

UNIVERSITY OF
BIRMINGHAM



TRIAL PROTOCOL

BABY PANDA

Bp response Assessment BY Pregnancy ANtihypertensive Drug treAtment: (Mechanism of Action of Health Intervention)

This protocol has regard for the HRA guidance and is compliant with the SPIRIT guidelines (2013)

Version Number: 1.1
Version Date: 04/03/2022

PROTOCOL DEVELOPMENT

Protocol amendments

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

<u>Amendment number</u>	<u>Date of amendment</u>	<u>Protocol version number</u>	<u>Type of amendment</u>	<u>Summary of amendment</u>

Funding and support in kind



<u>Funder(s)/Supporting Organisations</u>	<u>Financial and non-financial support given:</u>
National Institute for Health Research	
<u>Funding scheme (if applicable)</u>	Efficacy and Mechanism Evaluation Programme
<u>Funder's reference number</u>	NIHR133079
This project (NIHR unique award identifier) is funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership. The views expressed in this publication are those of the author(s) and not necessarily those of the MRC, NIHR or the Department of Health and Social Care.	

PROTOCOL SIGN OFF

Chief Investigator (CI) signature page

I, the Chief Investigator, confirm that I have read and agree with the following protocol, and that I will conduct the trial in compliance with the version of this protocol approved by the REC and any other responsible organisations.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor. I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as stated in this and any subsequent approved protocol will be explained.

Trial name:	Bp response Assessment BY Pregnancy ANtihypertensive Drug treAtment: (Mechanism of Action of Health Intervention): BABY PANDA study	
Protocol version number:	Version: __ __	
Protocol version date:	__ / __ / ____	
CI name:	Professor Lucy Chappell	
Signature and date:	_____	_04/03/2022_
		
Joint lead applicant/ deputy CI	Professor Jenny Myers	
Signature and date:	- _____	04/03/2022
		

Sponsor statement

Where the University of Birmingham takes on the sponsor role for protocol development oversight, the signing of the IRAS form by the sponsor will serve as confirmation of approval of this protocol

Compliance statement

This protocol describes the *BABY PANDA study* only. The protocol should not be used as a guide for the treatment of participants not taking part in the *BABY PANDA study*.

The study will be conducted in compliance with the approved protocol, the UK Policy Framework for Health and Social Care Research, Data Protection Act 2018, the Human Tissue Act of 2004, and the Principles of Good Clinical Practice (GCP) as set out in the UK Statutory Instrument (2004/1031) and subsequent amendments thereof. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

Principal Investigator (PI) signature page

As Principal Investigator, I confirm that the following protocol has been agreed and accepted, and that I will conduct the trial in compliance with the approved protocol where this does not compromise participant safety.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

Trial name:	Bp response Assessment BY Pregnancy ANtihypertensive Drug treAtment: (Mechanism of Action of Health Intervention): BABY PANDA study
Protocol version number:	Version: __ __
Protocol version date:	__ __ / __ __ / __ __ __ __
PI name:	
Name of Site:	
Signature and date:	_____ __ __ / __ __ / __ __ __ __

ADMINISTRATIVE INFORMATION

Reference Numbers	
Sponsor number	RG_21-199
ISRCTN reference number	< ISRCTN reference number >
IRAS reference number	307769

Sponsor	
University of Birmingham	Research Support Group c/o Room 106, B Block Aston Webb Building Edgbaston Birmingham B15 2TT
Contact Details	Dr Birgit Whitman Head of Research Governance and Integrity Research Support Group 07814 650003 researchgovernance@contacts.bham.ac.uk

Chief Investigator	
Professor Lucy Chappell	Professor of Obstetrics
10th floor, North Wing, St Thomas' Hospital London, SE1 7EH	+44 (0) 20271883629 lucy.chappell@kcl.ac.uk
Joint lead applicant/ Deputy Chief Investigator	
Professor Jenny Myers	Professor of Obstetrics & Maternal Medicine
Maternal & Fetal Health Research Centre St Mary's Hospital, Oxford Rd, Manchester M13 9WL	+44 161 7016963 Jenny.myers@manchester.ac.uk

<u>Trial office contact details</u>	
Ms Lisa Leighton Birmingham Clinical Trials Unit (BCTU) Institute of Applied Health Research College of Medical and Dental Sciences Public Health Building University of Birmingham Birmingham B15 2TT	Senior Trial Manager l.j.leighton@bham.ac.uk 0121 414 3902
Trial website	< tbc >
Trial social media	< tbc >
<u>Project Management Group</u>	
Professor Lucy Chappell (CI)	Obstetrics
Professor Jenny Myers	Obstetrics
Dr Kate Duhig	Obstetrics
Ms Lisa Leighton	Trial Manager
Ms Catherine Moakes	Statistics
<u>Co-investigator Group</u>	
Professor Lucy Chappell (CI)	Obstetrics
Professor Jenny Myers (Deputy CI)	Obstetrics
Professor Richard McManus	Primary Care
Dr Andrew Webb	Clinical Pharmacology
Mr Marcus Green	Patient and Public Involvement
Ms Catherine Moakes	Statistics
Ms Danielle Ashworth	Study Co-ordination
Dr Frances Conti-Ramsden	Research design
<u>Trial Steering Committee</u>	
Dr Sarah Stock (Chair)	Obstetrics
Professor Julia Sanders	Midwifery
Dr Trish Hepburn	Statistics
Dr David Odd	Neonatology
Ms Jacqui Williams	PPIE
Professor Susan Griffin	Health Economics
Professor Lucy Chappell (<i>non-independent</i>)	Obstetrics
<u>Data Monitoring Committee</u>	
Dr Fergus McCarthy (Chair)	Obstetrics
Professor John Norrie	Medical Statistics and Trial Methodology
Professor Ben Stenson	Neonatology

ABBREVIATIONS

Include a list of all abbreviations used in the main text

Abbreviation	Term
AE	Adverse Event
BCTU	Birmingham Clinical Trials Unit
BP	Blood Pressure
DMC	Data Monitoring Committee
CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice
HR	Heart Rate
HRA	Health Research Authority
ICF	Informed Consent Form
ISF	Investigator Site File
MICD	Minimally Important Clinical Difference
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NNU	Neonatal Unit
PI	Principal Investigator
PIS	Participant Information Sheet
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
UoB	University of Birmingham

STUDY SUMMARY

Title	Bp response Assessment BY Pregnancy ANtihypertensive Drug treAtment: (Mechanism of Action of Health Intervention): BABY PANDA study
Research Question	In women with pregnancy hypertension, what is the short-term blood pressure (BP) response to antihypertensive agents and how is this related to clinical effectiveness?
Objectives	<ol style="list-style-type: none"> 1) To determine short-term BP response of nifedipine versus labetalol 2) To explore the association between short-term BP response and long-term BP control (Giant PANDA primary outcome). 3) To assess whether maternal characteristics, disease markers or drug metabolites provide mechanistic insight into differing responses to antihypertensive agents between individuals.
Study Design	Prospective observational cohort study aligned with the Giant PANDA study
Participant population and size	A sample size of 246 women will provide 90% power to detect a minimally important clinical difference in 8-hour post-dose systolic BP response of 10%, assuming a standard deviation of 24 and a 5% two-sided alpha, which is equivalent to a standardised difference of 0.42. We aim to recruit 274 women to BABY PANDA to account for up to 10% attrition.
Setting	The study will be conducted in selected centres participating in the associated Giant PANDA trial.
Eligibility criteria	<p>Women will be approached for recruitment to the Baby PANDA study after they have agreed to participate in the Giant PANDA study.</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> - Pregnancy prior to 34+6 weeks' gestation - Diagnosis of pregnancy hypertension* (chronic or gestational hypertension) - Aged 18 years or over - Able to give informed consent <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> - Diagnosis of pre-eclampsia
Interventions	After consent, women will be provided with a pregnancy-validated ambulatory BP monitor to measure up to a 24-hour BP profile (every 30-60 mins) on up to three occasions across pregnancy. Drug ingestion times, sleep and wake times and side-effects will be self-reported. Urine and blood samples will be collected for renin-angiotensin system markers and drug metabolite levels.
Outcome measures	<p>Principle Outcome: 8 hour systolic BP post-dose response to labetalol or nifedipine.</p> <p>Secondary outcomes: Short-term BP response, including 8-hour diastolic BP post-dose response to labetalol or nifedipine (proportion of systolic BP readings ≥ 140mmHg), 8 hour post dose proportion of BP readings ≥ 140mmHg systolic or ≥ 90mmHg diastolic readings, BP variability, 24 hour post-dose BP parameters, medication adherence and renin and aldosterone concentrations.</p>

**Pregnancy hypertension (including chronic or gestational hypertension), will be defined by the NICE (National Institute for Health and Care Excellence 2019) criteria as sustained systolic blood pressure ≥ 140 and/or diastolic blood pressure ≥ 90 mmHg.*

