read it themselves. Partners and relatives will be included in the discussion but may not consent on the woman's behalf. Additionally, three short video clips addressing key topics (pre-eclampsia, trial participation and the neonatal unit) will be made available to all potentially eligible participants, particularly those with limited literacy. Written informed consent will be given using an informed consent form, completed, signed (thumbprints also accepted) and dated by the woman and signed by the member of the research team who obtained informed consent. After written informed consent has been obtained, a member of the research team will enter the baseline maternal details onto the online database and perform randomisation, communicating the results directly to the woman and her clinical team.

Antenatal, intrapartum and postpartum care will be in accordance with local guidelines and capacity at each site. Delivery will typically be through induction according to local protocol (most commonly oral or vaginal administration of misoprostol). The schedule of care for each group will be as follows:

Intervention (planned delivery) group

The intervention is planned delivery, to be undertaken as soon as feasible (aimed to be commenced within 48 h) after randomisation. Use of antenatal corticosteroids for fetal lung maturity will be at the discretion of the clinician, in accordance with local guidelines (confirmed as readily available across all facilities). Postnatal care will be in accordance with local protocols and guidelines.

Control (expectant management) group

Expectant management involves close monitoring of the maternal and fetal condition until the woman reaches 37 weeks, or a crisis develops necessitating delivery. Delivery is recommended if the woman develops severe pre-eclampsia. This is in accordance with the World Health Organization guidelines [4] which are followed at all of the proposed trial sites.

Time of delivery—adherence to protocol

Following randomisation to either the planned delivery group or expectant management group, the time of 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 protocol for both study groups to be reviewed and protocol deviations to be identified and investigated.

Sample size

The sample size for the CRADLE 4 study is calculated on the ability to detect a clinically important reduction in the primary maternal outcome: a short-term composite based on the presence of one or more of 22 maternal morbidities. Based on data acquired at the sites prior to start of the main trial, we anticipate an event rate of 80% for the primary maternal outcome in the expectant management arm. We have calculated that a sample size of 558 would provide 90% power to detect a 15% relative risk reduction. If the trial is recruiting well, we will continue to recruit 872 participants which would give 90% power to detect a 12.5% relative risk reduction and greater precision to detect secondary outcomes. The data monitoring committee (DMC) will review the primary event rate and usual safety data and make a recommendation to continue or stop. A one-sided non-inferiority analysis is planned for the primary neonatal composite. Our data acquired at the sites prior to starting the main trial showed an event rate of 24% for the primary neonatal outcome. Complete data on 480 women (240 per group) are required for 90% power to exclude a difference against planned delivery of 10% or more. To exclude a difference of 7.5%, 852 women (426 per group) are needed. The calculation uses a one-sided significance test and confidence interval and assumes that the true event rate is 24%. This is in line with the planned sample size as detailed above.

Randomisation

Randomisation will be managed by a secure web-based randomisation facility hosted by MedSciNet. The allocation ratio of intervention (planned early delivery) to control (expectant management) will be 1:1. Participants will be stratified by centre and minimised by parity (0 or ≥ 1), single/multi-fetal pregnancy (singleton or multi-fetal) and gestational age (34^{+0}–34^{+6}, 35^{+0}–35^{+6}, 36^{+0}–36^{+6}) at randomisation. MedSciNet will write the randomisation programme and hold the allocation code. Following randomisation, a clinician will then arrange for delivery or ongoing expectant management as the randomisation indicates.

Masking

Due to the nature of this study, masking of clinicians, nursing staff and participants is not possible. In view of arrangements for the conduct of the trial at these sites, it is not feasible to arrange for a separate team of outcome assessors masked to intervention allocation. Data analysis will be conducted masked to group allocation.

Data collection

Much of the outcome data for this trial are routinely recorded clinical items that can be obtained from the clinical notes. No additional blood or tissue samples are required for this study.

Outcomes will be recorded prospectively using case report forms (CRFs). When possible, online versions will be used (eCRFs) and outcomes therefore recorded directly on the trial database. If, due to power shortages or lack of internet connectivity, this is not feasible, paper case report forms will be used, and data then directly transcribed into the database.

Assessment of safety

The DMC will ensure the wellbeing of study participants and will periodically review study progress and outcomes as well as reports of unexpected serious adverse events (SAEs). The DMC will, if appropriate, make recommendations regarding continuance of the study or modification of the study protocol.

Adverse events

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

Serious adverse events

A serious adverse event is any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires participant hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity

Expected SAEs

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

The following events are expected in women with pre-eclampsia and their infants and will be recorded as part of outcome collection (during a woman's participation in the trial—from randomisation until primary hospital discharge of either mother or baby) but do not require reporting as SAEs.

