Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health 32 (2023) 35–42

Contents lists available at ScienceDirect

Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health

journal homepage: www.elsevier.com/locate/preghy

WILL (When to induce labour to limit risk in pregnancy hypertension): Protocol for a multicentre randomised trial

Katie Kirkham [a], Sue Tohill [b], Jennifer A. Hutcheon [c], Jon Dorling [d], Eleni Gkini [a], Catherine A Moakes [a], Clive Stubbs [a], Jim Thornton [e], Peter von Dadelszen [f,g], Laura A. Magee [f,g,*], the WILL Trial Study Group

[a] Birmingham Clinical Trials Unit, University of Birmingham, UK
[b] Maternity Services, Guy's and St Thomas' NHS Foundation Trust, London, UK
[c] Department of Obstetrics and Gynaecology, University of British Columbia, Canada
[d] Department of Paediatrics, University of Southampton, UK
[e] Department of Obstetrics and Gynaecology, University of Nottingham, UK
[f] Institute of Women and Children's Health, King's College London, UK
[g] Department of Women and Children's Health, School of Life Course Sciences, Faculty of Life Sciences and Medicine, King's College London, London, UK

ARTICLE INFO

Keywords:
Pregnancy
Hypertension
Timing of birth
Induction
Maternal outcomes
Perinatal outcomes

ABSTRACT

Objectives: To address optimal timing of birth for women with chronic or gestational hypertension who reach term and remain well.

Study design: Pragmatic, non-masked randomised trial. Inclusion: maternal age ≥16 years, chronic or gestational hypertension, singleton pregnancy, live fetus, 36^{+0}–37^{+6} weeks' gestation, and able to give documented informed consent. Exclusion: contraindication to either trial arm (e.g., pre-eclampsia or another indication for birth at term), blood pressure (BP) ≥ 160/110 mmHg until controlled, major fetal anomaly anticipated to require neonatal care unit admission, or participation in another timing of birth trial. Randomisation (1:1 ratio, minimised for key prognostic variables: site, hypertension type, and prior Caesarean) to 'planned early term birth at $38^{+0\text{-}3}$ weeks' or 'usual care at term' (revised from 'expectant care until at least 40^{+0} weeks', Aug 2022).

Outcomes: Maternal co-primary: composite of 'poor maternal outcome' (severe hypertension, maternal death, or maternal morbidity). Neonatal co-primary: neonatal care unit admission for ≥4 h. Each co-primary is measured until primary hospital discharge or 28 days post-birth (whichever is earlier). Key secondary: Caesarean birth.

Analysis: Sample of 1080 participants (540/arm) will detect an 8% reduction in the maternal co-primary (90% power, superiority hypothesis), and give 94% power for a between-group non-inferiority margin of difference of 9% in the neonatal co-primary. Analysis will be by intention-to-treat. Ethics approval has been obtained (NHS Health Research Authority London Fulham Research Ethics Committee, 18/LO/2033).

Conclusions: The study will provide data for women to make informed choices about their care and allow health systems to plan services.

1. Background

In the UK, up to 55,000 pregnancies/year are complicated by chronic hypertension (diagnosed before pregnancy or at <20 weeks' gestation) or gestational hypertension (diagnosed at ≥20 weeks), and half of these women will reach term gestational age (i.e., 37 weeks). Early term birth (at 37–38 weeks) may reduce maternal complications, Caesarean sections, and stillbirths, but it may also increase neonatal morbidity [1–3]. Expectant care may increase costs, related primarily to maternal and fetal surveillance [4]. There are no high-quality data on which to base clinical decision-making for timing of birth in hypertensive women. Current care at term involves maternal and fetal surveillance, and intervention for maternal morbidity or fetal compromise, either of which may be rapid or unexpected.

For timed birth in women with chronic or gestational hypertension, variation in guidelines and practice demonstrates clinical equipoise. The

* Corresponding author at: Becket House, 5th Floor, 1 Lambeth Palace Road, London, SE1 7EU, UK.
E-mail address: laura.a.magee@kcl.ac.uk (L.A. Magee).

https://doi.org/10.1016/j.preghy.2023.03.002
Received 10 January 2023; Received in revised form 23 February 2023; Accepted 17 March 2023
Available online 3 April 2023

National Institute for Health and Care Excellence (NICE), United Kingdom (UK), advises that timing of birth "be agreed between the woman and the senior obstetrician" [NG133 2019] [5]. The International Society for the Study of Hypertension in Pregnancy (ISSHP) states that timed birth may be offered from 37^{+0} weeks for women with gestational hypertension and 38^{+0} weeks for those with chronic hypertension (weak recommendations), but if women reach 40^{+0} weeks, they should be offered initiation of birth (strong recommendation) [6].

There are currently no definitive trials to establish how best to manage women with chronic or gestational hypertension who reach 37 weeks and remain well, without an indication for birth; yet, these women represent 1/3rd of all women with pregnancy hypertension. There are limited relevant data from five trials (1,819 women) in the 2017 Cochrane review [7]; the vast majority of these women either had proteinuric pre-eclampsia, or were randomised at earlier or later gestational ages than 37 weeks (or both). An additional trial of 100 women with gestational hypertension was similar to HYPITAT I, but was not prospectively registered [8] While these studies suggest that earlier birth at term may be beneficial to women with chronic or gestational hypertension, without increasing risk to babies, the number of women enrolled were small or the trials were conducted in settings (e.g., Egypt) where antenatal care differs to the UK, including less frequent use of antihypertensive medication [9,10].

WILL aims to address optimal timing of birth for women with chronic or gestational hypertension who reach term gestational age and are otherwise well.

2. Methods

This article is based on the current protocol V4.0 (25 May 2022), approved by the NHS Health Research Authority London Fulham Research Ethics Committee (reference 18/LO/2033).