TRIAL SCHEMA

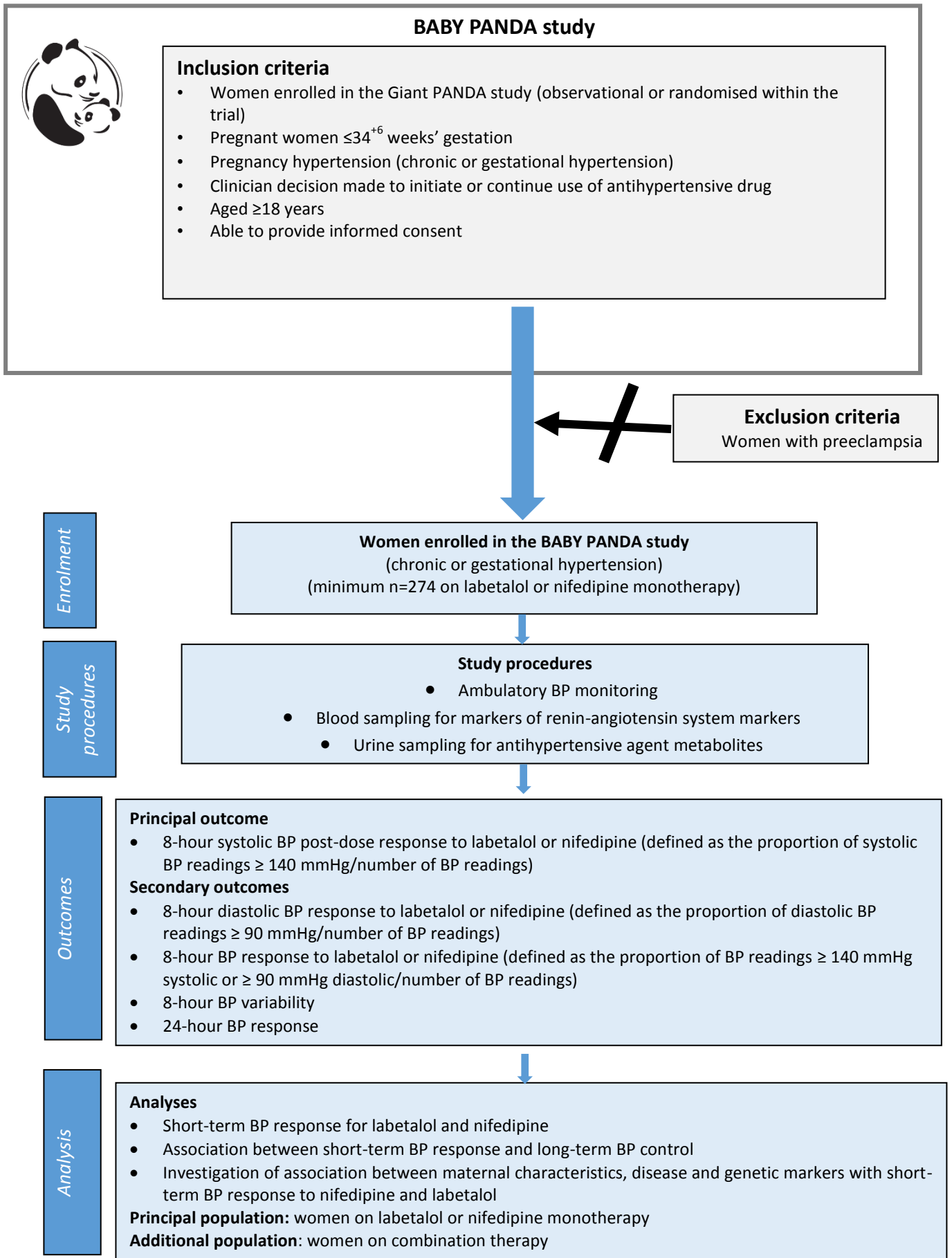


TABLE OF CONTENTS

1. BACKGROUND AND RATIONALE.....	12
1.1 Background.....	12
1.2 Existing literature	13
1.3 Study rationale.....	14
2. AIMS AND OBJECTIVES	15
2.1 Research question	15
2.2 Aims	15
2.3 Objectives	15
3. STUDY DESIGN AND SETTING	15
3.1. Study design	15
3.2 Study setting	15
3.2. Assessment of risk.....	15
4. ELIGIBILITY	15
4.1. Inclusion Criteria	15
4.2 Exclusion criteria	16
5. INFORMED CONSENT.....	16
6. ENROLMENT	17
6.1. Identification.....	17
6.2. Screening and enrolment.....	17
6.3 Registration.....	17
6.4 Informing the participant’s GP and other parties	17
7. STUDY INTERVENTION	17
7.1. Study Procedures	18
8. OUTCOME MEASURES AND TRIAL PROCEDURES	19
8.1 Outcome Measures	19
8.2 Withdrawal of consent	19
8.3 Schedule of assessments.....	20
9. ADVERSE EVENT REPORTING	20
9.1 Definitions	20
9.2 Adverse event recording – general.....	21
9.3 Adverse event reporting in BABY PANDA.....	21
9.4 Serious Adverse Adverts (SAE) reporting in BABY PANDA	21
10. DATA HANDLING AND RECORD KEEPING.....	21
10.1 Source data.....	22
10.2 Case Report Form (CRF) completion.....	22
10.3 Data management	23
10.4 Data security	23
10.5 Site Archiving.....	23
11. QUALITY CONTROL AND QUALITY ASSURANCE	23
11.1 Site set-up and initiation	23
11.2 Monitoring	24

11.3	Audit and inspection	24
11.4	Notification of Serious Breaches	24
12.	END OF STUDY DEFINITION	24
13.	STATISTICAL CONSIDERATIONS	24
13.1	Sample size	24
13.2	Analysis of outcomes.....	25
13.2.1	Short-term BP response of antihypertensive agents.....	25
13.2.1.1	Principal outcome	25
13.2.1.2	Secondary outcomes	26
13.2.2	Association between short-term BP response and long-term BP control	26
13.3	Planned final analyses.....	26
14.	STUDY ORGANISATIONAL STRUCTURE	26
14.1	Sponsor	26
14.2	Coordinating centre	26
14.3	Trial Management Group.....	27
14.4	Co-investigator group	27
14.5	Trial Steering Committee	27
14.6	Data Monitoring Committee	27
14.7	Finance	27
15.	ETHICAL CONSIDERATIONS	27
16.	DATA PROTECTION AND CONFIDENTIALITY	27
17.	FINANCIAL AND OTHER COMPETING INTERESTS.....	28
18.	INSURANCE AND INDEMNITY	28
19.	AMENDMENTS	28
20.	ACCESS TO FINAL DATASET	28
21.	PUBLICATION PLAN	28
22.	REFERENCE LIST	29

1. BACKGROUND AND RATIONALE

1.1 Background

1.1.1 The problem being addressed

Hypertension or high blood pressure (BP) affects approximately 70,000 women per year in the UK (8-10% of pregnancies). This includes chronic (pre-existing) hypertension and new-onset hypertensive disorders such as gestational hypertension and pre-eclampsia. Hypertensive disorders of pregnancy are associated with substantial maternal and perinatal morbidity and mortality. This includes maternal stroke, preterm birth, low birth weight and stillbirth. Pregnancy hypertension is responsible for 10-20% of preterm deliveries, and has an estimated stillbirth rate of 0.3-1.9% in high-income settings and up to 25% in low-income settings (Buchbinder et al. 2002; Steegers et al. 2010; Bramham et al. 2014; Gibbins et al. 2016; Webster, Bramham, et al. 2019).

Achieving timely and sustained BP control is of critical importance in the management of pregnancy hypertension, reducing the risk of maternal severe hypertension, organ dysfunction and adverse perinatal outcomes (Magee et al. 2015, 2020), as well as avoiding the need for hospital admission and reducing the risk of preterm birth. There is a clear need for evidence-based antihypertensive agent choice in pregnancy to optimise BP control, leading to improved maternal and perinatal outcomes in these high-risk pregnancies.

1.1.2 The evidence gap

Despite the importance of controlling BP in hypertensive pregnancies, there is a paucity of evidence to inform optimal antihypertensive agent choice in pregnancy. The most recent Cochrane systematic review of head-to-head antihypertensive agent trials for treatment of mild to moderate pregnancy hypertension (Abalos et al. 2018) identified just two studies (totalling 354 women) comparing the top two recommended antihypertensive agents in the UK: labetalol and nifedipine. Direct extrapolation of evidence from adult (non-pregnant) hypertension literature is neither possible nor appropriate. Many of the classes of drugs and specific agents recommended for treatment of adult hypertension, including angiotensin converting enzyme inhibitors, angiotensin receptor blockers and diuretics, are specifically contraindicated in pregnancy due to concerns regarding safety for the fetus. Conversely, antihypertensive agents commonly used in pregnancy are rarely used outside of pregnancy, and therefore appropriate head-to-head comparisons are lacking. Extrapolation is further precluded by the physiological and pathological changes of pregnancy (Costantine 2014; Feghali, Venkataramanan, and Caritis 2015), which are likely to have profound influences on drug pharmacokinetics, pharmacodynamics and tolerability. Most drug studies exclude pregnant women (Chappell and David 2016), further highlighting the importance of pregnancy-specific trials. In view of the current evidence base, considerable uncertainty regarding the risks and benefits of contemporaneous antihypertensive agent therapy in pregnancy remains. Due to this uncertainty, substantial variation in first and second-line antihypertensive agent prescribing exists in clinical practice (Whybrow et al. 2020). In the absence of evidence, current National Institute for Health and Care Excellence Hypertension in Pregnancy Guidelines (NICE Guideline 133, updated 2019) recommend labetalol as a 'safe' first-line treatment for all pregnancy hypertension. Notably, beta-blockers are a fourth-line treatment option for chronic hypertension in non-pregnant adults (NICE Guideline 136, updated 2019).