Expected maternal SAEs

- Hepatic dysfunction
- Hepatic haematoma or rupture
- Coma/impaired consciousness (Glasgow coma score < 13)
- Maternal stroke

- Cortical blindness
- Reversible ischaemic neurological deficit
- Retinal detachment
- Acute renal insufficiency or failure
- Postpartum haemorrhage requiring transfusion or hysterectomy
- Placental abruption
- Platelet count < 50,000
- Severe uncontrolled hypertension
- Myocardial ischaemia/infarction
- Eclampsia
- Severe breathing difficulty
- Pulmonary oedema
- Sepsis
- Venous thrombo-embolism
- Admission to hospital for pregnancy and any related pregnancy complications
- Admission to ITU for pregnancy and any related pregnancy complications
- Any pregnancy-related complication requiring surgical management

Expected infant SAEs

- Congenital anomaly
- Low birth weight
- Requirement for supplemental oxygen or ventilation support
- Sepsis confirmed by positive cerebrospinal fluid or blood cultures
- Necrotising enterocolitis
- Seizures
- Hypoxic ischaemic encephalopathy
- Hypoglycaemia
- Admission to neonatal unit for any indication

Unexpected SAEs

An unexpected SAE is any event that meets the definition of a SAE and is not detailed in the list above as expected.

The following events, whilst not entirely unexpected in this population, are nevertheless serious enough that they should be reported. However, we anticipate that these will be more related to the disease process in this setting and not directly related to the intervention. With this in mind, they will be aggregated and reviewed on a 3-monthly basis by the DMC.

- Maternal death
- Neonatal death
- Antepartum or intrapartum stillbirth

Safety reporting procedures

All SAEs (described above) will be recorded from randomisation to postnatal discharge from hospital of mother and baby. Unexpected SAEs for both the mother and infant will be recorded and reported to the DMC as described above. Details of the SAE should be recorded on an SAE form (either electronically via the study database or in paper format). Paper forms will be emailed to the trial coordinating team. An SAE occurring to a participant will be reported to the research ethics committee that gave a favourable opinion of the study where in the opinion of the principal investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs will be submitted within 15 working days of the principal investigator becoming aware of the event, using the health research authority (HRA) report of serious adverse event form. All reported SAEs will be reviewed by the DMC at regular intervals throughout the study. The principal investigator will inform all investigators concerned of relevant information that could adversely affect the safety of participants.

Data 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 central trial research team 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.

Statistical analysis

The primary analysis for all maternal outcomes will be by the intention to treat principle with participants analysed in the groups to which they are assigned regardless of deviation from the protocol or intervention received. We will analyse the difference between arms in the randomisation to delivery interval (3 monthly) to ensure intervention compliance. Women in the expectant management arm will frequently be delivered prior to 37 weeks of gestation due to clinical need and this will not be considered a protocol deviation.

The primary analysis for all perinatal and infant outcomes will be both an intention to treat and a per-protocol analysis, since the hypothesis under examination for these outcomes is a non-inferiority hypothesis. The per-protocol analysis will exclude babies of women who do not receive the allocated intervention as per protocol and will be further defined in the statistical analysis plan.

All outcomes will be analysed adjusting for minimisation factors at randomisation where possible [14]. Where possible, continuous outcomes will be adjusted for baseline measurements of the same variable [15]. Binary

outcomes will be analysed using log binomial regression models. Results will be presented as adjusted risk ratios with associated confidence intervals (CI). If the model does not converge, logistic regression with robust variance estimation will be used [16]. Continuous outcomes will be analysed using linear regression models. Results will be presented as differences in means with associated CIs. 95% CIs will be presented for all primary outcomes and 99% CIs for secondary outcomes.

For the analysis of perinatal outcomes, we will treat all infants (singletons or multiples) separately, adjusting standard errors for clustering by mother. Prespecified subgroup analyses will be undertaken for gestation at randomisation (test for trend) and for single vs. multi-fetal pregnancy, country and region (with a region being tertiary centre and referring healthcare facilities). The consistency of the effect of planned delivery vs. expectant management across subgroups will be assessed using a likelihood ratio test for interaction. Loss to follow-up is expected to be about 5% for the short-term outcomes.

A secondary per-protocol analysis will look at the primary outcomes according to the treatment actually received and time of randomisation.

The primary maternal outcome is maternal mortality and morbidity based on miniPIERS [11] plus severe hypertension (Table 1) during pregnancy or before hospital discharge. The maternal mortality and morbidity component of the primary outcome will be reported separately, as will the severe hypertension component. Additionally, a maternal mortality and morbidity composite of components detected by a clinical diagnosis only will be reported separately (outlined in further detail in the statistical analysis plan).

Health care resource use will include information collected on the management of pre-eclampsia, maternal hospital length of stay related to pre-eclampsia and delivery, maternal intensive care unit admissions and perinatal neonatal unit admissions and hospital length of stay. Health care resource use will be costed using published sources and will be reported in United States Dollars (USD); costs will be reported in local currencies where possible. Mode of onset and mode of delivery will also be included in the costing. Means and standard deviations will be reported for health care resource items and costs. Linear regression and bootstrapping will be used to calculate the difference between treatment groups and 95% confidence intervals, adjusting for minimisation factors at randomisation.

