TRIAL PROTOCOL

Giant PANDA

Pregnancy ANtihypertensive Drugs: which Agent is best?

This protocol has regard for the HRA and SPIRIT guidance

Version Number:	1.2
Version Date:	16.08.2023

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.				
Amendment number	**Date of amendment**	**Protocol version number**	**Type of amendment**	**Summary of amendment**

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Protocol Sign Off

CI Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol.
I agree to ensure that the confidential 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 study publically 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 planned in this protocol will be explained.
This protocol has been approved by:

Trial Name:	Pregnancy ANtihypertensive Drugs: which Agent is best? Giant PANDA study
Protocol Version Number: Protocol Version Date:	Version: 1.2 16.08.2023
CI Name:	Professor Lucy Chappell
Trial Role:	Chief Investigator
Signature and date:	 22/ 08/ 2023

Sponsor statement:

By signing the IRAS form for this trial, University of Birmingham, acting as sponsor of this trial confirm approval of this protocol.

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PI Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the trial in compliance with the approved protocol.
I agree to ensure that the confidential 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.

This protocol has been approved by:

Trial Name:	Pregnancy ANtihypertensive Drugs: which Agent is best? Giant PANDA study
Protocol Version Number:	Version: 1.2
Protocol Version Date:	16.08.2023
PI Name:	
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Trial website	TBA
Trial social media	TBA

ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
BCTU	Birmingham Clinical Trials Unit
CI	Chief Investigator
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Forms
GCP	Good Clinical Practice
HRA	Health Research Authority
ICF	Informed Consent Form
ISF	Investigator Site File
ITT	Intention To Treat
MHRA	Medicines and Healthcare products Regulatory Agency
NICE	The National Institute for Health and Care Excellence
PI	Principal Investigator
PIS	Participant Information Sheet
PPIE	Public and patient involvement and engagement
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
QALYs	Quality-Adjusted Life Years
UoB	University of Birmingham

DEFINITIONS

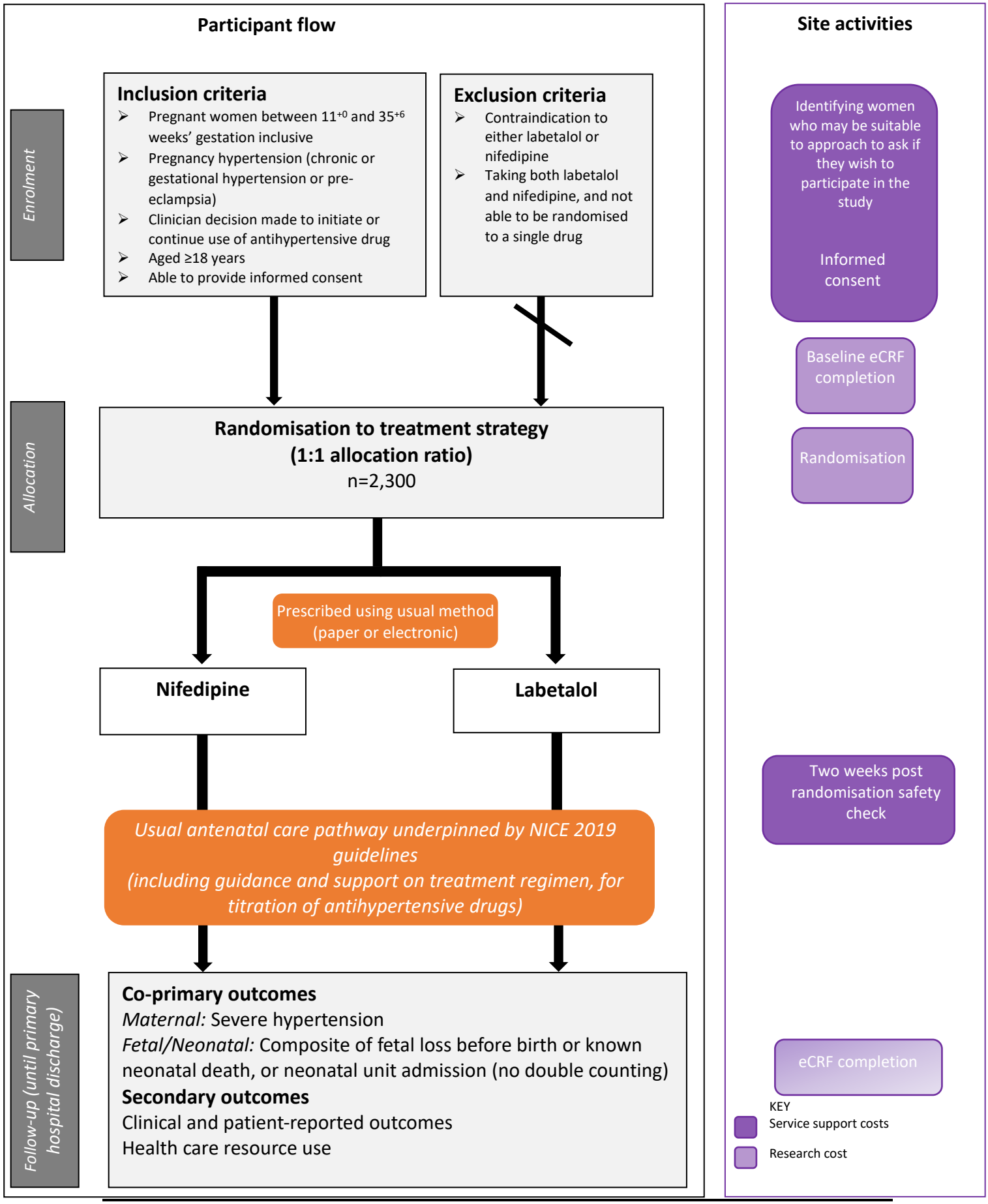
Term	Abbreviation	Description
Policies	POL	Policies are developed to describe the approach of the University of Birmingham (UoB) on areas that heavily regulated. Policies may also be developed when there is ambiguity in how regulatory requirements should be implemented in the QMS or when procedures to be captured in the QMS address areas controversial within the UoB at the time of implementation. Policies explain why the UoB has its procedures, especially when they seem to deviate from the regulatory requirements. Policies should be read in conjunction with the relevant SOP. Policies that are not part of a Quality Manual are coded up as 'POL'.
Quality Control Documents	QCD	Quality Control Documents can be instructions, forms, templates or checklists. They are developed to share best practices, promote standardisation to guarantee quality standards are maintained and reduce resources otherwise