It is likely that a 'one-size fits all' approach to treatment of pregnancy hypertension is not optimal. The NICE clinical algorithm for antihypertensive agent choice in non-pregnant adults stratifies treatments by ethnicity and age, reflecting proposed differences in hypertension aetiology including response to antihypertensive agents at a population level (NICE Guideline 136, updated 2019). Assuming similar differences in pregnancy hypertension, we can hypothesise that women of Black African/ African Caribbean backgrounds may be more likely to experience suboptimal BP control on beta-blockers such as labetalol. This has been suggested in a study of 120 pregnant hypertensive women prescribed labetalol monotherapy. BP control (defined as BP <140/90mmHg) was achieved in 77% of women categorised as of Black ethnicity vs 80% of women categorised as of White ethnicity 1 hour after treatment, but this diverged to 63.9% v 83.1% at 24h after treatment (p-value: 0.02), and to 70.4% v 89.8% from study enrolment to delivery (p-value: 0.007) (Stott,

Bolten, Paraschiv, et al. 2016). In a study of 50 women prescribed labetalol monotherapy, 26% failed to achieve long-term BP control (BP <140/90mmHg), with maternal ethnicity, baseline heart rate and stroke volume index shown to be independent predictors of labetalol response (Stott, Bolten, Salman, et al. 2016). Whilst drug adherence was not investigated in either of these studies, these findings suggest that whilst labetalol is likely to be effective in the majority of pregnant women, a substantial proportion of women may benefit from an alternative antihypertensive agent.

1.2 Existing literature

1.2.1 Evidence of proof-of-concept: Short-term BP response to nifedipine and labetalol

One study has used 24-hour ambulatory BP monitoring to compare the short-term BP response of a single dose of modified release nifedipine versus labetalol (dose as clinically indicated for each woman) in hypertensive pregnant women (Shawkat et al. 2018). This was an exploratory, non-randomised study of 48 women with chronic hypertension. Differences in drug effects on systolic and diastolic BP time series were noted ($p=0.015$), with labetalol having a sharper, short-lasting BP lowering effect compared to nifedipine. Although exploratory, the findings suggest that there may be clinically significant differences in the short-term BP response to labetalol and nifedipine. To our knowledge, this is the only study that has specifically investigated 24-hour ambulatory BP profiles in pregnant women on antihypertensive treatment. Marked differences in BP response profiles between nifedipine and labetalol were suggested, indicating that nifedipine may provide more stable BP control with less BP variation in pregnancy. The greater initial fall in BP observed in the labetalol group could have important clinical implications.

Recent studies have suggested that BP variability in pregnancy (as assessed from clinic BPs) may be an important determinant of maternal and perinatal clinical outcomes (Magee et al. 2020; Liu et al. 2020). BP variability over 24 hours and the longer-term represents complex interactions between environmental and behavioural factors with cardiovascular regulatory mechanisms. BP variability may also relate to drug half-life; labetalol has a shorter half-life of 4-6 hours (Webster, Webb, and Chappell 2018) and usually requires three times a day dosing in pregnancy, whilst modified release nifedipine has a longer half-life of 6-11 hours (EMC 2017), and is routinely given up to twice daily. Frequency of dosing may also impact adherence. Increased short-term BP variability (as assessed by ambulatory BP monitoring) and long-term BP variability (as assessed by outpatient/intermittent BP monitoring) are associated with development, progression and severity of cardiovascular and end-organ damage with increased incidence of cardiovascular events and mortality in hypertensive non-pregnant adults (Parati et al. 2013).

1.2.2 Why is short-term BP response important?

The Giant PANDA study will assess the pragmatic, real-world effectiveness of nifedipine versus labetalol. The primary maternal BP outcome will be derived from serial BP readings, in keeping with what is available to healthcare professionals in clinical practice. As outpatient BP readings are intermittent samples of a continuous physiological variable that exhibits marked short-term fluctuations, it is unsurprising that evidence to date strongly suggests that detailed BP profiles produced by ambulatory BP monitoring provide more insight into hypertension physiology and treatment response, and stronger association with clinical outcomes, than outpatient BP monitoring. The aim of BABY PANDA, a mechanistic observational cohort study, aligned with Giant PANDA, is to determine the short term blood pressure response to labetalol or nifedipine, by measuring 24 hour BP to see if short term BP response is related to overall clinical effectiveness.

In non-pregnant treated and untreated hypertensive patients, ambulatory BP monitoring has repeatedly been shown to be a superior diagnostic tool and predictor of cardiovascular events compared to outpatient clinic and self-measured BP measurements (Turner, Viera, and Shimbo 2015; Pickering, Shimbo, and Haas 2006; O'Brien 2008; Gabbai et al. 2012). Ambulatory BP devices have been validated for use in pregnancy (Abou-Dakn and Wenzel 2018), and have been found to be well tolerated by the majority of pregnant women: in a study of 110 women, 89% reported they would undergo further ambulatory BP monitoring in future pregnancies (Rhodes, Beevers, and Churchill 2018).

1.2.4 Biomarkers

- Antihypertensive agent metabolites

Urine samples will be assayed for antihypertensive agent metabolites as described in the PANDA feasibility study (ISRCTN40973936) conducted by Professor Chappell's (CI) group (Webster, Reed, et al. 2019). In this study, 12% of women were non-adherent with their prescribed antihypertensive agent as determined by urinary metabolite assays.

- Markers of renin-angiotensin system activation

By examining the relationship between plasma renin and aldosterone concentration, maternal ethnicity and short-term BP response and effectiveness of labetalol and nifedipine in pregnancy, mechanistic insight into variation in drug response between ethnic groups or between individuals may be acquired. This may provide evidence for antihypertensive agent selection, facilitating shared decision-making between pregnant women and healthcare professionals.

- Genotyping (Samples to be biobanked)

Studies evaluating treatment response to antihypertensive agent categorised by genomic ancestry markers rather than self-reported ethnicity could pave the way for personalised treatment in pregnant women in the future. We will optionally store samples for the purpose of securing funding for genotyping in the future, should clinically significant differences be shown.

1.3 Study rationale

There is a clear need for clinical trials to address the current large evidence gap concerning antihypertensive agent choice for treatment of pregnancy hypertension, including addressing differing responses across individuals with careful consideration of ensuring equity of evidence for women of diverse ethnic backgrounds. This evidence gap is the rationale for the Giant PANDA study (<https://fundingawards.nihr.ac.uk/award/NIHR128721>), which will evaluate the clinical effectiveness of nifedipine versus labetalol, the two most commonly prescribed antihypertensive agents in pregnancy in reducing severe maternal hypertension, without increasing fetal or neonatal death, or Neonatal Unit (NNU) admission. The Giant PANDA trial determines severe maternal hypertension as the proportion of days with healthcare professional measured systolic BP readings ≥ 160 mmHg.

In this mechanistic observational study (BABY PANDA), we will determine the short-term BP response of antihypertensive agents, focusing on nifedipine and labetalol, using 24-hour ambulatory BP monitoring, and explore the association between short-term BP response and longer-term clinical effectiveness. The BABY PANDA study is open to women enrolled in the Giant PANDA observational arm, as well as women randomised within the study. 24-hour ambulatory BP profiles provide a depth of information in comparison to one-off clinic BP measurements including detailed assessment of antihypertensive agent BP response, BP variability, and diurnal/nocturnal BP patterns. This information may provide mechanistic insight into the clinical effectiveness of nifedipine versus labetalol in pregnancy, as well as having the potential for translation into clinical practice as a tool for early identification of women with a suboptimal response to the prescribed antihypertensive agent. Collection of blood and urine samples in this study will also allow us to investigate whether drug adherence (as assessed by drug metabolite assays) or markers of renin-angiotensin system activation provide mechanistic insight into differing responses to nifedipine and labetalol in pregnancy.

If a relationship between short-term BP response to labetalol and nifedipine and long-term BP control is demonstrated, this would provide rationale for further exploration of the use of short-term BP response monitoring to identify individual women who are unlikely to achieve good BP control on initial prescribed antihypertensive agent therapy. If a significant association is found, the minimum number of BP measurements required to identify women with a suboptimal response would also be explored in order to

facilitate translation into clinical practice. Short-term BP response monitoring may be a cost-effective, pragmatic mechanism to identify women with a suboptimal response and allow early switching of antihypertensive agent in pregnancy which has the potential to improve BP control and clinical outcomes for these women.

Investigation of the association between maternal ethnicity, renin-angiotensin system markers, drug adherence and genotype with short-term BP response profiles may provide mechanistic insight into factors underlying differential responses to labetalol and nifedipine across individuals. This has the potential to lead to further studies which compare a personalised approach to antihypertensive choice in pregnancy on the basis of ethnicity or disease markers to standard care, which may pave the way for individualised treatment of pregnancy hypertension in the future with the aim of optimising BP control and clinical outcomes. In contrast, should adherence be identified as the primary determinant of short-term BP response and effectiveness, further studies must focus on how health care professionals and healthcare systems can best support pregnant women to adhere with prescribed medication.

2. AIMS AND OBJECTIVES

2.1 Research question

In women with pregnancy hypertension, what is the short-term BP response to antihypertensive medication, and how is this related to clinical effectiveness?

2.2 Aims

To determine the short-term BP response of antihypertensive treatments in women with pregnancy hypertension, how this may relate to long-term clinical effectiveness, and to explore mechanisms of differing responses to these antihypertensive agents.

2.3 Objectives

1. To determine short-term BP response of labetalol and nifedipine in women with gestational or chronic hypertension in pregnancy.
2. To explore the association between short-term BP response and long-term BP control (Giant PANDA study primary outcome).
3. To assess whether maternal characteristics, drug metabolites or disease markers provide mechanistic insight into differing responses to antihypertensive agents across individuals.

3. STUDY DESIGN AND SETTING

3.1. Study design

Prospective observational cohort study, aligned with the Giant PANDA trial, measuring short term BP response to antihypertensive agents using 24-hour ambulatory BP monitoring, alongside the collection of blood and urine samples to measure drug adherence and candidate biomarkers.

3.2 Study setting

The study will be conducted in selected centres participating in the Giant PANDA trial.