End of trial

The end of the intervention phase will be when the last participating mother and infant have been discharged from hospital, or 42 days after the final participant has been recruited (whichever occurs sooner). For regulatory purposes, the end of the trial is defined as the date when the study database is locked. An end of study declaration will be made to the approving research ethics committees within 3 months of this date.

Early cessation

In the light of interim data and other evidence from relevant studies, the DMC will inform the trial steering committee (TSC) if, in its view, there is proof beyond reasonable doubt that the data indicate that the trial should be terminated. A decision to inform the TSC of such a finding will in part be based on statistical considerations.

Evaluation of women's experiences

A purposeful sample of participants will be approached for consent to a qualitative interview exploring their experience of the trial intervention (or usual care arm).

Evaluation of implementation

The impact of external factors (specifically resource availability and health system factors) on the effectiveness of the implementation of the intervention will be assessed by conducting an audit of key resources available at each participating healthcare facility at regular (6 monthly) intervals during the trial, which will be reported using descriptive statistics. A subgroup analysis of the main trial results by site will identify any meaningful variations by site, which may be influenced by local resource availability.

Data handling

Anonymised data be will collected by the local research team under the supervision of the trial coordinator.

When possible, all anonymised data will be directly entered onto a secure, online database (MedSciNet). If the low-resource nature of the environments where we will be collecting the data means this is not possible, the local research team will be trained to accurately transfer any paper-based data onto MedSciNet, whilst maintaining confidentiality always.

Consent forms and source data where paper based will be kept in files in secure areas at each central site. Only healthcare providers involved in trial participants' care, research assistants, the local trial coordinator and the UK-based trial manager will have access to these. All paper documents will be stored securely and kept in confidence in compliance with the UK Data Protection Act 1998.

All data entered on the MedSciNet database in each facility will be automatically stored and backed up. Collection and storage of clinical data in the database will be governed by the UK Data Protection Act 1998. All

participants will be given a unique trial identifier and no personal information will be entered into the clinical trial database or sample database. Personal contact information will be held on a local database kept in a locked environment, after gaining written informed consent from trial participants.

All MedSciNet data is stored on high-capacity servers that are operated by an external company. Servers are stored in locked rooms, with system monitoring 24 × 7, physical surveillance and surveillance cameras. A tape backup system is used for backing up the database.

The MedSciNet database will remain live for 1 year following completion of the main trial. A copy of this will then be kept on the KCL server for 20 years following the trial completion date, in accordance with the KCL Data retention schedule.

Discussion

Management of late preterm pre-eclampsia remains a challenging clinical scenario for clinicians around the world. Current evidence does not address those populations and contexts where the primary disease burden of pre-eclampsia lies. Whilst early-onset pre-eclampsia (before 34 weeks' gestation) is typically regarded as a more 'severe' phenotype of the condition, pre-eclampsia at 34 weeks' gestation onwards is responsible for significant maternal and perinatal morbidity [17]. This is particularly true in low-resource settings where delays in seeking appropriate care and suboptimal quality of care contribute to high rates of maternal and perinatal mortality [18]. Planned early delivery beyond 34 weeks has the potential to reduce serious maternal complications (such as stroke, eclampsia and death) as well as poor perinatal outcomes (such as severe growth restriction and stillbirth). Designing a trial protocol to evaluate this research question in a robust manner, whilst taking into consideration the reality of the trial environment, is challenging and highlights many of the wider barriers to maternal health in low- and middle-income countries. The feasibility phase identified several key issues which informed the design of the main trial protocol, for example, a lack of availability of first trimester ultrasound scanning impacting upon gestational age assessment and lack of laboratory reagents for performing routine kidney and liver function tests. Diagnostic criteria for pre-eclampsia and outcome definitions required adapting to suit the local context, taking into account limited diagnostic resources (e.g. radiology services) and facilities (e.g. neonatal intensive care). Our intervention, if shown to be beneficial, must be reproducible and feasible to implement within a real-world scenario. The inclusion of two diverse countries (India and Zambia) will produce results that are generalisable to similar settings. Furthermore, ensuring that the trial protocol and procedures reflect the reality of maternity care in a low- and middle-income setting is essential in order to produce findings that will be of importance to local, national and international policy makers.

Trial status

The current CRADLE-4 protocol is version 1.1 (14 November 2019). The trial opened to recruitment on 16 December 2019. The first participant was recruited on 19 December 2019. All trials sites were open by 24 January 2020. Recruitment is ongoing. We anticipate recruitment will be complete by 31 August 2021.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13063-020-04888-w.

Additional file 1. SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents.

Additional file 2. Model consent form (English version).

Additional file 3. Model participant information leaflet (English version).

Additional file 4. Statistical Analysis Plan.