		needed to develop similar documents. Unless indicated otherwise in the relevant SOP, QCDs are not mandatory and are designed to be an optional aid to UoB staff.
Quality Management System	QMS	A Quality Management System (QMS) is a system that includes procedures and policies to describe how certain tasks should be performed and that encapsulate any standards and/or regulatory requirements that may apply to those tasks. By adhering to the Quality Management System, the user and the UoB will be assured that applicable regulations are adhered to.
Standard Operating Procedures	SOP	Standard Operating Procedures are detailed written instructions to achieve uniformity in the performance of a specific function. They define tasks, allocate responsibilities, detail processes, indicate documents and templates to be used and cross-reference to other work instructions and guidance or policy documents. They are standards to which the UoB may be audited or inspected.
Adverse Event	AE	Any untoward medical occurrence in a participant or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
Adverse Reaction	AR	All untoward and unintended responses to an IMP related to any dose administered.
Serious Adverse Event	SAE	Any untoward medical occurrence or effect that: • Results in death or is life-threatening* • Requires hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability or incapacity • Is a congenital anomaly/birth defect • Or is otherwise considered medically significant by the Investigator**
Serious Adverse Reaction	SAR	An Adverse Reaction which also meets the definition of a Serious Adverse Event
Unexpected Adverse Reaction	UAR	An AR, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unapproved IMP or (compendium of) Summary of Product Characteristics (SPC) for a licensed product). When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.
Suspected Unexpected Serious Adverse Reaction	SUSAR	A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information. A SUSAR should meet the definition of an AR, UAR and SAR.
Source data	Case Note Review	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial
Birmingham Clinical Trials Unit	BCTU	The co-ordinating centre for the trial.