2.1. Trial design and setting

WILL is a pragmatic, two-arm, parallel-group, open-label, multicentre, randomised controlled trial (with a nine-month internal pilot), with two co-primary outcomes: a maternal composite outcome assessing superiority and a neonatal outcome assessing non-inferiority. Participants are recruited from National Health Service (NHS) consultant-led maternity units in the UK.

The nine-month internal pilot was undertaken in 20 centres chosen to be representative of sites overall (e.g. number of births and region) to test trial processes prior to all centres opening. 'Stop-go' criteria (predefined in the study protocol) assessed the proportion of women randomised of those who gave consent to participate, recruitment rate relative to the overall target, and randomisation and birth at $<38^{+0}$ weeks of those who gave consent, as well as the median between-group difference in gestational age at birth (**Table S2**). These criteria were reviewed by the Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) in a joint meeting held at the end of the pilot period; it was recommended that the trial continue.

2.2. Participants

Inclusion criteria are: Maternal age ≥16 years, chronic or gestational hypertension, gestational age 36^{+0}–37^{+6} weeks inclusive, singleton pregnancy, live fetus, and able to give documented informed consent to participate.

Exclusion criteria are: contraindication to either trial arm (e.g., evidence of pre-eclampsia); severe hypertension [i.e., blood pressure (BP) ≥ 160 mmHg systolic or ≥110 mmHg diastolic] until BP falls below this level (i.e. is 'controlled'); major fetal anomaly anticipated to require neonatal unit admission; or participation in another timing of birth trial. Of note, neither maternal co-morbidities (e.g. gestational diabetes) nor fetal size are exclusion criteria, although pre-randomisation ultrasound was not mandatory.

Ideally, women learn about WILL early in pregnancy. However, eligibility is confirmed and consent for randomisation given at 36^{+0}-37^{+6} weeks, usually at their routine antenatal visit, to minimise enrolment of women (estimated to number ≈18%) [11] who may develop an indication for birth (e.g., pre-eclampsia) or go into spontaneous labour prior to $38^{+0\text{-}3}$ weeks.

If the woman agrees to participate, documented consent is obtained by the research midwife or medically-qualified member of the obstetric team prior to randomisation. To facilitate recruitment when in-person consent is not possible or desirable, remote documented consent may be undertaken. Informed consent discussions may proceed by telephone or videoconference, and the details are recorded. Women may either sign a copy of the consent that was sent to her (and return a copy to the trial team), or give verbal permission for the midwife/obstetrician to sign the consent, with this witnessed, with a copy of the consent sent to the woman thereafter.

2.3. After consent, baseline data are collected.

If women consent to participate between 36^{+0} and 36^{+6} weeks gestational age, they are then re-contacted by the research midwife between 37^{+0} and 37^{+6} weeks, by phone or in person, to confirm that they 'remain well' (i.e., have no new symptoms of pre-eclampsia, have acceptable BP according to her care-provider, and report no change in fetal movement pattern), and no new plans have been made for birth (that would preclude randomisation into either trial arm). Women who remain eligible, re-confirm their consent and are randomised. Women who are not randomised have a minimal dataset collected, focussed on the co-primary and key secondary outcomes.

Consent and randomisation usually occur simultaneously if the woman provides consent to participate between 37^{+0} and 37^{+6} weeks' gestational age.

2.4. Randomisation

Randomisation is provided by a central computerised randomisation service at the Birmingham Clinical Trials Unit (BCTU), available by a secure online randomisation system (24 h/day) or by telephone (during working hours).

Randomisation is in a 1:1 ratio and uses a minimisation algorithm to ensure balance in treatment allocation for key prognostic variables: recruiting site, hypertension type (chronic or gestational hypertension), and prior Caesarean (yes/no). A 'random element' is included in the algorithm, so that each woman has a probability (unspecified here), of being randomised to the opposite intervention that they would have otherwise received. To avoid bias, the random allocation sequence is concealed from those responsible for recruiting women into the study.

2.5. Intervention

Randomisation is to 'planned early term birth at $38^{+0\text{-}3}$ weeks' or 'usual care at term'. WILL compares clinical interventions that cannot be masked.

In the intervention arm (planned early term birth at $38^{+0\text{-}3}$ weeks' gestation), birth can be initiated by labour induction or elective Caesarean, according to local protocols and procedures.

The control arm was changed to 'usual care at term' from 'expectant care until at least 40^{+0} weeks' from 11 August 2022, as approved by the TSC and funder. The change was made to reflect a change in clinical practice; underlying this change was the ARRIVE and similar trials (showing the benefit of labour induction for nulliparous women at 39 weeks) [12,13], greater use of timed birth during the pandemic [14], and a suggestion in draft (but not final) UK NICE labour induction guidelines that timed birth at 39 weeks may be appropriate for women at increased risk of complications at term gestational age [NG207] [15].

Care in the control arm involves maternal and fetal surveillance (clinical, laboratory, and/or ultrasonographic) and management (e.g., antihypertensive therapy), as an integrated package of care based on current NICE NG133 care pathways [NG133] and standard departmental policy, as below.

Women in both groups undergo maternal and fetal surveillance, according to national guidance [NG133] [5]. Women are reminded to report, between and at routine antenatal visits, new symptoms consistent with abruption (abdominal pain, vaginal bleeding, and decreased fetal movement) or possible pre-eclampsia. Clinical concerns should be investigated by maternal proteinuria testing, relevant blood tests for pre-eclampsia, fetal cardiotocography, and fetal ultrasound, as appropriate. Target BP should be ≤135/85 mmHg. Maternal indications for birth are: (i) sustained systolic BP ≥ 160 mmHg or diastolic BP ≥ 110 mmHg for at least 4 h despite antihypertensive therapy; (ii) development of pre-eclampsia, eclampsia, abruption, or another complication of hypertensive pregnancy (e.g., pulmonary oedema), including abnormal haematologic or biochemical parameters; or (iii) other obstetric complications. Fetal indications for birth include: (i) abnormal cardiotocography; (ii) intrauterine fetal growth restriction or oligohydramnios (local criteria); (iii) abnormal umbilical artery Doppler velocimetry; or (iv) stillbirth. Balance between groups in centre-related practices should be achieved by minimisation of randomisation by centre. Data are collected on potential co-interventions, such as: number and type of outpatient antenatal visits, hospitalisation or bedrest, home BP monitoring, antihypertensive therapy, maternal blood and urine testing, and tests of fetal well-being.