Abbreviations

LMIC: Low- and middle-income countries; HIV: Human immunodeficiency virus; DMC: Data monitoring committee; TSC: Trial steering committee; SAE: Serious adverse event; CI: Confidence interval; ITU: Intensive care unit; PI: Principal investigator; Co-I: Co-investigator; PMG: Project management group; HRA: Health research authority; KCL: King's College London; REC: Research ethics committee

Acknowledgements

None.

Oversight committees

Project Management Group (PMG)
The Project Management Group will monitor the day-to-day running of the Trial and will meet on a regular basis (monthly) either in person or via teleconference.
Members of the PMG will include:
Prof Andrew Shennan (PI)
Prof Lucy Chappell (Co-I)
Prof Bellington Vwalika (Co-I)
Dr. Sebastian Chinkoyo (Co-I)
Dr. Alice Beardmore-Gray (Trial Coordinator)
Dr. Umesh Charantimath (Local trial Coordinator)
Dr. Geetanjali Katageri (Local trial Coordinator)
Trial Steering Committee (TSC)
The role of the TSC is to provide the overall supervision of the study. The TSC will monitor the progress of the study and conduct and advise on its scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the data monitoring committee (DMC) and ultimately carries the responsibility for deciding whether the trial needs to be stopped on grounds of efficacy. A TSC charter will be agreed at the first TSC meeting to document how the committee will operate.
Members of the TSC are as follows:
Prof Christine McArthur (Chair)
Dr. Cheryl Battersby
Dr. Francis Gidiri
Mr. Marcus Green
Ms. Rebecca Best
Dr. Jenny Myers
Data Monitoring Committee (DMC)
A DMC independent of the applicants and the TSC will review the progress of the trial at least annually and provide advice on the conduct of the trial to

the TSC. The committee will periodically review study progress and outcomes. The timings and content of the DMC reviews are detailed in a DMC Charter, which has been completed following the recommendations of the DAMOCLES study [19].
The appointed members of the Data Monitoring Committee (DMC) will be:
Prof Basky Thilanganathan (Chair)
Dr. Kelly Handley
Dr. Karen Luyt

Sponsor
The study is sponsored by King's College London (KCL). As sponsor, KCL has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research.

Authors' contributions
The protocol was drafted by AB. NV, LC and AS provided comments on the initial draft and on subsequent revisions. All authors have seen and approved the final version.

Funding
This trial is funded by the UK Medical Research Council in conjunction with the Indian Department of Biotechnology (project reference MR/R021376/1). The study sponsor and funding source have had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Availability of data and materials
King's College London will coordinate dissemination of the results from this trial. All publications using data from this trial to undertake original analyses will be submitted to the Trial Steering Committee for review before release. The research will be published in high-impact, peer-reviewed, scientific journals. More general dissemination of the results will be achieved through publication of summary findings. There are no commercial or intellectual rights issues that would delay publication of results. A writing committee drawn from the co-investigators, trial coordinators and others substantially involved in execution, analysis and interpretation will be named authors on the principal publications arising from the trial provided they meet the authorship criteria used by most high-impact peer-reviewed journals (see http://www.icmje.org). 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 in publications. 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. Given that the majority of participants in this trial will not speak English as a first language and may have limited literacy and computer literacy skills, extensive efforts will be made to disseminate key findings in local languages via community meetings at times convenient to trial participants and their families. 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. Requests for the final dataset can be made through the chief investigator in accordance with the data-sharing policies of King's College London, with input from the co-investigator group where applicable.

Ethics approval and consent to participate
The trial will be conducted according to the principles of the Declaration of Helsinki (October 2008) and all applicable regulatory requirements. The conduct of this study will be in full compliance with Good Clinical Practice. Copies of the protocol, participant information leaflet and informed consent form have been approved by national or institutional research ethics committees in both India and Zambia, and in the UK:
King's College London: HR-19/20-13535
University of Zambia: UNZA-301/2019
Bagalkot (India): SNMCIEC/1.1/2019-2020
Belagavi (India): KAHER/IEC/2019-20/D-251119016
The chief investigator or their delegate will submit and, where necessary, obtain approval from the relevant research ethics committee (REC) 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 member of the study team with delegated authority.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Publisher's Note

CRADLE-4: Statistical Analysis Plan

Title of clinical trial:	The CRADLE-4 Trial - Planned early delivery versus expectant management to reduce adverse pregnancy outcomes in pre-eclampsia in a low and middle-income setting.
Sponsor:	King's College London
Chief Investigator:	Professor Andrew Shennan
Senior Statistician:	Mr. Paul Seed
ISRCTN number:	ISRCTN 10672137
REC number:	King's College London: HR-19/20-13535 University of Zambia: UNZA-301/2019 Bagalkot (India): SNMCIEC/1.1/2019-2020 Belagavi (India): KAHER/IEC/2019-20/D-251119016
Version	1.0
Authors	Paul T Seed, Andrew Shennan, Lucy Chappell & Alice Beardmore-Gray

Final version approved by:

Name	Signature	Date
Andrew Shennan		29.07.2020
Paul Seed		29.07.2020

Table of Contents

1 STUDY SYNOPSIS

1.1 Synopsis

This is an individual patient randomised controlled trial which aims to establish the optimal timing of delivery in late preterm pre-eclampsia in a low and middle-income setting.