TRIAL SUMMARY:

Title	Pregnancy ANtihypertensive Drugs: which Agent is best?
Research question	In women with pregnancy hypertension (P), what is the effect of a treatment strategy with nifedipine (I) versus labetalol (C) on severe maternal hypertension (O) and a composite of fetal or neonatal death, or neonatal unit admissions (O)?
Aim	To evaluate the effect of different antihypertensive drugs in women with pregnancy hypertension on maternal and fetal/neonatal outcomes.
Objectives	Primary objective: • To evaluate if treatment with nifedipine (calcium channel blocker), compared to labetalol (mixed alpha/beta blocker) in women with pregnancy hypertension, reduces severe maternal hypertension without increasing fetal or neonatal death, or neonatal unit admission. Secondary objectives: • To investigate the effect of treatment with nifedipine versus labetalol on other secondary maternal and fetal/neonatal outcomes including patient-reported outcome measures. • To evaluate the cost-effectiveness of nifedipine versus labetalol as antihypertensive drugs from an NHS perspective.
Trial Design	A prospective, late phase, pragmatic, parallel group, open-label, multicentre, two-arm randomised controlled trial. Women who decline randomisation or are unable to be randomised (due to contraindications to either labetalol or nifedipine or women taking both drugs and not able to be randomised to a single drug) will be offered participation in an observational study, involving data collection only.
Setting	The study will be conducted in around 50 consultant-led maternity units across the UK.
Participant Population and Sample Size	2,300 pregnant women with hypertension. Assuming 90% power, 2.5% one-sided significance for non-inferiority, 25% control group event rate for the co-primary outcome of neonatal unit admissions, 5% loss to follow up, a total of approximately 2,300 women would be required to detect a clinically meaningful non-inferiority margin of 6%. For the maternal co-primary outcome, this sample size of 2,190 will allow detection of a 2.3% superiority difference between the mean proportion of days with a healthcare professional measured systolic blood pressure readings ≥160mmHg (increased to 2300 for attrition). This is equivalent to an effect size of 0.14 of a standard deviation, based on a two-sample t-test (5% two-sided alpha, 90% power), e.g. from around a mean of 9.6% to 11.9%.
Eligibility Criteria	Inclusion criteria: pregnant women between 11^{+0} and 35^{+6} weeks' gestation inclusive; pregnancy hypertension (chronic or gestational hypertension or pre-eclampsia); clinician decision made to initiate or continue use of an antihypertensive drug; aged ≥18 years; able to provide informed consent. Exclusion criterion: contraindication to either labetalol or nifedipine; already taking both labetalol and nifedipine and not able to be randomised onto a single drug.
Interventions	Treatment with any preparation of modified release nifedipine, a calcium channel blocker, (intervention arm) versus any preparation of labetalol, a mixed alpha/beta blocker, (active control arm) by random allocation (1:1). All other aspects of antenatal and delivery care will follow usual clinical care pathways underpinned by NICE 2019 guidelines for pregnancy hypertension.
Outcome Measures	Primary maternal outcome: Severe hypertension (proportion of days with a healthcare professional measured systolic blood pressure reading ≥160 mmHg between randomisation and birth). Primary fetal/neonatal outcome: Composite of fetal loss before birth or known neonatal death, or neonatal unit admission between randomisation up to primary hospital discharge or 28 days post-birth, whichever occurs sooner (with no double counting of outcomes). Secondary maternal and fetal/neonatal outcomes include clinical and patient-reported outcomes in addition to health care resource use.

Trial Flow Diagram



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1. BACKGROUND AND RATIONALE

1.1. Background

Problem being addressed

Approximately 70,000 pregnant women per year (8-10% of UK pregnancies) have hypertension or high blood pressure in pregnancy. This includes chronic (pre-existing, typically essential) and gestational (new after 20 weeks' gestation) hypertension and pre-eclampsia (hypertension with additional features of multiorgan involvement). The evidence base for choosing antihypertensive treatment in pregnancy is limited, in contrast to antihypertensive trials out of pregnancy. A systematic review of antihypertensive trials out of pregnancy included 613,815 participants from 123 studies (Ettehad, Emdin et al. 2016), compared with the Cochrane systematic review of antihypertensive trials in pregnancy, which identified 29 trials involving 2,774 women which compared one blood pressure-lowering drug with another one (Abalos, Duley et al. 2018). Only two trials, a total of 354 women, compared the top two antihypertensive treatments recommended in the UK, namely labetalol and nifedipine.

Labetalol is a mixed alpha/beta-adrenoceptor blocker that is administered orally or intravenously with a 6-hour half-life. Labetalol decreases peripheral vascular resistance and blood pressure with little change in heart rate or cardiac output. Labetalol is licenced for use throughout pregnancy. Nifedipine is a calcium channel blocker administered orally. Nifedipine blocks calcium channels leading to vascular smooth muscle relaxation and vasodilation. Nifedipine holds a licence for use in threatened preterm labour.