2.6. Adherence

It is possible that women in either the intervention or control arms may have birth initiated at times different to which they were assigned. Reasons for this are documented, as are methods of birth initiation (i.e., labour induction or elective Caesarean).

Adherence is defined as timing of birth initiation that is consistent with the allocated group or a result of either spontaneous onset of labour or birth for clinical need. Reasons for non-adherence in the intervention ('planned early term birth') group include: busy hospital induction or theatre schedules, women's preference, or clinicians' preference; reasons do not include spontaneous onset of labour or birth for clinical need before 38^{+0} weeks. In the control arm, when phrased as 'expectant care at term until at least 40^{+0} weeks', reasons for non-adherence included initiation of birth before 40^{+0} weeks because of clinician's or women's preferences; reasons did not include spontaneous onset of labour or birth for clinical need before 40^{+0} weeks. With the revision of the control arm to 'usual care at term', adherence will no longer be measured as a binary outcome in this arm. However, throughout the trial, adherence in intervention and control arms is monitored by gestational age at initiation of birth and reported to individual centres to maximise the between-group difference in gestational age at birth, targeted to be at least seven days.

2.7. Follow-up

After birth, women are followed-up to a maximum of six weeks postpartum. They are asked to complete two questionnaires for assessment of: (i) maternal satisfaction with the intervention, and (ii) any post-discharge maternal or neonatal morbidity (as below). Participants may discontinue participation in the trial at any time. Reasons are documented and wishes clarified regarding use of previously-collected data and ongoing data collection.

2.8. Outcomes

The maternal co-primary outcome is a composite of poor maternal outcome until primary hospital discharge home or 28 days after birth (whichever is earlier), specified as severe hypertension, maternal death, or maternal morbidity, adapted from Delphi consensus in hypertensive pregnancy [16,17] (Table 1**)**. There is local site principal investigator (PI)/delegate sign-off based on review, masked to allocated group, of primary case notes. Should the local PI have been involved in the care of

Table 1
Trial maternal co-primary outcome, as assessed from randomisation until primary hospital discharge home or 28 days after birth (whichever is earlier)*.

One/more of:	Definition
Severe hypertension	Systolic BP ≥ 160 mmHg or diastolic BP ≥ 110 mmHg, measured twice, 15 min apart
Maternal death	As stated, irrespective of the cause
Maternal morbidity, defined as one or more of the following:	
GCS < 13	–
Stroke	Acute symptoms of focal brain injury that have lasted >24 h, with type (ischaemic or haemorrhage) confirmed by neuroimaging
TIA	Acute symptoms of focal brain injury that have lasted <24 h
Eclampsia	Onset of convulsions in a woman with pre-eclampsia, and not attributable to other causes
Blindness	Partial/complete, or either retinal or cortical. Retinal detachment is defined as the peeling away of the retina from its underlying layer of support tissue diagnosed by ophthalmological exam. Cortical blindness is defined as loss of visual acuity in the presence of intact pupillary response to light.
Uncontrolled hypertension	Hypertension requiring administration of 3 or more different parenteral [intravenous or intramuscular] antihypertensive agents within a 12 h period
Inotropic support	Use of vasopressors to keep sBP > 90 mm Hg or a MAP > 70 mmHg
Pulmonary oedema	Excess fluid in the lungs diagnosed clinically with one/more of oxygen saturation < 95%, directive treatment (e.g., diuretic therapy), or x-ray confirmation)
Respiratory failure	Intubation, ventilation by endotracheal tube or non-invasively, or need for > 50% oxygen for > 1 hr, not due to Caesarean delivery
SpO2 < 90%	–
Myocardial ischaemia or infarction	By characteristic ECG changes and markers of myocardial necrosis
Hepatic dysfunction	INR > 1.2 in absence of DIC or treatment with warfarin, or, in the presence of DIC or treatment with warfarin: either mixed hyperbilirubinemia > 1.0 mg/dL (or > 17 μM) or hypoglycaemia < 45 mg/dL (<2.5 mM) in absence of insulin
Hepatic haematoma or rupture	Presence of a blood collection under the hepatic capsule as confirmed by imaging or at laparotomy
Acute kidney injury or dialysis	One/more of: serum creatinine >150 μM in absence of a baseline serum creatinine; rise in serum creatinine ≥ 26 μM within 48 h; >50% rise in serum creatinine within the past 7 days; urine output < 0.5 ml/kg/hr for >6hr); or new dialysis (of any type)
Platelet count < 50×10^9/L	–
Transfusion	Of any blood product
Placental abruption	Diagnosed either: (i) clinically, by abdominal pain or uterine contractions of sudden onset with one/more of: vaginal bleeding other than show, intrauterine fetal death or DIC; or (ii) by presence of a retroplacental clot at time of delivery; or (iii) by placental pathology demonstrating retroplacental clot or histological findings of a chronic abruption

BP (blood pressure), DIC (disseminated intravascular coagulation), ECG (electrocardiogram), GCS (Glasgow Coma Scale), MAP (mean arterial pressure), sBP (systolic blood pressure), SpO2 (peripheral arterial oxygen saturation), TIA (transient ischaemic attack).
*For women who were consented but not randomised, the co-primary outcomes were assessed from consent (rather than randomisation).

the woman, they arrange for a designate to undertake sign-off.