Pregnant women in India and Zambia with a confirmed diagnosis of pre-eclampsia between 34^{+0} and 36^{+6} weeks, not requiring immediate delivery, will be invited to take part. Following randomisation, they will be allocated to either planned early delivery (intervention arm) or expectant management (control arm). Maternal and infant outcome data will be collected until primary discharge from hospital.

Results will be reported according to the recommendations of the CONSORT group(1).

2 STUDY OBJECTIVES

2.1 Primary objectives

The aim of this trial is to establish whether planned early delivery in pre-eclampsia between 34^{+0} and 36^{+6} weeks can reduce adverse pregnancy outcomes compared to expectant management in a low and middle-income setting, without significantly increasing risk to the infant.

The primary objectives are:

1. Effectiveness: To evaluate whether planned early delivery for women with pre-eclampsia between 34^{+0} and 36^{+6} weeks of gestation can reduce maternal mortality and morbidity based on a composite of outcomes during pregnancy and delivery, until primary hospital discharge.

2. Safety: To evaluate the impact of the intervention on short term perinatal outcomes. These will be assessed based on a composite of one or more of stillbirth, neonatal death or neonatal unit admission for >48hrs due to neonatal morbidity, until primary hospital discharge.

2.2 Secondary objectives

The secondary objectives are:

1. To evaluate the impact of the intervention on individual components of the primary outcomes and other secondary short-term outcomes for the woman and baby
2. To evaluate the impact of the intervention on health resource use
3. To assess how the intervention influences the experiences of women and their families

4. To evaluate how the effectiveness of the intervention and its implementation is influenced by external factors - specifically resource availability and health system factors

3 STUDY METHODS

3.1 Trial design

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

Following an informed consent process, trial participants will be randomised via an online database (MedSciNet) to one of two treatment arms:

Intervention arm - planned early delivery (via induction of labour or caesarean section as appropriate) within 48hrs following randomisation.

Control arm - expectant management (according to local guidelines) until either 37 weeks' gestation is reached or an indication necessitating preterm delivery develops (as judged by the responsible clinician).

The allocation ratio of intervention (planned early delivery) to control (expectant management) will be 1:1. Participants will be stratified by centre and minimised by parity (0 or ≥1), single/multi-fetal pregnancy (singleton or multi-fetal) and gestational age (34^{+0}-34^{+6}, 35^{+0}-35^{+6}, 36^{+0}-36^{+6}) at randomisation. MedSciNet will write the randomisation programme and hold the allocation code.

Women and their infants will be followed up until their primary discharge from hospital.

3.2 Setting

The trial will be taking place across multiple urban and peri-urban sites in India and Zambia. There are central sites and referring healthcare facilities (a mixture of primary level hospitals and clinics). Trial sites will therefore comprise a mixture of CEmONC (comprehensive emergency obstetric and newborn care) and BEmONC (basic emergency obstetric and newborn care) facilities, with delivery rates ranging from 500-1000 per month at each of the central sites.

3.3 Inclusion and exclusion criteria

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

- Able to give valid written, informed consent

- Viable ongoing pregnancy at time of recruitment
- Clinical diagnosis of pre-eclampsia confirmed by the obstetric team: must fulfil minimum criteria of hypertension and proteinuria after 20 weeks' gestation. Hypertension will be defined as a systolic blood pressure of ≥ 140mmHg and/or a diastolic blood pressure of ≥90mmHg (or on anti-hypertensive drug at enrolment). Proteinuria will be defined as a 'positive' (≥ 1 + protein) urine dipstick result(2).
- Gestational age between 34^{+0} and 36^{+6} confirmed by a doctor (as determined by known LMP date validated by early or late ultrasound scan if available)

Exclusion Criteria:

Women will be ineligible if a decision to deliver within 48hrs has already been made by a senior clinician.

3.4 Comparative analysis population

3.4.1 Short term maternal outcomes

All women randomised will be included in the intention to treat (ITT) population, minus post-randomisation exclusions (see section 3.4.5).

3.4.2 Short-term perinatal outcomes

Since the hypothesis being tested for these outcomes is a non-inferiority hypothesis, both an ITT and per protocol (PP) analysis will be undertaken. The per protocol population will include the babies of all mothers randomised, minus post-randomisation exclusions (see section 3.4.5), minus those randomised in error and minus those who did not receive the allocated intervention (see section 3.4.3).