3.2. Assessment of risk

There are no anticipated clinical risks for participants in the BABY PANDA study as the planned procedures are low-risk and regularly performed in clinical care (blood sampling and ambulatory blood pressure monitoring).

4. ELIGIBILITY

4.1. Inclusion Criteria

Women will be approached for recruitment to the BABY PANDA study after they have agreed to participate in the Giant PANDA study. Eligibility for the BABY PANDA study includes:

- Pregnancy $\leq 34^{+6}$ weeks' gestation

- Diagnosis of pregnancy hypertension* (chronic or gestational hypertension)
- Aged 18 years or over
- Able to give informed consent

* *Pregnancy hypertension (including chronic or gestational hypertension), will be defined by the NICE (National Institute for Health and Care Excellence 2019) criteria as sustained systolic blood pressure ≥ 140 and/or diastolic blood pressure ≥ 90 mmHg.*

4.2 Exclusion criteria

To reduce the potential for heterogeneity in pregnancy hypertension type to affect interpretability of results of this smaller, mechanistic study, only women with a diagnosis of chronic or gestational hypertension (and not those with pre-eclampsia) at time of recruitment to BABY PANDA, will be eligible for inclusion in the study.

5. INFORMED CONSENT

It will be the responsibility of an appropriately trained healthcare professional (on the 'BABY PANDA Trial Signature and Delegation Log') to obtain informed consent (on paper or electronically) for each participant prior to performing any study related procedures.

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the study, summary of discussion, version number of the PIS given to participant, version number of ICF signed and date consent received. Where consent is obtained on the same day that the study related assessments are due to start, a note should be made in the medical notes as to what time the consent was obtained and what time the procedures started.

A Participant Information Sheet (PIS) (enabled for both paper and electronic versions) will be provided to facilitate this process. The person taking consent will ensure they explain the aims of the study, the study procedures, the anticipated benefits and potential risks of taking part in the study. They will also make it clear that participation is voluntary, and that the woman is free to decline to take part and may withdraw from the BABY PANDA study at any time. The woman will be given appropriate time to read the PIS and to discuss their participation with others outside of the site research team. The woman will be given the opportunity to ask questions before signing and dating the latest version on the Informed Consent Form (ICF).

If the woman wishes to participate in the study and has been confirmed as eligible to participate by a medically qualified individual, they will be asked to complete an ICF. The ICF will include a statement to explain that direct access to maternal and child medical records is required for participation. We will also request consent for electronic data linkage between routinely collated electronic data records (for the woman and the baby) to ascertain future outcomes without participant recall, as well as to establish a 'consent-to-contact' to facilitate recall for future research. A woman will be free to decline provision of expanded consent for the above.

1. **Electronic Consent:** an appropriately trained healthcare professional will sign and date and electronic ICF (which will include the participant's GIANT PANDA study number, date of discussion and name of the study)The participant will also be asked to sign the electronic ICF, and a copy of the ICF will be sent to the woman's email address (stored within the study database), a record made in the medical notes and it will be electronically stored in the site-specific section of the study database.
2. **Paper Consent:** if completing the ICF by paper, a copy will be given to the woman, a copy will be filed in the medical notes, and the original placed in the Investigator Site File (ISF). The participant also understands and acknowledges that a copy will be transmitted to the BCTU for review, and agreement (or not) to each section of the ICF will be inputted onto the study database. Where clinical consultations are undertaken remotely, this option can be followed for approach and

consent, following current authentication procedures used in clinical antenatal care for confirmation of the woman's identity.

Throughout the study, the woman will have the opportunity to ask questions. Any new information that may be relevant to the woman's continued participation will be provided. Where new information becomes available which may affect the woman's decision to continue, women will be given time to consider and if happy to continue will be re-consented. Re-consent will be documented in the medical notes. The woman's right to withdraw from the study will remain. Where English language is limited, an interpreter may be used to translate the study materials and ensure the woman understands all that is involved with participation prior to signing consent. Where translation is required, this will be at the discretion of the local team using their provisions for translating material according to local practice.

Electronic or paper copies of the PIS and ICF will be available from the BCTU Trials Office and will be provided on headed paper of the local institution.

6. ENROLMENT

6.1. Identification

Women will be identified by the research team in the antenatal care setting and approached if deemed eligible. Those working in the clinical research team are part of the direct care team responsible for the participant's clinical care. Women will be approached after they have agreed to participate in the Giant PANDA study and will be invited to consider the BABY PANDA study, being given as much time as they need to decide. Women may be approached to join the BABY PANDA study immediately after they have been enrolled in Giant PANDA, or be considered any time following enrolment to Giant PANDA up to 34+6 weeks gestation inclusive. An appropriately trained healthcare professional on the 'BABY PANDA Trial Signature and Delegation Log' will obtain informed consent (on paper or electronically) for participation (informed consent detailed in section 5). Arrangements for participation will align with women's usual clinical antenatal care wherever possible.

6.2. Screening and enrolment

Details of all patients approached about the study will be recorded on the BABY PANDA Participant Screening/Enrolment Log which will be kept in the ISF, and should be available to be sent to the Trials Office upon request.

6.3 Registration

After eligibility for registration has been confirmed and informed consent has been received the participant can be registered to the study using the online database system. There will be Case Report Form (CRFs) embedded within the Giant PANDA database for those participating in the BABY PANDA sub study, and women will be identified using their Giant PANDA Trial number. A confirmation email will be sent to the CIs, local Principal Investigator (PI) and the enrolling site following a participant registering for BABY PANDA.

The local research team should add the participant to the BABY PANDA Participant Recruitment and Identification Log which links participants with their Giant PANDA Registration/Trial Number. PIs must maintain this document securely and it must not be submitted to the Trial Office. The BABY PANDA Participant Recruitment and Identification Log should be held in strict confidence at the local recruiting centres.

6.4 Informing the participant's GP and other parties

Information on participation in the study will be entered into the handheld paper or electronic maternity record as in usual clinical care, as the standard way of communicating with GPs and other relevant healthcare professionals (e.g. community-based midwives).

7. STUDY INTERVENTION

7.1. Study Procedures

7.1.1 Ambulatory blood pressure monitoring

Women who participate in this study will be provided with a pregnancy validated ambulatory BP monitor to measure up to a 24-hour BP response profile up to three times during pregnancy. It will be made clear to participants that further ambulatory BP monitoring sessions, beyond the first, are optional. The local research team will explain how to use and fit the ambulatory BP monitors and discuss a convenient time for the woman to undertake the 24-hour BP monitoring period in keeping with women's preferences and schedule of care.

The research team will encourage the woman to fit the monitor in the daytime, to maximise data capture of an 8-hour post-dose response window during daytime hours (08:00- 22:00). Women will also be offered phone and video support for home fitting to enable initiation of the 24-hour monitoring episode at their convenience. BP and heart rate will be recorded every 30 min during the day (08:00-22:00 h) and hourly at night (22:00-08:00 h).

Clear instructions will be given to the women about fitting the monitor in the minutes prior to ingesting her blood pressure medication and allowing the first BP reading to be taken. Following the first BP reading being successfully obtained (indicated by being displayed on the screen of the ambulatory device), the woman will then be asked to immediately take her dose of antihypertensives and record the time of ingestion on the participant diary.

Women will be asked to record antihypertensive medication ingestion times, sleep and wake times during the ambulatory monitoring periods (up to 24 hours) using a participant diary (paper and electronic versions available). Women will be asked to take their morning antihypertensive dose after having the ambulatory BP monitor fitted. Between episodes of monitoring or at completion of the study, women will have the option to return the ambulatory BP monitor at their next face-to-face antenatal contact, or for return to be arranged from their home via courier

7.1.2 Sample collection and processing

Urine and blood (ethylenediaminetetraacetic acid, serum) samples will be collected at routine antenatal visits up to 4 times in the antenatal period, alongside routine clinical bloods wherever possible. Blood samples will ideally be drawn in the morning following 15 minutes of being seated at rest to minimise physiological variation in renin and aldosterone concentrations between participants. Research teams will be asked to record the date and time of blood sampling, and data will be collected regarding medication ingestion times for the day the blood and urine samples were taken.

Samples will be transported to the lab within 4 hours and spun in a non-refrigerated centrifuge. Plasma will be separated following centrifugation and aliquoted immediately into tubes and stored at -20°C until assay. Women will be asked to provide mid-stream urine samples in a sterile urine pot. Samples will be stored at -20°C until assay. Blood and urine samples will be stored at participating sites and sent to the King's College London Department of Women and Children's Health, or the Maternal and Fetal Health Research Centre at the University of Manchester in batches by courier in appropriate environmental conditions over the course of the study (as undertaken in previous similar mechanistic studies by this group). A standard operating procedure (SOP) document will be provided to sites participating in the BABY PANDA study, detailing the sample collection, storage and transportation procedures. Where appropriate, Material Transfer Agreements will be arranged at sites where the samples will be transferred for analysis from an NHS facility to a University research laboratory. Blood and urine samples will be run in batches following completion of the study. Results therefore will not be available to clinicians for clinical interpretation. Sample disposal will be in accordance with all applicable legal and regulatory requirements, including the Human Tissue Act 2004 and any amendments thereto.

7.1.2 Follow up of results

If any abnormal results are found following processing of blood samples that may be relevant to clinical care (for example the detection of hyperaldosteronism), the sample will be deanonymized and follow up will be arranged as per NHS clinical protocol.

8. OUTCOME MEASURES AND TRIAL PROCEDURES

8.1 Outcome Measures

The following outcome measures in 8.1.1 and 8.1.2 will be used to characterise short-term BP response.

8.1.1 Principal Outcome

The principal outcome is 8-hour systolic BP post-dose response to labetalol/nifedipine. This is defined as the proportion of systolic BP readings ≥ 140 mmHg/number of BP readings within that time period.