The neonatal co-primary outcome is neonatal care unit admission for ≥4 h, until primary hospital discharge home or 28 days after birth (whichever is earlier) [18]. Neonatal admission is to any of the following types of units, according to definitions provided in the British Association of Perinatal Medicine 2011 classification of neonatal care: (i) intensive care, provided for babies who are the most unwell or unstable and have the greatest needs in relation to staff skills and staff to patient ratios; (ii) high-dependency care, provided for babies who require highly skilled staff, but where the ratio of nurse to patient is less than intensive care; and (iii) special care, provided for babies who require additional care delivered by the neonatal service, but do not require either intensive or high-dependency care; 'transitional care' is not included, because the baby receives care with the mother.

Secondary outcomes are assessed until primary discharge home or 28 days after birth, whichever is earlier, unless otherwise specified. Secondary outcomes (Table 2) include: Caesarean birth, individual components of the primary outcome, pre-eclampsia, potential co-interventions, maternal intensive care unit admission, maternal satisfaction, other neonatal outcomes (e.g., stillbirth and neonatal death) and health economics.

Women's satisfaction with the intervention and trial participation is evaluated according to the Childbirth Experience Questionnaire, a 22-item self-administered questionnaire validated in the UK [20]. Higher scales reflect greater satisfaction, as do higher domain scores that cover own capacity (8 items), professional support (5 items), perceived safety (6 items), and participation (3 items).

Participants are followed to six weeks postpartum, when any post-discharge maternal morbidity (to six weeks postpartum) or neonatal morbidity (to 28 days after birth) is assessed via an online, text-based questionnaire, unless the woman has requested a phone call from site staff to complete the questions. Morbidity information is collected directly from the mother for her and her baby, unless *either* is known to have died, *both* are known to have experienced the primary outcome prior to hospital discharge, or the *mother* has become incapacitated to such an extent that she is unable to complete the questionnaire. We have modified the relevant Control of Hypertension In Pregnancy (CHIPS) trial questionnaire [21], previously NRES-approved (2009–12), for administration by text message or online through an encrypted service provided by TextLocal (https://www.textlocal.com), or by post or phone, if necessary. If we are unable to contact mothers directly, information is requested of the general practitioner, if consent to do so were provided by the woman.

If the woman gave consent to long-term follow up of her and her baby, then their study data may, in future, be linked with other routinely-collected health, educational, or social data, to learn more about the impact of planned timing of birth on long-term health.

If women gave consent to trial participation (at 36^{+0}-37^{+6} weeks) but were not randomised (possible only at $37^{+0\text{-}6}$ weeks), data on the maternal and neonatal co-primary outcomes, Caesarean birth, and other secondary outcomes (other than satisfaction) will be collected only to hospital discharge.

Fig. 1 presents the Trial Schema.

2.9. Adverse events

Due to the high incidence of adverse events (AEs) routinely expected in this patient population (e.g. abnormal laboratory findings and new symptoms), AEs will be reported via case report forms and captured via pre-defined outcome measures.

A serious AE (SAE) is any AE that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, may jeopardise the pregnancy, or may require intervention to prevent one of the other outcomes listed above. SAEs are reported up to six weeks after birth, and classified as 'protocol-exempt and expected' (given the high-risk nature

Table 2
Secondary outcomes: maternal, fetal/neonatal, and health economic.

Maternal
Caesarean delivery (key maternal)
Instrumental vaginal delivery or Caesarean delivery (vs. spontaneous vaginal delivery), with indications
Infection of the caesarean wound, episiotomy, or vaginal tear, as applicable, at six weeks postpartum
Individual components of maternal co-primary outcome (as defined in Table 1), up to discharge or 28 days postpartum (whichever is earlier)
Poor maternal outcome (assessed as one or more of the components of the maternal co-primary outcome) measured at six weeks postpartum (as assessed post-discharge after birth by maternal questionnaire)
Elevated liver enzymes (AST or ALT > 40 IU/L)
Platelet count < $100x10^9$/L
Pre-eclampsia by ISSHP 2018 criteria*[6]
PPH (perceived abnormal bleeding following birth and either hypotension or medical/surgical intervention for postpartum haemorrhage)
Sepsis (known or suspected maternal infection with two or more of Quick Sequential Organ Failure Assessment criteria: respiratory rate ≥ 22/min, altered mentation, or systolic BP ≤ 100 mmHg)
ITU admission (to receive advanced respiratory support alone or monitoring and support for two or more organ systems)
Potential co-interventions (post-randomisation), before birth admission unless otherwise specified:
Antihypertensive therapy taken and type (antepartum, postpartum, or at either time point)
Magnesium sulphate (antepartum or postpartum)
Bedrest at home
Use of home BP monitoring
Maternal blood or urine testing at the laboratory prior to birth admission, and number of such episodes of testing (median [IQR])
Seen as outpatient (in office/clinic) and number of visits (median [IQR])
Seen as outpatient (in her home) and number of visits (median [IQR])
Where available, seen in medical, day, or maternity assessment unit and number of visits (median [IQR])
Seen in an acute care area (such as Accident & Emergency) for urgent/emergent visit other than in labour and number of such visits (median [IQR])
Number of antenatal admission days prior to birth (median [IQR])
Underwent fetal cardiotocography
Underwent fetal ultrasound
Clinical indications for birth
Maternal satisfaction assessed at hospital discharge or 28 days postpartum (whichever is earlier), as measured by the Childbirth Experience Questionnaire, assessed as the overall score, and domain scores (i.e., own capacity, professional support, perceived safety, and participation)[20]
Fetal/neonatal
Neonatal care unit admission ≥4 h assessed to 28 days after birth
Indication for neonatal care unit admission for ≥4 h as a respiratory problem, as identified by the clinical team by the principle indication for admission on the BadgerNet discharge summary (with the clinical diagnosis presented descriptively, as meconium aspiration syndrome, pneumonia, pneumothorax/pneumomediastinum, transient tachypnoea of the newborn, or 'other' [specified])
Other indications, as identified clinically, will be presented descriptively (e.g., 5-min Apgar score < 7, birthweight < 10th centile, birthweight > 90th centile, sepsis work-up, hyper- or hypo-glycaemia, or other)
Respiratory morbidity, defined as the need for supplemental oxygen and/or positive pressure ventilation beyond the initial resuscitation period
Clinical respiratory problem, defined as meconium aspiration syndrome, pneumonia, pneumothorax/pneumomediastinum, transient tachypnoea of newborn, or other [unspecified])
Chest x-ray, N performed, N abnormal and nature of abnormality (i.e., meconium aspiration syndrome, pneumonia, pneumothorax/pneumomediastinum, transient tachypnoea of newborn, or other [unspecified])
HIE, defined as therapeutic hypothermia for ≥ 72 h
Sepsis requiring antibiotics for at least five days, with confirmed blood or cerebrospinal fluid culture
Major operation (laparotomy, thoracotomy, craniotomy, or other)
Birthweight
Apgar scores (recorded at 1, 5, and 10 min)
Stillbirth (i.e., death of a fetus after randomisation)
Neonatal death (of a liveborn infant within the first 28 days of birth)
Breastfeeding established assessed at hospital discharge or 28 days postpartum (whichever is earlier)
Exclusive breastfeeding assessed at hospital discharge or 28 days postpartum (whichever is earlier)