3.4.3 Protocol non-compliances

All protocol non compliances will be listed in the final report. Non compliances are defined below:

3.4.3.1 Major

The following will be defined as major protocol non-compliances:

- Data considered fraudulent

3.4.3.2 Minor

The following will be defined as minor protocol non-compliances:

Participants randomised in error

These include women:

- who are not between 34^{+0} and 36^{+6} weeks' gestation inclusive
- who do not have a clinical diagnosis of pre-eclampsia as defined in the inclusion criteria
- who do not have a viable fetus
- whose consent to take part has not been fully documented
- for whom a decision has already been made to deliver within the next 48 hours

Participants who do not receive allocated intervention

These include women:

- in the 'expectant management' arm who received non-indicated delivery prior to 37 weeks' gestation
- in the 'planned immediate delivery' arm who discontinued the intervention i.e. changed their mind after being randomised to 'planned immediate delivery' arm
- who were randomised to 'planned immediate delivery' but initiation of delivery is beyond 48 hours post-randomisation.

3.4.4 Descriptive analysis population

Baseline demographic and clinical characteristics will be reported for all women randomised excluding post-randomisation exclusions (see section 3.4.5).

3.4.5 Post randomisation exclusions

Exclusions to the analysis population post randomisation consist of the following:-

- Women for whom a consent form was not received

- Women for whom consent to use their data was withdrawn

  (Women can specify whether data collected up to the point of withdrawal can be used. If the response is 'No', then they will be considered post-randomisation exclusions. If the response is 'Yes', then they will be reported as 'missing' for any data not collected after withdrawal).

- Women for whom an entire record of fraudulent data was detected

  (Should fraudulent data be detected, consideration will be given to excluding all data for the site where such data was found).

The numbers (with percentages of the randomised population) of post-randomisation exclusions will be reported by randomised treatment group, and reasons summarised.

4 STUDY OUTCOMES

All outcomes are collected from trial randomisation to primary hospital discharge of the woman or infant (or 42 days post birth, whichever occurs sooner).

4.1 Primary outcomes

The co-primary short-term maternal outcome is:

Composite of maternal mortality and morbidity based on miniPIERS outcomes (3) with the addition of recorded systolic blood pressure ≥160mmHg (with or without medication) post randomisation. Individual components of the composite are listed in section 4.2.

The co-primary short-term perinatal outcome is:

Composite of one or more of the following: antenatal/intrapartum stillbirth or neonatal death (but not deaths due to congenital anomalies) or neonatal unit admission >48hrs due to neonatal morbidity (as defined by an indication for admission to the neonatal unit according to local tertiary hospital neonatal guidelines, provided in Appendix 1) until primary hospital discharge. Each neonate will be considered separately, with no double counting of outcomes.

4.2 Secondary outcomes (maternal)

Secondary short-term maternal outcomes

	Component of primary outcome	Component detected by a clinical diagnosis	Component detected using additional resources with variable availability	Tested
Number of women with maternal morbidity and mortality component of the primary outcome	Yes	N/A	N/A	Yes
Number of women with severe hypertension component of the primary outcome	Yes	N/A	N/A	Yes
Number of women with maternal morbidity and mortality composite of components detected by a clinical diagnosis only	Yes	Yes	No	Yes
Individual components of the primary outcome (non-exclusive):				

Maternal death	Yes	Yes	No	No
Hepatic hematoma or rupture	Yes	Yes	No	No
Glasgow coma score <13	Yes	Yes	No	No
Stroke	Yes	Yes	No	No
Cortical blindness	Yes	Yes	No	No
Reversible ischaemic neurological deficit	Yes	Yes	No	No
Retinal detachment	Yes	Yes	No	No
Postpartum haemorrhage requiring transfusion or hysterectomy	Yes	Yes	No	Yes
Placental abruption	Yes	Yes	No	Yes
Myocardial ischaemia/infarction	Yes	Yes	No	No
Eclampsia	Yes	Yes	No	Yes
Require >50% oxygen for greater than one hour	Yes	Yes	No	No
Severe breathing difficulty[ǂ]	Yes	Yes	No	No
Pulmonary oedema	Yes	Yes	No	No
Hepatic dysfunction	Yes	No	Yes	Yes*
Acute renal insufficiency	Yes	No	Yes	Yes*
Dialysis	Yes	No	Yes	No
Transfusion of blood products	Yes	No	Yes	No
Platelet count <50, 000 without blood transfusion	Yes	No	Yes	Yes*
Positive inotropic support	Yes	No	Yes	No
Intubation other than for caesarean section	Yes	No	Yes	No
Additional secondary outcomes:				
Length of stay in hospital (prior to delivery and after delivery)	No	N/A	N/A	Yes
Time from randomisation to delivery (process outcome)	No	N/A	N/A	Yes
Intensive care unit admission	No	N/A	N/A	No
Use of Magnesium Sulfate	No	N/A	N/A	No
Use of Antenatal Corticosteroids	No	N/A	N/A	No
Use of Antihypertensives	No	N/A	N/A	No
Time from randomisation to initiation of delivery	No	N/A	N/A	No
Mode of onset of birth (spontaneous, induced or pre-labour caesarean section)	No	NA	NA	No
Primary indication for delivery in both arms	No	NA	NA	No
Serious adverse events	No	NA	NA	No

* These will only be tested if missing data is <20% in both arms

4.3 Secondary outcomes (infant)

Tested:

- Individual components of the primary outcome:
    - Stillbirth
    - Neonatal death before primary hospital discharge*
    - Neonatal unit admission >48hrs due to neonatal morbidity

*Subject to a minimum pooled event rate of 5%.