The post-dose 8-hour response window will begin at the time of the ingestion of the antihypertensive agent, within the 24-hour ambulatory BP monitoring episode (as captured by the participant self-reported diaries). The time of the first dose will be classified as time point 0.

8.1.2 Secondary outcomes

- 8-hour diastolic BP post-dose response to labetalol/nifedipine (defined as the proportion of diastolic BP readings ≥ 90 mmHg/number of BP readings, where the 8-hour post-dose window is defined as per the primary outcome)
- 8-hour BP post-dose response to labetalol/nifedipine (defined as the proportion of BP readings ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic/number of BP readings, where the 8-hour post-dose window is defined as per the primary outcome)
- 8-hour BP post-dose variability expressed as reading to reading variability and standard deviation
- 8-hour post-dose mean arterial pressure (MAP)
- 8-hour post-dose mean maternal heart rate (HR)
- 8 hour BP response (systolic, diastolic, proportion of readings ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic/number of BP readings, and BP variability described for women on combination therapy (labetalol and nifedipine or another antihypertensive agent).
- 24-hour post-dose systolic BP response to antihypertensive agent: the proportion of systolic BP readings ≥ 140 mmHg/number of BP readings
- 24-hour post-dose diastolic, combined and BP response to antihypertensive agent: the proportion of diastolic BP readings ≥ 90 mmHg/number of BP readings.
- 24-hour post-dose BP response to antihypertensive agent: the proportion of BP readings ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic/number of BP readings.
- 24-hour post-dose BP variability
- 24-hour post-dose mean arterial pressure (MAP)
- 24-hour post-dose mean maternal heart rate (HR)

8.1.3 Blood and urine samples

Adherence to medication will be presented using urinary drug metabolite concentrations, presented descriptively. Renin and aldosterone concentrations will be presented, and will be considered in a multivariable model as part of an exploratory analysis.

8.2 Withdrawal of consent

If a woman wishes to withdraw consent to participate in the study, or for further contact or subsequent case note review, this should be clearly documented in the source data (date, reason and type of withdrawal) and on a withdrawal of consent form. Women will be able to withdraw consent for further contact at any time without giving a reason and with no effect on their (or their baby's) on-going care. Women will continue to receive usual clinical care if they withdraw from the study.

8.3 Schedule of assessments

Table 1: Schedule of Assessments

Visit	Screening	Baseline	Antenatal Period	Post Delivery
Eligibility check	x			
Valid informed consent	x			
Relevant medical history taken	x	x		
24-hour blood pressure monitoring (up to 3 times)			x	
Bloods and urine collected (during antenatal visits)		x	x	
Outcome data collection from case notes				x

Following valid informed consent being obtained, women will be provided with the 24 hour blood pressure monitor to take home, and given contact details for telephone support. Women will be given a diary with instructions of how to undertake the 24 hour monitoring, which will be done on a day to suit the woman and agreed with the research team. Women will also asked to complete sections of the diary during the 24 hour monitoring period. The 24 hour ambulatory BP monitoring procedure is described in section 7.1.1.

Blood and urine samples will be collected during scheduled antenatal visits, alongside clinical blood samples where possible to minimise inconvenience. Blood and urine tests will be collected up to 4 times during the antenatal period, at the scheduled antenatal visits.

Clinical data are routinely collected in maternity care during the antenatal period, birth, and up to the primary hospital discharge or 28 days post birth, whichever occurs sooner. Data will be collected within the Giant PANDA trial and includes details on dosage, undesirable effects of antihypertensive drugs, discontinuation of antihypertensive treatment, alterations to dose, additional/alternative antihypertensive drugs and persistence with treatment (where documented) will be captured from standard maternity notes, by case note review, as used in each maternity unit. Data collected as part of the Giant PANDA trial will include baseline demographic and pregnancy characteristics, health related quality of life, maternal, birth and neonatal outcomes and entered onto a secure online study-specific database (further details can be found in the Giant PANDA trial protocol

<https://www.birmingham.ac.uk/research/bctu/trials/womens/giantpanda/documentation.aspx> Additional data collected for BABY PANDA will include the participant completed diary, drug ingestion times, sleep and wake cycles.

9. ADVERSE EVENT REPORTING

9.1 Definitions

Table 2: Adverse event reporting definitions

Severity Definitions	Mild	Awareness of signs or symptoms that do not interfere with the participant's usual activity or are transient and resolved without treatment and with no sequelae.
	Moderate	A sign or symptom, which interferes with the participant's usual activity.
	Severe	Incapacity with inability to do work or perform usual activities.
Non-CTIMPs only		
Adverse Event	AE	Any untoward medical occurrence in a participant participating in the trial which does not necessarily have a causal relationship with the intervention received.

Related Event	RE	An event which resulted from the administration of any of the research procedures.
Serious Adverse Event	SAE	An untoward occurrence that: Results in death Is life-threatening* Requires hospitalisation or prolongation of existing hospitalisation Results in persistent or significant disability or incapacity Consists of a congenital anomaly/ birth defect Or is otherwise considered medically significant by the Investigator**
Unexpected Event	UE	The type of event that is not listed in the protocol as an expected occurrence.
Related and Unexpected Serious Adverse Event	N/A	A SAE that meets both the definition of a Related and Unexpected Event.

* The term life-threatening is defined as diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted.

** Medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definitions above.

9.2 Adverse event recording – general

The recording and reporting of Adverse Events (AEs) will be in accordance with the UK Policy Framework for Health and Social Care Research, the Principles of Good Clinical Practice (GCP) as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments) and the requirements of the Health Research Authority (HRA). Definitions for adverse event reporting are listed in Table 2: Adverse event reporting definitions in Section 9.1.

It is routine practice to record AEs in the participant's medical notes and it is also recommended that this includes the documentation of the assessment of severity and seriousness and also of causality (relatedness) in relation to the intervention(s) in accordance with the protocol.

9.3 Adverse event reporting in BABY PANDA

All BABY PANDA participant must be Giant PANDA participants and therefore AEs related to the intervention will be reported within the Giant PANDA trial as per the Giant PANDA trial protocol

(<https://www.birmingham.ac.uk/research/bctu/trials/womens/giantpanda/documentation.aspx>).

AEs related to BABY PANDA procedures (e.g. blood tests and 24 hour blood pressure monitoring) will be reported in BABY PANDA. There are not expected to be severe or numerous as the BABY PANDA procedures are part of routine clinical care.

9.4 Serious Adverse Advents (SAE) reporting in BABY PANDA

SAEs for women participating in the BABY PANDA trial will be reported as per the Giant PANDA trial protocol (<https://www.birmingham.ac.uk/research/bctu/trials/womens/giantpanda/documentation.aspx>).

There are no additional SAEs anticipated as being related to any of the study processes within BABY PANDA.

10.0 DATA HANDLING AND RECORD KEEPING

10.1 Source data

All women participating in the BABY PANDA study will have been enrolled in the Giant PANDA study. Data from the Giant PANDA database will only be used in BABY PANDA if the participant has given explicit consent to be enrolled in the BABY PANDA study. Use of the secure online Giant PANDA study-specific database will allow access to relevant clinical data and outcomes including baseline demographic and pregnancy characteristics, maternal, birth and neonatal outcomes, data on dosage, side-effects, continuation of antihypertensive treatment, alterations to dose, additional treatments and adherence. The additional data generated in this study (participant diary data, ambulatory BP monitoring data, renin-angiotensin system markers and drug metabolite concentrations) will be entered into dedicated e-Clinical Research Forms within the Giant PANDA study secure online study-specific database.

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. In order to allow for the accurate reconstruction of the study and clinical management of participants, source data will be accessible and maintained. Some data variables may be entered directly onto the CRF, these are clearly identified and detailed below in Table 3: Source data in .

Table 3: Source data in the BABY PANDA study

Data	Source
<i>Participant Reported Outcomes</i>	Outcome data (e.g. medication dosages) will be collected and stored as in the Giant PANDA study. The participant-completed CRF (e.g. the participant diary) is the source and will be completed on paper (the original record of the participant diary will be kept with the participant's trial record at site, and copies posted to the BCTU Trial Office). The data from the participant diaries will be uploaded on to the database by the recruiting sites.
<i>Lab results</i>	The original lab report (which may be electronic) is the source and will be kept and maintained, in line with normal local practice. Information will be transcribed onto the Giant PANDA CRFs. The urine and blood samples will be processed after study closure, and the results will not be available to treating clinicians for clinical interpretation.
<i>24 hour Blood pressure</i>	Data from the 24 hour ambulatory blood pressure monitor will be downloaded and transcribed on to the BABY PANDA CRF
<i>Clinical event data</i>	The original clinical annotation is the source document. This may be found on clinical correspondence, or electronic or paper participant records. Clinical events reported by the participant, either in or out of clinic (e.g., phone calls), must be documented in the source documents.
<i>Recruitment</i>	The original record of the recruitment is the source. It is held on BCTU servers as part of the Giant PANDA study database, and data entry system.
<i>Withdrawal</i>	Were a participant expresses a wish to withdraw, the conversation must be recorded in the medical record.

10.2 Case Report Form (CRF) completion

Data reported on each form will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried. Staff delegated to complete electronic case report forms (eCRFs) will be trained to adhere to eCRF completion guidelines.

In all cases it remains the responsibility of the site's PI to ensure that the eCRF has been completed correctly and that the data are accurate. This will be evidenced by the signature of the site's PI, or delegate(s), on the eCRF. Site PIs will be provided with a copy of their site data (or access to download their site data) after

database lock. Data from the participant completed diaries will be uploaded on to the study database (<https://bctu-redcap.bham.ac.uk/>) by the recruiting sites.