(*continued on next page*)

Table 2 (*continued*)

Maternal
Health economic
Cost-consequence analysis from NHS perspective (enrolment to hospital discharge)

BP (blood pressure), ITU (intensive care unit), PPH (postpartum haemorrhage), AST or ALT (aspartate aminotransferase or alanine aminotransferase), GCS (Glasgow Coma Scale), DIC (Disseminated Intravascular Coagulation), IQR (Inter Quartile Range), HIE (Hypoxic Ischaemic Encephalopathy), NHS (National Health Service).

*Pre-eclampsia is defined by ISSHP 2018 criteria [6], as chronic or gestational hypertension with development of one or more of the following new-onset conditions at ≥20 weeks: (i) proteinuria; (ii) serum creatinine ≥90 μM; (iii) elevated AST or ALT to >40 IU/L; (iv) neurological complications including eclampsia, altered mental status [as measured by GCS < 13], blindness, stroke, clonus, severe headache, persistent visual scotomata); (iv) haematological complications (i.e., platelet count < 150x109/L, DIC, haemolysis); or (v) uteroplacental dysfunction (including fetal growth restriction defined as birthweight < 10th centile presented descriptively [19], abnormal umbilical artery Doppler waveform analysis, or stillbirth).

of women enrolled in WILL), 'protocol-exempt and unrelated to the intervention' (as the serious nature of the event is related to the woman's routine care), or 'expeditable'; for details, see **Table S3**. Protocol-exempt SAEs must be recorded in the medical notes, but expeditable SAEs also require completion of an SAE form and reporting to the WILL trial office within 24 h of the site becoming aware of the event.

2.10. Data management

Electronic case report forms, with programmed range checks, are entered online at https://www.trials.bham.ac.uk/WILL. Authorised staff require an individual secure login username and password to access online data entry. All missing and ambiguous data are queried through the online system. The security of the System is governed by the policies of the University of Birmingham (Data Protection Registration number Z6195856), and each study site has arrangements in place for secure storage and processing of study data, in compliance with the University of Birmingham policies. The University carries appropriate Data Protection Registration coverage.

2.11. Sample size

1,080 women (540 per group) will be required to detect an 8% reduction in the maternal co-primary outcome, from 25% to 17% (RR 0.68; estimate of 25% based on women who experienced poor maternal outcome at term in the CHIPS Trial [21] [unpublished data]), assuming 90% power, a two-sided type I error rate of 5%, and using the standard method of difference between proportions, based on a superiority hypothesis.

Assuming a control group (usual care at term) incidence of our neonatal co-primary (safety) outcome of 23% (likely dominated by severe hypertension), a sample size of 1,080 will achieve 94% power to provide a non-inferiority margin of difference in incidence between groups of 9% (i.e., the upper bound of the 95% confidence interval [CI] is <9%), and 88% power to provide a margin of 8% (one-sided 2.5% type I error rate, non-inferiority hypothesis).

This sample size will detect a 10% decrease in Caesarean birth, assuming a control group risk of 45% (45% to 35%; 90% power; 5% type I error rate, superiority hypothesis), as previously observed [HYPITAT I] [9]. In this way, women and clinicians will have the information that they require (about complications for them and their babies, and Caesarean birth) to make informed decisions about care.

There is no single minimum clinically important difference in maternal or perinatal outcomes that is likely to influence all clinicians. The anticipated relative risk reduction in our maternal co-primary outcome was chosen because a similar reduction was seen in the HYPITAT I trial, and this effect size was shown to be of sufficient magnitude to change clinical practice in the Netherlands [22,23]. The incidence in the control group of our neonatal co-primary (safety) outcome of high-level neonatal care for ≥4hr is based on a rate of 23% in HYPITAT.

Given the short time between consent (at 36^{+0}-37^{+6} weeks), randomisation (at 37^{+0-6} weeks), and birth (by 41^{+6} weeks, even in the usual care arm), no adjustment has been made for loss to follow-up or drop-outs.

2.12. Statistical methods

To maintain the rigour of randomisation, primary analyses will be based on the intention-to-treat (ITT) principle, for the maternal co-primary (on a superiority hypothesis), neonatal co-primary (on a non-inferiority hypothesis), and all secondary outcomes. Estimates of between-group differences will be presented with two-sided 95% confidence intervals (CIs), adjusted for the minimisation variables [24]. No adjustment for multiple comparisons will be made. The maternal and neonatal co-primary outcomes will be summarised by treatment group using frequencies and percentages. Log-binomial models will be used to generate risk ratios (95% CIs), and adjusted risk differences (95% CIs) presented [25]. For the maternal co-primary, the p-value relating to the treatment group parameter (as generated by the model) will be presented. For the neonatal co-primary, non-inferiority will be assessed based on the upper limit of the 95% CI; no p-value will be presented. Binary secondary outcomes will be analysed as for the neonatal co-primary. Continuous outcomes deemed to be normally distributed will be summarised using means and standard deviations, and a linear model will be fitted to generate adjusted mean differences (95% CIs). Continuous outcomes not deemed to be normally distributed will be summarised using medians and interquartile ranges and unadjusted differences in medians (95% CI) produced.