- Mode of delivery (vaginal vs. all others)
- Respiratory support required
- Supplementary oxygen required
- Median gestational age at delivery
- Birthweight centile
- Birthweight centile less than tenth centile
- Admissions to neonatal unit
- Number of nights in neonatal unit (acute and sub-acute level of care) for babies admitted.
- APGAR score at 5 minutes post birth
- Neonatal resuscitation required

Not tested:

- Delivery before 37 weeks
- Median Birthweight (kg)
- Birthweight centile less than the third centile
- Hypoglycaemia requiring intervention
- Respiratory Distress Syndrome (RDS)
- Supplementary oxygen (Yes/No and duration)
- Continuous positive airways pressure (Yes/No and duration)
- Invasive ventilation support (Yes/No and duration)
- Primary indication for neonatal unit admission
- Sepsis - with evidence of confirmed infection
- Course of antibiotics given for Possible Serious Bacterial Infection (according to WHO's Integrated Management of Childhood Illness (IMCI) guidelines)
- Apgar score at 10 minutes post birth
- Hypoxic Ischaemic Encephalopathy and Grade
- Administration of surfactant
- Diagnosis of necrotising enterocolitis (diagnosed at surgery or resulting in death)
- Neonatal seizures requiring anti-convulsants
- Nasogastric feeding required and indication

- Hypothermia (Temperature <36.5 degrees Celsius)
- Neonatal jaundice requiring phototherapy
- Exclusively breast fed at discharge
- Serious adverse events

5 Health resource evaluation

A health economics analysis plan will be provided separately.

6 SAMPLE SIZE

Each country will use the same intervention and work to the same protocol. The sample size for the CRADLE 4 study is calculated on the ability to detect a clinically important reduction in the primary maternal outcome: a short-term composite based on the presence of one or more of 22 maternal morbidities.

Based on the data available from the CRADLE-4 Phase 1 Feasibility Study we anticipate an event rate of 80% in the expectant management arm. We have calculated that a sample size of 558 would provide 90% power to detect a 15% relative risk reduction. If the trial is recruiting well, we will continue to recruit 872 participants which would give 90% power to detect a 12.5% relative risk reduction and greater precision to detect secondary outcomes. The Data Monitoring Committee (DMC) will review the primary event rate and usual safety data and make a recommendation to continue or stop.

Relative risk reduction	Event rate (expectant management)	Event rate (planned delivery)	Sample size (women with complete data)	Recruitment target allowing for up to 10% loss to follow up
15%	80%	68%	558	620
12.5%	80%	70%	784	872

A one-sided non-inferiority analysis is planned for the primary perinatal composite. Our Phase 1 data suggests 54 neonatal events out of 234 deliveries (24.35%). Complete data on 480 women (240 per group) are required for 90% power to exclude a difference against planned delivery of 10% or more. To exclude a difference of 7.5%, 852 women (426 per group) are needed. The calculation uses a one-sided significance test and confidence interval and assumes that the true event rate is 24%, as in the Phase 1 Study. This is in line with the planned sample size as detailed above. There will be an additional analysis (subject to approval by the Trial Steering Committee) to test efficacy of the intervention on the primary perinatal outcome.

7 STATISTICAL METHODS

7.1 Intent-to-treat (ITT)

All analyses will be based on the intention-to-treat (ITT) principle, except as described in section 3.4.

7.2 Interim analyses

No formal interim analysis is planned. The Data Monitoring Committee (DMC) will review the primary event rate and usual safety data and make a recommendation to continue or stop. Stopping for efficacy will be based on the Haybittle-Peto principle that overwhelming evidence is needed in favour of one treatment option such that randomisation is no longer ethical.

7.3 Main analysis

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

For the analysis of perinatal outcomes, we will treat all infants (singletons or multiples) separately, adjusting standard errors for clustering by mother. Loss to follow-up is expected to be about 5% for the short-term outcomes.

A secondary per-protocol analysis will look at the primary perinatal outcomes according to the treatment actually received and time of randomisation (see section 3.4 for per-protocol population).

The primary maternal outcome will be reported as a composite of maternal morbidity and mortality, and severe hypertension. Individual components of the maternal morbidity composite will be further divided and reported separately as a maternal morbidity and mortality composite of components detected by a clinical diagnosis only.