10.3 Data management

Data entry will be completed by the sites via a bespoke BCTU trial database. The data capture system will conduct automatic range checks for specific data values to ensure high levels of data quality. Queries will be raised using data clarification forms (DCFs) via the trial database, with the expectation that these queries will be completed by the site within 30 days of receipt. Overdue data entry and data queries will be requested on a monthly basis. Processes will be employed to facilitate the accuracy of the data included in the final report. These processes will be detailed in the data management plan and include the processes of data entry, data queries and self-evident corrections on trial data.

Samples will be shipped to the Maternal and Fetal Health Research Centre at the University of Manchester, or to the Department of Women and Children's Health at King's College London. Samples will be identified by their Giant PANDA participant ID number, and date of sampling only. Following sample processing, results will be uploaded on to the Giant PANDA database (<https://bctu-redcap.bham.ac.uk/>) by the central coordinating research team.

10.4 Data security

University of Birmingham has policies in place, which are designed to protect the security, accuracy, integrity and confidentiality of Personal Data. The study will hold data in accordance with the Data Protection Act (2018 and subsequent amendments). The Trial Office has arrangements in place for the secure storage and processing of the trial data which comply with University of Birmingham policies.

The Trial Database System incorporates the following security countermeasures:

Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.

Logical measures for access control and privilege management: including restricted accessibility, access controlled servers, separate controls of non-identifiable data.

Network security measures: including site firewalls, antivirus software and separate secure network protected hosting.

System management: the system will be developed by the Programming Team at the Trial Office, and will be implemented and maintained by the Programming Team

System design: the system will comprise of a database and a data entry application with firewalls, restricted access, encryption and role based security controls.

Operational processes: the data will be processed and stored within BCTU

System audit: The system will benefit from the following internal/external audit arrangements:

- Internal audit of the system
- Periodic IT risk assessment

Data Protection Registration: University of Birmingham's Data Protection Registration number is Z6195856.

10.5 Site Archiving

It is the responsibility of the PI and their institution to ensure all essential study documentation and source documents at their site are securely retained for at least 25 years. No documents should be destroyed without prior approval from the Trials Office.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Site set-up and initiation

All PIs will be asked to sign the necessary agreements including a Site Signature and Delegation log between the PI and the Study Office and supply a current CV and GCP certificate. All members of the site research team are required to sign the Site Signature and Delegation Log, which details which tasks have been

delegated to them by the PI. The Site Signature and Delegation Log should be kept up to date by the PI. It is the PI's responsibility to inform the Trial Office of any changes in the site research team.

Prior to commencing recruitment, each recruiting site will undergo a process of site initiation, either a meeting or a teleconference, at which key members of the site research team are required to attend, covering aspects of the study design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an ISF containing essential documentation, instructions, and other documentation required for the conduct of the study.

11.2 Monitoring

Monitoring is carried out as part of the Giant PANDA study, as required following study-specific risk assessment by BCTU and as documented in the monitoring plan (<https://www.birmingham.ac.uk/research/bctu/trials/womens/giantpanda/documentation.aspx>). Given the low-risk nature of this sub-study, central monitoring will be routine. In addition to the monitoring for Giant PANDA, the study team will monitor data for quality and additional eCRF completion for those participating in the BABY PANDA study.

11.3 Audit and inspection

The Investigator will permit trial-related monitoring, audits and ethical review at their site and provide direct access to source data/documents. The investigator will comply with these visits and any required follow-up. Sites are also requested to notify the Trial Office of any relevant inspections or local audits.

11.4 Notification of Serious Breaches

The sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of GCP in connection with that study or of the protocol relating to that study. Sites are therefore requested to notify the Trial Office of any suspected study-related serious breach of GCP and/or the trial protocol as soon as they become aware of them. Where the Trial Office is investigating whether or not a serious breach has occurred, sites are also requested to co-operate with the Trial Office in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action. Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment.

12. END OF STUDY DEFINITION

The end of study will be 3 months after the database lock of the Giant PANDA trial.

13. STATISTICAL CONSIDERATIONS

13.1 Sample size

The sample size calculation for this study is driven by the principal outcome (8-hour BP post-dose systolic BP response to nifedipine or labetalol: proportion of systolic BP readings ≥ 140 mmHg/ number of BP readings). There are no published data to inform this sample size calculation as the paper by Shawkat et al. reported the number of women who spent the whole of the defined 8-hour response window in specified BP target ranges rather than the proportion of BP readings in target per individual. Unpublished ambulatory BP data generated by the same research team (Maternal Antenatal Vascular Team led by Prof Jenny Myers, University of Manchester) comparing the proportion of ambulatory BP readings in target ($<140/90$ mmHg) over 24 hours between women taking labetalol ($n = 19$) and nifedipine ($n = 25$) reported a mean difference of 12.5% (95% CI -1.7% to 26.8%) between treatment groups with standard deviations in each group ranging from 22-24%.

Assuming a standard deviation of 24%, a sample size of 246 women (123 women per group) will have 90% power to detect a minimally important clinical difference (MICD) in 8-hour post-dose systolic BP response of

10%, using a 5% two-sided alpha, which is equivalent to a standardised difference of 0.42. We aim to recruit 274 women (137 women per group) to BABY PANDA to account for up to 10% attrition.

This sample size also retains power to detect clinically meaningful differences in short-term BP response to labetalol or nifedipine monotherapy in Black women. Assuming at least 26% of women recruited are Black and a standard deviation of 24%, we would have 90% power to detect a 20% difference in 8-hour BP response (based on Stott, Bolten, Paraschiv, et al. 2016) for those in the labetalol or nifedipine monotherapy groups. As the proportion of Black women recruited to the BABY PANDA study increases, the smaller the BP differences we will be able to detect in response to labetalol or nifedipine monotherapy, whilst retaining high levels of power.

13.2 Analysis of outcomes

A separate Statistical Analysis Plan (SAP) will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of the planned analyses is given below.

The principal analyses will only include short-term monitoring windows where the woman was taking either nifedipine monotherapy or labetalol monotherapy at the time of the short-term monitoring. Further exploratory analyses will be conducted which include all short-term monitoring windows regardless of what type of antihypertensive therapy a woman was taking at the time of the short-term monitoring, further details will be available in the SAP.

13.2.1 Short-term BP response of antihypertensive agents

This section outlines the analysis methods intended to assess the first objective (to determine short-term BP response of antihypertensive agents in women with pregnancy hypertension).

13.2.1.1 Principal outcome

The principal outcome will be calculated as the proportion of systolic BP readings ≥ 140 mmHg out of the total number of BP readings during the short-term monitoring window (8-hour post-dose). The planned primary analysis will exclude any BP recordings following a second dose of antihypertensive agent within the 8-hour post-dose response window. A sensitivity analysis will be conducted to assess the impact of this. In women who have their BP monitored using the ambulatory BP monitor on more than one occasion during their pregnancy, only one BP monitoring period will be included in the analysis (i.e. the woman will only be included in the model once). Covariate-constrained selection methods will be used to select which ambulatory BP monitor reading is included in the analysis, to minimise imbalances in gestational age and type of antihypertensive drug taken at the time of monitoring. Means and standard deviations will be reported and an adjusted generalised linear model will be used with an appropriate link function that provides the best fit for the data to calculate the mean difference in proportions (and 95% confidence intervals) between the groups. All analyses will be adjusted for variables which include hypertension type, ethnicity, diabetes and singleton pregnancy.

To account for the fact that some women will have their BP monitored using the ambulatory BP monitor on more than one occasion during their pregnancy, a further analysis will be conducted which includes all short-term monitoring windows using a repeated measures (multi-level) mixed model. In this model, time will be regarded as the gestational age when the short-term monitoring was performed. Time by antihypertensive therapy effects will be examined by including the corresponding parameter in the model. To assess the fact that a woman's antihypertensive therapy may be different at different BP monitoring assessments, a time-varying co-variate for antihypertensive therapy will be explored. Gestational age will be considered as a continuous variable in these analyses, providing insight into whether BP response differs according to gestational age. It is possible that ambulatory BP monitoring episodes will be clustered around certain gestational age time windows relating to antenatal visits. We will examine the pattern of gestational ages and ensure that interpretation and clinical applicability of results are appropriate to any limitations of the data in this regard.

13.2.1.2 Secondary outcomes

The secondary outcomes (8-hr post-and 24-hr post-dose response (as defined above in section 8.1.2) will be analysed in a similar manner to the principal outcome. BP variability and response profiles (8-hr post-dose and 24-hr) will be modelled using an indirect response model (Shawkat et al. 2018).

13.2.2 Association between short-term BP response and long-term BP control

This section outlines the analysis methods used to assess the second objective (to explore the association between short-term BP response and long-term BP control).

Primarily, long-term BP control will be defined as the proportion of days with systolic BP readings ≥ 160 mmHg out of the total number of days with BP readings (measured by a healthcare professional) (as per the primary maternal outcome in the Giant PANDA study) and short-term BP response as the principal outcome in BABY PANDA. The association between short-term BP response with long-term BP control will be assessed by including the short-term BP response as a covariate in an adjusted generalised linear model (with appropriate link function) where long-term BP control is the outcome. Non-linear effects will be explored as appropriate.

Further analyses will include redefining short-term BP response (using secondary outcomes) and using alternative clinical outcomes related to long-term BP control (including but not limited to birthweight centiles and non-severe hypertension).). These will be assessed in a similar manner as above. Additional work will explore the relationship between short-term BP response and ongoing persistence with antihypertensive drug. We will further aim to explain how these relate to long-term BP control.