Subgroup analyses will be limited to the co-primary outcomes and undertaken on: (i) variables used in the minimisation algorithm, with the exception of recruiting centre; and (ii) other variables of prognostic significance, pre-specified as: ethnicity, body mass index, prior severe hypertension in the index pregnancy, or any of the following at randomisation: antihypertensive therapy, gestational diabetes mellitus, or smoking. Tests for statistical heterogeneity (e.g., by including the treatment group by subgroup interaction parameter in the regression model) will be presented alongside the effect estimate and 95% CI within each subgroup. The results of subgroup analyses will be treated with caution and used for hypothesis generation only.

Three sensitivity analyses are planned. First, since the ITT analysis could provide results biased towards non-inferiority, for the co-primary outcomes only, sensitivity analyses based on the per-protocol populations will also be performed. Second, to examine the robustness of the conclusions, sensitivity and supportive analyses will be undertaken for: (i) the two co-primary outcomes, excluding women and their babies who were randomised and delivered before 38^{+0} weeks, prior to when the intervention could be applied; (ii) the neonatal co-primary outcome among liveborns, and (iii) the neonatal co-primary outcome including babies who either died without admission to neonatal care, or died following admission to neonatal care for <4 h. Third, while it is anticipated that missing data will be minimal, women or babies with missing co-primary outcome data who will not be included in the primary analysis, present a risk of bias; sensitivity analyses with multiple imputation will be undertaken to assess the possible impact of this risk.

Women who gave consent at 36^{+0}-37^{+6} weeks, but who were not randomised (possible only at 37^{+0-6} weeks) will be included in separate descriptive analyses.

A separate statistical analysis plan will provide a detailed description of planned analyses.

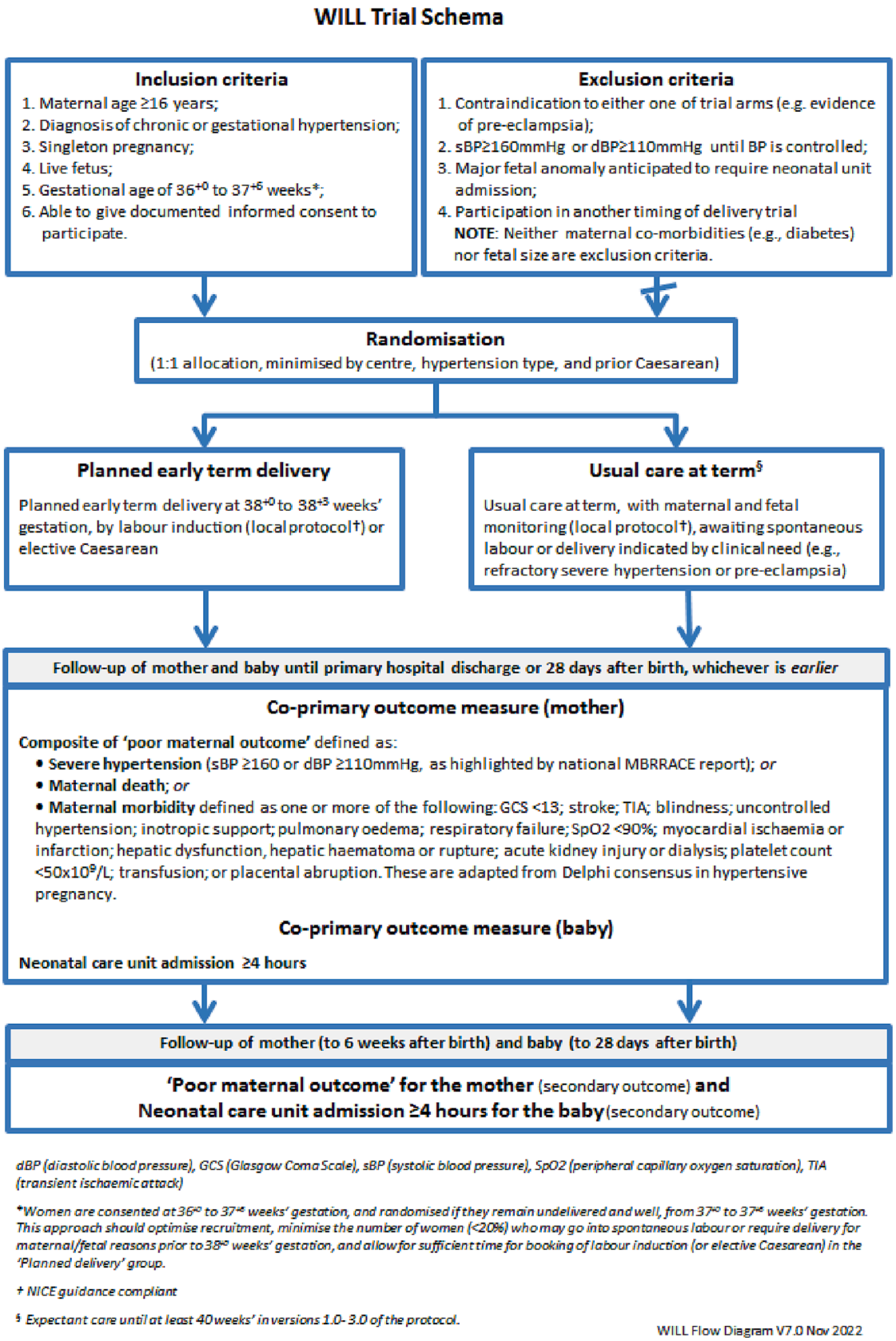

Fig. 1. Trial schema.