7.3.1 Subgroup analysis

Pre-specified subgroup analyses will be undertaken for gestation at randomisation (test for trend) and for single vs. multi-fetal pregnancy, country and region (with a region being

tertiary centre and referring healthcare facilities). The consistency of the effect of planned delivery vs. expectant management across subgroups will be assessed using a likelihood ratio test for interaction.

7.3.2 Sensitivity analysis

A sensitivity analysis for the co-primary outcomes (maternal and perinatal) in those women whose delivery was initiated within 96hrs will be performed.

7.4 Methods for dealing with missing data, unused data and false data.

7.4.1 Missing data

We will follow a four-point framework for dealing with incomplete observations which will allow the correct method to be chosen and subsequently implemented(4).

1. Attempt to follow up all randomised participants, even if they withdraw from allocated treatment
2. Perform a main analysis of all observed data that is valid under a plausible assumption about the missing data. Specifically, we will assume data is missing at random (MAR). Under this assumption, imbalances between treatment groups due to dropout can be corrected by appropriate multiple regression models.
3. Perform a sensitivity analyses to explore the effect of departures from the assumption made in the main analysis. The MNAR (missing not at random) analysis will use the method of White et al.(4) as implemented in the Stata command rctmiss.
4. Account for all randomised participants, at least in the sensitivity analyses

This framework highlights the importance of using plausible assumptions with regards to the nature of the missing data. These assumptions will then be tested using appropriate sensitivity analyses on observed data using complete case analysis. For the purpose of the main analysis we will make the assumption that missing data is missing at random and the effect of the intervention is the same in those with and without the observations.

Furthermore, we will check whether or not there is an imbalance in the percentage of missing data within each treatment allocation.

7.4.2 False data

We will take all reasonable precautions to minimise the number of data errors. Everyone responsible for collecting data will be trained in the procedures to follow, as laid down in the trial protocol and handbook. All data entered will be checked by the trial coordinator when entered on the data base and again by the statistician at the time of analysis. Corrections will be made wherever possible. Fraudulent data is discussed in section 3.4.

7.5 Software

Analyses will be performed using Stata Version 16 or later (StataCorp, College Station, Texas, USA).

7.6 Statistical reporting conventions

Rounding: percentages will be presented to the nearest whole number. Averages, SD etc. of continuous measures will be given to 2 or (where appropriate) 3 significant figures. Arithmetic means (SD) presented for continuous variables which are approximately normally distributed; geometric means (SD) for log-Normal distributions. Medians (quartiles) otherwise.

Comparisons between treatment groups will be presented with 95% Confidence intervals, and standard errors.

P-values will be given to 2 significant figures or 3 decimal places, except where <0.0001 is appropriate. 95% Confidence Intervals used, and conventional significance will be taken at P<0.05.

8 SECONDARY OBJECTIVES (Qualitative data and healthcare facilities audit)

8.1 Qualitative data (secondary objective 3)

To assess how the intervention influences the experiences of women and their families:

- We will conduct in depth patient interviews with a purposeful sample of trial participants
- The qualitative data will be analysed using NVivo software and a thematic framework approach.

8.2 Audit of facilities (secondary objective 4)

To evaluate how the effectiveness of the intervention and its implementation is influenced by resource availability and external factors affecting the performance of the health system

- We will conduct facility level resources audit every 6 months during the trial
- The audit data will be reported using descriptive statistics only

9 REFERENCES

1. The Lancet. Consort 2010. Lancet. 2010;375(9721):1136.
2. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al. Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. Hypertension. 2018;72(1):24–43.
3. Payne BA, Hutcheon JA, Ansermino JM, Hall DR, Bhutta ZA, Bhutta SZ, et al. A Risk Prediction Model for the Assessment and Triage of Women with Hypertensive Disorders of Pregnancy in Low-Resourced Settings: The miniPIERS (Pre-eclampsia Integrated Estimate of RiSk) Multi-country Prospective Cohort Study. PLoS Med. 2014;11(1).
4. White IR, Horton NJ, Carpenter J, Pocock SJ. Strategy for intention to treat analysis in randomised trials with missing outcome data. Bmj. 2011;342(7803):910–2.

10 APPENDIX 1

Indications for admission to neonatal intensive care unit

- Weight less than 1.8kg
- In respiratory distress
- Temperature greater than 38 degrees Celsius
- Hypo-glycaemia unresponsive to feeds
- Macrosomic baby above 4kg
- All infants of diabetic mums
- Infants with meconium aspiration
- Infants with congenital anomalies
- Asphyxiated babies
- Babies with convulsions
- Babies with Jaundice
- Persistent vomiting
- All infants with a septic risk (PROM >18 hours, maternal UTI etc.)
- Hypothermia (temperature <36 degrees Celsius) unresponsive to warming by radiant warmer/KMC)

(according to the Neonatal Protocols of University Teaching Hospital, Lusaka, Zambia and approved by co-investigators at KLE Academy of Higher Education and Research, JNMC, Belagavi, Karnataka, India)