13.2.3 Association between maternal characteristics, disease and genetic markers with short-term BP response

This section outlines the analysis methods used to assess the third objective (to assess whether maternal characteristics, drug metabolites or disease markers provide mechanistic insight into differing responses to antihypertensive agents across individuals.).

An exploratory analysis will investigate if predefined variables of interest have any relationship with short-term BP response to labetalol or nifedipine (defined using outcomes described in A). The following variables will be considered: (a) maternal and pregnancy characteristics (ethnicity, gestational age, pregnancy hypertension type), (b) adherence to prescribed antihypertensive agent (as assessed by urinary antihypertensive agent metabolite concentration), and (c) renin-angiotensin system activity markers (direct renin concentration, aldosterone concentration). These variables will be considered together in a multivariable model. Interaction terms will be included as appropriate to assess for varying treatment effect. Standard methods and thresholds for variable selection will be agreed in the statistical analysis plan prior to any analyses being performed using the approach outlined by Heinze (Heinze, Wallisch, and Dunkler 2018).

13.3 Planned final analyses

The primary analysis for the study will occur once all participants have completed the assessment and corresponding outcome data has been entered onto the trial database and validated as being ready for analysis. The BABY PANDA study will be reported following the publication of the Giant PANDA trial.

14. STUDY ORGANISATIONAL STRUCTURE

14.1 Sponsor

The Sponsor for this study is University of Birmingham (UoB).

14.2 Coordinating centre

The trial coordinating centre (Trial Office) is Birmingham Clinical Trials Unit (BCTU), based at UoB.

14.3 Trial Management Group

The role of the trial management group is to monitor all aspects of the conduct and progress of the study, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the study itself. The TMG will meet sufficiently frequently to fulfil its function.

14.4 Co-investigator group

The Co-investigator group, an extended TMG, will comprise all members of the co-applicant group and the members of the TMG to review progress, troubleshoot and plan strategically.

14.5 Trial Steering Committee

As an aligned study, BABY PANDA will utilise the infrastructure of Giant PANDA, and fall under the remit of the Giant PANDA TSC. Further details can be found in the Giant PANDA protocol (<https://www.birmingham.ac.uk/research/bctu/trials/womens/giantpanda/documentation.aspx>).

14.6 Data Monitoring Committee

As an aligned study, BABY PANDA will **utilise the infrastructure of Giant PANDA**, fall under the remit of the Giant PANDA DMC, and BABY PANDA will be discussed at Giant PANDA DMC meetings. Further details can be found in the Giant PANDA protocol (<https://www.birmingham.ac.uk/research/bctu/trials/womens/giantpanda/documentation.aspx>).

14.7 Finance

BABY PANDA is funded by the National Institute for Health Research Evaluation of Efficacy and Mechanism programme and is registered on the CRN portfolio.

15. ETHICAL CONSIDERATIONS

The study will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and applicable UK Acts of Parliament and Statutory Instruments (and relevant subsequent amendments), and the Principles of GCP as set out in the UK Statutory Instrument (2004/1031; the Data Protection Act 2018, and the Human Tissue Act 2004 and subsequent amendments). The protocol will be submitted to and approved by the REC prior to the start of the trial. Before any participants are enrolled into the study, the PI at each site is required to obtain the necessary local approval.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

16. DATA PROTECTION AND CONFIDENTIALITY

Personal data and sensitive personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018 (and subsequent amendments). Women will always be identified using their unique study number, on eCRFs and any correspondence with the BCTU. Participants will acknowledge the transfer and storage of their informed consent form to the Trial Office. This will be used to perform central monitoring of the consent process.

Personal data that will be collected and/or analysed include name, date of birth, NHS number, email and telephone numbers, postal address, health information (of both the woman, and the baby from the index pregnancy) and medical history. The BCTU will maintain the confidentiality of all participant data and will not disclose information by which women may be identified to any third party other than those directly involved in the treatment of the woman and organisations for which the woman has given explicit consent for data transfer. Representatives of the trial team and sponsor may be required to have access to participant's notes for quality assurance purposes, but participants should be reassured that their confidentiality will be respected at all times.

17. FINANCIAL AND OTHER COMPETING INTERESTS

There are no financial or other competing interests related to the results of this study. Members of the TSC and DMC are required to provide declarations on potential competing interests as part of their membership of the committees. Authors are similarly required to provide declarations at the time of submission to publishers.

18. INSURANCE AND INDEMNITY

UoB has in place Clinical Trials indemnity coverage for this trial which provides cover to UoB for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at UoB's discretion provide cover for non-negligent harm to participants.

With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

19. AMENDMENTS

Approval for the study will be sought from the Health Research Authority, REC and local Research & Development departments at study sites. Any amendments will be submitted as required with the sponsor's approval and implemented following regulatory approval.

20. ACCESS TO FINAL DATASET

The final dataset will be available to members of the Trial Management and co-applicant group who need access to the data to undertake the final analyses. The CI will have access to the full Giant PANDA dataset after database lock.. Site investigators will not have access to the full data set and must not use, disseminate or publish any data without the prior written consent of the CIG and TSC. Site-specific data will be provided to site PIs at the end of the study. Requests for the dataset from appropriate academic parties will be considered by the chief investigator in accordance with the data-sharing policies of King's College London, the University of Manchester, and the BCTU, with input from the co-investigator group where applicable.

21. PUBLICATION PLAN

Results of this study will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the CI and authorship will be determined by the CI in collaboration with the CIG and TMG. The publications from the trial will be accessible from the trial website, and via academic search engines (<https://pubmed.ncbi.nlm.nih.gov/>). During the consent process to the Giant PANDA study, women are asked if they wish to be emailed a copy of the findings of the study following study completion and peer reviewed publication. BABY PANDA results will be communicated to women participating in the BABY PANDA study who requested to be informed of the outcome of the Giant PANDA trial.

Any secondary publications and presentations prepared by other investigators must be reviewed and approved by the co-investigators. Manuscripts must be submitted in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the study was performed with the support of UoB. Intellectual property rights will be addressed in the External CI agreement and Clinical Study Site Agreement between Sponsor and site.

22. REFERENCE LIST

1. Abalos, E., L. Duley, D. W. Steyn, C. Gialdini. 2018. "Antihypertensive Drug Therapy for Mild to Moderate Hypertension during Pregnancy", *Cochrane Database Syst Rev*, 10: CD002252.
2. <https://doi.org/10.1002/14651858.CD002252.pub4>. Copyright.
3. Abou-Dakn, M. and S. Wenzel. 2018. "Validation of the PHYSIO-PORT UP Ambulatory Blood Pressure Monitor in Pregnant Women According to the European Society of Hypertension International Protocol Revision 2010." *Journal of Human Hypertension*, **32**, 770–774 (2018).
<https://doi.org/10.1038/s41371-018-0101-y>.
4. Agyemang, C., R. Bhopal, and M. Bruijnzeels. 2005. "Negro, Black, Black African, African Caribbean, African American or What? Labelling African Origin Populations in the Health Arena in the 21st Century." *Journal of Epidemiology and Community Health* 59 (12): 1014 LP – 1018.
<https://doi.org/10.1136/jech.2005.035964>.
5. Bellomo, G., P. L. Narducci, F. Rondoni, G. Pastorelli, G. Stangoni, G. Angeli, and P. Verdecchia. 1999. "Prognostic Value of 24-Hour Blood Pressure in Pregnancy." *Journal of the American Medical Association*. 1999 Oct 20;282(15):1447-52. <https://doi.org/10.1001/jama.282.15.1447>.
6. Bradby, H. 2003. "Describing Ethnicity in Health Research." *Ethnicity & Health* 8 (1): 5–13.
7. <https://doi.org/10.1080/135578503033555>.
8. Bramham, K., B. Parnell, C. Nelson-Piercy, P. T. Seed, L. Poston, and L. C. Chappell. 2014. "Chronic Hypertension and Pregnancy Outcomes: Systematic Review and Meta-Analysis." *BMJ* 348 (apr15 7): g2301– g2301. <https://doi.org/10.1136/bmj.g2301>.
10. Buchbinder, A., B. M. Sibai, S. Caritis, C. MacPherson, J. Hauth, M. D. Lindheimer, M. Klebanoff, et al. 2002. "Adverse Perinatal Outcomes Are Significantly Higher in Severe Gestational Hypertension than in Mild Preeclampsia." *American Journal of Obstetrics and Gynecology*. Jan;186(1):66-71. <https://doi.org/10.1067/mob.2002.120080>.
12. Chappell, L., C., and A. L. David. 2016. "Improving the Pipeline for Developing and Testing Pharmacological Treatments in Pregnancy." *PLoS Medicine* 13(11): e1002161.
<https://doi.org/10.1371/journal.pmed.1002161>.
13. Costantine, M., M. 2014. "Physiologic and Pharmacokinetic Changes in Pregnancy." *Frontiers in Pharmacology*. <https://doi.org/10.3389/fphar.2014.00065>.
15. Dadelszen, P., V., and L. A. Magee. 2002. "Fall in Mean Arterial Pressure and Fetal Growth Restriction in Pregnancy Hypertension: An Updated Metaregression Analysis." *Journal of Obstetrics and Gynaecology Canada*. Dec;24(12):941-5. [https://doi.org/10.1016/S1701-2163\(16\)30592-8](https://doi.org/10.1016/S1701-2163(16)30592-8).
16. Feghali, M., R. Venkataramanan, and S. Caritis. 2015. "Pharmacokinetics of Drugs in Pregnancy." *Seminars in Perinatology*. <https://doi.org/10.1053/j.semperi.2015.08.003>.
17. Gabbai, F., B., M. Rahman, B. Hu, L. J. Appel, J. Charleston, G. Contreras, M. L. Faulkner, et al. 2012. "Relationship between Ambulatory BP and Clinical Outcomes in Patients with Hypertensive CKD." *Clinical Journal of the American Society of Nephrology*. Nov;7(11):1770-6.
<https://doi.org/10.2215/CJN.11301111>.
18. Gibbins, K., J., R. M. Silver, H. Pinar, U. M. Reddy, C. B. Parker, V. Thorsten, M. Willinger, et al. 2016. "Stillbirth, Hypertensive Disorders of Pregnancy, and Placental Pathology." *Placenta*. Jul;43:61-8.
<https://doi.org/10.1016/j.placenta.2016.04.020>.
19. Gupta, A., K., N. R. Poulter, J. Dobson, S. Eldridge, et al on behalf of ASCOT investigators. 2010. "Ethnic Differences in Blood Pressure Response to First and Second-Line Antihypertensive Therapies in Patients Randomized in the ASCOT Trial." *American Journal of Hypertension* 23 (9): 1023–30.
<https://doi.org/10.1038/ajh.2010.105>.
21. Heinze, G., C. Wallisch, and D. Dunkler. 2018. "Variable Selection – A Review and Recommendations for the Practicing Statistician." *Biometrical Journal*. <https://doi.org/10.1002/bimj.201700067>.
22. Ho, A., L. Webster, L. Bowen, F. Creighton, S. Findlay, C. Gale, M. Green, et al. 2020. "Research Priorities for Pregnancy Hypertension: A UK Priority Setting Partnership with the James Lind Alliance." *BMJ Open* 10 (7): e036347. <https://doi.org/10.1136/bmjopen-2019-036347>.