2.13. Trial management and oversight

The trial is funded by the National Institute of Health Research (NIHR) Health Technology Assessment (project number 16/167/123). The co-sponsor is King's College London and Guy's and St Thomas' NHS Foundation Trust. The trial is co-ordinated by the Birmingham Clinical Trials Unit. Neither the funder nor co-sponsor are (or will be) involved in data collection or analysis.

The trial was registered (ISRCTN 77258279, 05 December 2018) prior to recruitment. Data will be kept in accordance with General Data Protection Regulations 2018.

The Trial Management Group is responsible for day-to-day running of the trial. The TSC and DMC provide independent oversight, including assessment of the pilot phase (as above). The DMC comprises one obstetrician, one neonatologist and two statisticians with extensive trial experience. Responsibility for continuation or modification of the trial is held by the TSC and includes guidance from the DMC. The DMC terms of reference and charter are guided by the DAMOCLES project. The DMC and TSC meet at least annually.

2.14. Patient and public involvement

The trial has two patient and public involvement and engagement (PPIE) co-applicants, from the Action on Pre-Eclampsia and Sands charities. An additional PPIE representative sits on the TSC, providing important oversight into trial management and decision making. Our bespoke PPIE group is active in reviewing patient and public-facing material for trial promotion and recruitment.

3. Discussion

WILL is an RCT assessing optimal timing of birth for women with chronic or gestational hypertension in pregnancy, who reach term gestational age and remain well, without an indication for birth. WILL aims to address whether these women should be offered timed birth, or usual care at term, and specifically whether such an approach would reduce maternal risk without increasing fetal/neonatal risk.

The study will provide data for women to make informed choices about maternal and perinatal risk and health systems to plan services. As the management undertaken in the trial intervention and usual care arms is part of routine clinical care, we anticipate receptiveness to the WILL results.

3.1. Trial status

WILL opened to recruitment in June 2019. The internal pilot study completed in March 2020. The main trial began on 9 July 2020 following a pause due to the COVID-19 pandemic, and is currently contracted to recruit until July 2023, with all trial follow-up complete by October 2023. Trial findings will be disseminated to participants and published in a peer-reviewed journal.

Funding

The project was funded by the National Institute of Health Research (NIHR) Health Technology Assessment (project number 16/167/123). The views expressed are those of the author(s) and not necessarily those of NIHR, the NHS, or the Department of Health and Social Care.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We wish to thank the women who participate in the trial, and the countless site contributors without whose support, a multicentre trial is not possible. Also, we extend our sincere thanks to our independent Trial Steering (Tim Draycott [Chair], Graeme MacLennan, Lucy MacKillop, Paul Mannix, Ruth Unstead-Joss) and Data Monitoring (Diana Elbourne (Chair), Henk Groen (Vice-Chair), Deborah Harrington, Edile Murdoch, Sarah Stock) Committees for generously contributing their time and guidance (**Table S4**).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2023.03.002.

References

[1] M.O. Cruz, W. Gao, J.U. Hibbard, What is the optimal time for delivery in women with gestational hypertension? Am J Obstet Gynecol 207 (3) (2012) 214–216.
[2] J.A. Hutcheon, S. Lisonkova, L.A. Magee, P. Von Dadelszen, H.L. Woo, S. Liu, K. S. Joseph, Optimal timing of delivery in pregnancies with pre-existing hypertension, BJOG 118 (1) (2011) 49–54.
[3] M. Ram, H. Berger, M. Geary, S.D. McDonald, B. Murray-Davis, C. Riddell, H. Hasan, J. Barrett, N. Melamed, Timing of delivery in women with chronic hypertension, Obstet Gynecol. 132 (3) (2018) 669–677.
[4] S.M.C. Vijgen, C.M. Koopmans, B.C. Opmeer, H. Groen, D. Bijlenga, J. G. Aarnoudse, D.J. Bekedam, P.P. van den Berg, K. de Boer, J.M. Burggraaff, K.W. M. Bloemenkamp, A.P. Drogtrop, A. Franx, C.J.M. de Groot, A.J.M. Huisjes, A. Kwee, A.J. van Loon, A. Lub, D.N.M. Papatsonis, J.A.M. van der Post, F.J.M. E Roumen, H.C.J. Scheepers, R.H. Stigter, C. Willekes, B.W.J. Mol, M.G. Van Pampus, An economic analysis of induction of labour and expectant monitoring in women with gestational hypertension or pre-eclampsia at term (HYPITAT trial), BJOG 117 (13) (2010) 1577–1585.
[5] Hypertension in pregnancy: diagnosis and management: NICE clinical guideline [NG133] Published 25 June 2019. https://www.nice.org.uk/guidance/NG133.
[6] M.A. Brown, L.A. Magee, L.C. Kenny, S.A. Karumanchi, F.P. McCarthy, S. Saito, D. R. Hall, C.E. Warren, G. Adoyi, S. Ishaku, on behalf of the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertensive Disorders of Pregnancy - ISSHP Classification, Diagnosis, and Management Recommendations for International Practice, Hypertension 72 (2018) 24–43.
[7] C. Cluver, N. Novikova, C.M. Koopmans, H.M. West, Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term, Cochrane Database Syst. Rev. 15 (1) (2017) CD009273.
[8] P.S. Bhageerathy, V. Thomas, A. Regi, R. Jose, Induction of labour versus conservative management for mild gestational hypertension at term, IJRCOG 5 (3) (2017) 689–695.
[9] C.M. Koopmans, D. Bijlenga, H. Groen, S.MC. Vijgen, J.G. Aarnoudse, D. J. Bekedam, P.P. van den Berg, K. de Boer, J.M. Burggraaff, K.WM. Bloemenkamp, A.P. Drogtrop, A. Franx, C.JM. de Groot, A.JM. Huisjes, A. Kwee, A.J. van Loon, A. Lub, D.NM. Papatsonis, J.AM. van der Post, F.J. Roumen, H.CJ. Scheepers, C. Willekes, B.WJ. Mol, M.G. van Pampus, Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial, Lancet 374 (9694) (2009) 979–988.
[10] H.O. Hamed, M.A. Alsheeha, A.M. Abu-Elhasan, A.E. Abd Elmoniem, M.M. Kamal, Pregnancy outcomes of expectant management of stable mild to moderate chronic hypertension as compared with planned delivery, Int. J. Gynaecol. Obstet. 127 (1) (2014) 15–20.
[11] Public Health Agency of Canada. Canadian Perinatal Health Report. 2008.
[12] W.A. Grobman, M.M. Rice, U.M. Reddy, A.T.N. Tita, R.M. Silver, G. Mallett, K. Hill, E.A. Thom, Y.Y. El-Sayed, A. Perez-Delboy, D.J. Rouse, G.R. Saade, K.A. Boggess, S. P. Chauhan, J.D. Iams, E.K. Chien, B.M. Casey, R.S. Gibbs, S.K. Srinivas, G. K. Swamy, H.N. Simhan, G.A. Macones, Macones GA, for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Labor induction versus expectant management in low-risk nulliparous women, NEJM 379 (6) (2018) 513–523.
[13] S. Dong, S. Bapoo, M. Shukla, N. Abbasi, D. Horn, R. D'Souza, Induction of labour in low-risk pregnancies before 40 weeks of gestation: a systematic review and meta-analysis of randomized trials, Best Pract. Res. Clin. Obstet. Gynaecol. 79 (2022) 107–125, https://doi.org/10.1016/j.bpobgyn.2021.12.007. Epub 2022 Jan 15.PMID: 35086752 Review.
[14] I. Gurol-Urganci, L. Waite, K. Webster, J. Jardine, F. Carroll, G. Dunn, A. Frémeaux, T. Harris, J. Hawdon, P. Muller, J. van der Meulen, A. Khalil, Obstetric interventions and pregnancy outcomes during the COVID-19 pandemic in England: a nationwide cohort study, PLoS Med. 19 (1) (2022) e1003884.
[15] Inducing labour: NICE clinical guideline [NG207] Published 04 Nov 2021. https://www.nice.org.uk/guidance/ng207.
[16] P. von Dadelszen, B. Payne, J. Li, J.M. Ansermino, F.B. Pipkin, A.-M. Côté, M. J. Douglas, A. Gruslin, J.A. Hutcheon, K.S. Joseph, P.M. Kyle, T. Lee, P. Loughna, J. M. Menzies, M. Merialdi, A.L. Millman, M.P. Moore, J.-M. Moutquin, A.B. Ouellet,

G.N. Smith, J.J. Walker, K.R. Walley, B.N. Walters, M. Widmer, S.K. Lee, J. A. Russell, L.A. Magee, Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model, Lancet 377 (9761) (2011) 219–227.

[17] J.M.N. Duffy, J. van 't Hooft, C. Gale, M. Brown, W. Grobman, R. Fitzpatrick, S. A. Karumanchi, N. Lucas, L. Magee, B. Mol, M. Stark, S. Thangaratinam, M. Wilson, P. von Dadelszen, P. Williamson, K.S. Khan, S. Ziebland, R.J. McManus, A protocol for developing, disseminating, and implementing a core outcome set for pre-eclampsia, Pregnancy Hypertens. 6 (4) (2016) 274–278.

[18] British Association of Perinatal Medicine, Categories of Care (http://www.bapm.org/publications/documents/guidelines/CatsofcarereportAug11.pdf). 2011.

[19] J. Villar, L.C. Ismail, C.G. Victora, E.O. Ohuma, E. Bertino, D.G. Altman, A. Lambert, A.T. Papageorghiou, M. Carvalho, Y.A. Jaffer, M.G. Gravett, M. Purwar, I.O. Frederick, A.J. Noble, R. Pang, F.C. Barros, C. Chumlea, Z. A. Bhutta, S.H. Kennedy, for the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st). International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21ST Project, Lancet 384 (9946) (2014) 857–868.

[20] K.F. Walker, P. Wilson, G.J. Bugg, A. Dencker, J.G. Thornton, Childbirth experience questionnaire: validating its use in the United Kingdom, BMC Pregnancy Childbirth 15 (2015) 86.

[21] L.A. Magee, P. von Dadelszen, E. Rey, S. Ross, E. Asztalos, K.E. Murphy, J. Menzies, J. Sanchez, J. Singer, A. Gafni, A. Gruslin, M. Helewa, E. Hutton, S.K. Lee, T. Lee, A. G. Logan, W. Ganzevoort, R. Welch, J.G. Thornton, J.-M. Moutquin, Less-tight versus tight control of hypertension in pregnancy, N. Engl. J. Med. 372 (5) (2015) 407–417.

[22] K. van der Tuuk, C.M. Koopmans, H. Groen, B.W. Mol, M.G. van Pampus, Impact of the HYPITAT trial on doctors' behaviour and prevalence of eclampsia in the Netherlands, BJOG 118 (13) (2011) 1658–1660.

[23] J.M. Pauli, J.R. Lauring, C.M. Stetter, J.T. Repke, J.J. Botti, S.H. Ural, A. Ambrose, Management of gestational hypertension - the impact of HYPITATa, J. Perinat. Med. 41 (4) (2013) 415–420.

[24] B.C. Kahan, T.P. Morris, Reporting and analysis of trials using stratified randomisation in leading medical journals: review and reanalysis, BMJ 345 (2012) e5840.

[25] G. Zou, A modified poisson regression approach to prospective studies with binary data, Am. J. Epidemiol. 159 (7) (2004) 702–706.