23. Iniesta, R., D. Campbell, C. Venturini, L. Faconti, S. Singh, M. R. Irvin, R. M. Cooper-DeHoff, et al. 2019. "Gene Variants at Loci Related to Blood Pressure Account for Variation in Response to Antihypertensive Drugs Between Black and White Individuals." *Hypertension* 74 (3): 614–22.
24. <https://doi.org/10.1161/hypertensionaha.118.12177>.
25. Liu, J., L. Yang, H. Teng, Y. Cao, J. Wang, B. Han, L. Tao, et al. 2020. "Visit-to-Visit Blood Pressure Variability and Risk of Adverse Birth Outcomes in Pregnancies in East China." *Hypertension Research*.
26. <https://doi.org/10.1038/s41440-020-00544-7>.
27. Magee, L., A., P. V. Dadelszen, E. Rey, S. Ross, E. Asztalos, K. E. Murphy, J. Menzies, et al. 2015. "Less-Tight versus Tight Control of Hypertension in Pregnancy." *New England Journal of Medicine*. Jan;372:407- 417. <https://doi.org/10.1056/NEJMoa1404595>.
28. Magee, L., A., J. Singer, T. Lee, R. J. McManus, S. Lay-Flurrie, E. Rey, L. C. Chappell, J. Myers, A. G. Logan, and P. V. Dadelszen. 2020. "Are Blood Pressure Level and Variability Related to Pregnancy Outcome? Analysis of Control of Hypertension in Pregnancy Study Data." *Pregnancy Hypertension*. Jan;19: 87-93. <https://doi.org/10.1016/j.preghy.2019.12.002>.
29. Materson, B., J. 2007. "Variability in Response to Antihypertensive Drugs." *The American Journal of Medicine* 120 (4, Supplement 1): S10–20.
<https://doi.org/https://doi.org/10.1016/j.amjmed.2007.02.003>.
30. O'Brien, E. 2008. "Ambulatory Blood Pressure Measurement: The Case for Implementation in Primary Care." *Hypertension*. Jun;51(6):1435-41.
<https://doi.org/10.1161/HYPERTENSIONAHA.107.100008>.
31. Parati, G., J. E. Ochoa, C. Lombardi, and G. Bilo. 2013. "Assessment and Management of Blood-Pressure Variability." *Nature Reviews Cardiology*. Mar;10(3):143-55.
<https://doi.org/10.1038/nrcardio.2013.1>.
32. Pickering, T., G., D. Shimbo, and D. Haas. 2006. "Ambulatory Blood-Pressure Monitoring." *New England Journal of Medicine*. June; 354:2368-2374. <https://doi.org/10.1056/NEJMra060433>.
33. Rhodes, C., A., D. G. Beevers and D. Churchill. 2018. "A Randomized Trial of Ambulatory Blood Pressure Monitoring versus Clinical Blood Pressure Measurement in the Management of Hypertension in Pregnancy. A Feasibility Study." *Pregnancy Hypertension*. Jan;11:142-144.
<https://doi.org/10.1016/j.preghy.2017.09.006>.
34. Salazar, M., R., W. G. Espeche, C. E. L. Sisniegues, B. C. L. Sisniegues, E. Balbín, R. N. Stavile, C. March, et al. 2019. "Nocturnal Hypertension in High-Risk Mid-Pregnancies Predict the Development of Preeclampsia/Eclampsia." *Journal of Hypertension* 37 (1): 182–86.
35. <https://doi.org/10.1097/HJH.0000000000001848>.
36. Saremi, A., T., M-A. Shafiee, M. Montazeri, N. Rashidi, and M. Montazeri. 2018. "Blunted Overnight Blood Pressure Dipping in Second Trimester; A Strong Predictor of Gestational Hypertension and Preeclampsia." *Current Hypertension Reviews*. 15(1):70-75.
<https://doi.org/10.2174/1573402114666180924143801>.
37. Shawkat, E., H., M. C. Chmiel, L. Webster, L. Chappell, E. D. Johnstone, and J. E. Myers. 2018. "The Effect of Labetalol and Nifedipine MR on Blood Pressure in Women with Chronic Hypertension in Pregnancy." *Pregnancy Hypertension*. Jan;11:92-98. <https://doi.org/10.1016/j.preghy.2017.12.007>.
38. Steegers, E., A., P., P. V. Dadelszen, J. J. Duvekot, and R. Pijnenborg. 2010. "Pre-Eclampsia." In *The Lancet*. [https://doi.org/10.1016/S0140-6736\(10\)60279-6](https://doi.org/10.1016/S0140-6736(10)60279-6).
39. Stott, D., M. Bolten, D. Paraschiv, I. Papastefanou, J. B. Chambers, and N. A. Kametas. 2016. "Maternal Ethnicity and Its Impact on the Haemodynamic and Blood Pressure Response to Labetalol for the Treatment of Antenatal Hypertension." *Open Heart*. Mar 22;3(1):e000351.
<https://doi.org/10.1136/openhrt-2015-000351>.
40. Stott, D., M. Bolten, M. Salman, D. Paraschiv, A. Douiri, and N. A. Kametas. 2016. "A Prediction Model for the Response to Oral Labetalol for the Treatment of Antenatal Hypertension". *Journal of Human Hypertension*. 31 (2): 126–31. <https://doi.org/10.1038/jhh.2016.50>.

-
41. Turner, J., R., A. J. Viera, and D. Shimbo. 2015. "Ambulatory Blood Pressure Monitoring in Clinical Practice: A Review." *American Journal of Medicine*. Jan;128(1):14-20. <https://doi.org/10.1016/j.amjmed.2014.07.021>.
 42. Webster, L., M., K. Bramham, P. T. Seed, M. Homsy, K. Widdows, A. J. Webb, C. Nelson-Piercy, et al. 2019. "The Impact of Ethnicity on Adverse Perinatal Outcome in Women with Chronic Hypertension: A Cohort Study." *Ultrasound in Obstetrics and Gynecology*. Jul;54(1):72-78. <https://doi.org/10.1002/uog.20132>.
 43. Webster, L., M., J. E. Myers, C. Nelson-Piercy, K. Harding, J. K. Cruickshank, I. Watt-Coote, A. Khalil, C. Wiesender, P. T. Seed, and L. C. Chappell. 2017. "Labetalol Versus Nifedipine as Antihypertensive Treatment for Chronic Hypertension in Pregnancy: A Randomized Controlled Trial." *Hypertension*. Nov;70(5):915-922. <https://doi.org/10.1161/HYPERTENSIONAHA.117.09972>.
 44. Webster, L., M., K. Reed, J. E. Myers, A. Burns, P. Gupta, P. Patel, C. Wiesender, P. T. Seed, C. Nelson-Piercy, and L. C. Chappell. 2019. "Quantifying Adherence to Antihypertensive Medication for Chronic Hypertension during Pregnancy." *Pregnancy Hypertension*. Jul;17:12-14. <https://doi.org/10.1016/j.preghy.2019.05.004>.
 46. Webster, L., M., C. Gill, P. T. Seed, K. Bramham, C. Wiesender, C. Nelson-Piercy, J. E. Myers, and L. C. Chappell. 2018. "Chronic Hypertension in Pregnancy: Impact of Ethnicity and Superimposed Preeclampsia on Placental, Endothelial, and Renal Biomarkers." *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* 315 (1): R36–47. <https://doi.org/10.1152/ajpregu.00139.2017>.
 47. Webster, L., M., A. Webb and L. C. Chappell. 2018. "What is the evidence for using labetalol as a first-line treatment option for hypertension in pregnancy?" *Drug and therapeutics bulletin* 56(9): 107-111, <https://doi.org/10.1136/dtb.2018.9.000008>.
 48. Whybrow, R., L. Webster, J. Girling, H. Brown, H. Wilson, J. Sandall, and L. C. Chappell. 2020.
 49. "Implementation of National Antenatal Hypertension Guidelines: A Multicentre Multiple Methods Study." *BMJ Open* 10 (10): e035762. <https://doi.org/10.1136/bmjopen-2019-035762>.