Literature review

The Cochrane systematic review of antihypertensive drugs for hypertension in pregnancy concludes, "Antihypertensive drug therapy for mild to moderate hypertension during pregnancy reduces the risk of severe hypertension… If antihypertensive drugs are used, beta blockers and calcium channel blockers appear to be more effective than the alternatives for preventing severe hypertension. High-quality, large-sized randomised controlled trials are required in order to provide reliable estimates of the true benefits and adverse effects of antihypertensive treatment for mild to moderate hypertension. We need to know the effects for both mother and baby, as well as the costs to the health services, to women and to their families." (Abalos, Duley et al. 2018).

The Cochrane review concluded that treatment benefit for pregnancy hypertension is such that no further research is needed on treatment versus no treatment, noting that use of any antihypertensive drug (versus placebo or no antihypertensive drug) halves the risk of developing severe hypertension (20 trials, 2,558 women; risk ratio (RR) 0.49; 95% CI 0.40-0.60), but should focus on head to head assessment of antihypertensive drugs. The Cochrane review reports comparison of antihypertensive drugs versus another (29 trials, 2,774 women), concluding

- beta-blockers and calcium channel blockers together in the meta-analysis appear more effective than methyldopa in avoiding severe hypertension (11 trials, 638 women; RR 0.70; 95% CI 0.56-0.88)
- calcium channel blockers appear more effective than other antihypertensive drugs in avoiding severe hypertension (5 trials, 223 women; RR 1.86, other antihypertensive drugs versus calcium channel blockers; 95% CI 1.09-3.15)

Although this suggests a signal of efficacy for preference of calcium channel blockers, the vast majority of the trials included in this review date from the 1970s to 1990s, using

antihypertensive drugs not currently prescribed in clinical practice, and very few having recruited more than 200 women. Of 58 trials included in the Cochrane review, three small trials compared calcium channel blockers and beta blockers directly (Jannet, Carbonne et al. 1994, Babbar, Armo et al. 2015, Webster, Myers et al. 2017), of which only two evaluated head to head the two antihypertensive drugs currently most commonly used in the UK (nifedipine and labetalol). This includes our PANDA feasibility study (Webster, Myers et al. 2017) which is detailed below.

1.2. Study Rationale

Antihypertensive drug choice in pregnancy is currently largely arbitrary (based on recent clinician surveys of antihypertensive prescribing in pregnancy) despite The National Institute for Health and Care Excellence (NICE) guidelines detailing labetalol as first line treatment based on its licensed status. This study aims to fill the gap in the evidence and enable evaluation of maternal and infant benefits and risks for antihypertensive prescribing in pregnancy. An optimal antihypertensive drug in pregnancy may result in one or more of the following:

- maternal benefit (reduction in maternal blood pressure and adverse outcomes, improvement in health-related quality of life),
- reduced maternal side-effects (impacting blood pressure control and adherence to treatment),
- infant benefit (reduction in adverse outcomes),
- reduced infant side-effects (such as hypoglycaemia).

This study, to evaluate antihypertensive drugs in pregnancy, will establish whether one is better for the woman (i.e. superior) and whether the outcomes for the infant are not worse (i.e. not inferior) and add to the sparse evidence on which women and clinicians share value-based decision-making.

This topic has remained an unanswered research recommendation by NICE since 2010 and has been reiterated in the 2019 update.

1.2.1. Justification for participant population

Evidence of effectiveness and safety of antihypertensive drugs in pregnancy cannot be extrapolated from adult hypertension treatment because many of the classes of drugs (including angiotensin converting enzyme inhibitors, angiotensin receptor blockers and diuretics) are contraindicated in pregnancy (National Institute for Health and Care Excellence 2019).

Pregnancy hypertension is associated with increased adverse maternal and perinatal outcomes (Buchbinder, Sibai et al. 2002, Steegers, von Dadelszen et al. 2010, Bramham, Parnell et al. 2014). Confidential Enquiries into Maternal Deaths have reported the association between pregnancy hypertension and maternal deaths and continue to emphasise the importance of prompt treatment of systolic hypertension (≥150mmHg) in pregnancy (Knight M, Nair M et al. 2016), a key driver in clinical practice. A recent analysis of temporal trends in maternal deaths from the confidential enquiry reports concluded that the decline in maternal deaths from pregnancy hypertension was driven by recommendations from confidential enquiry reports and national guidelines (Conti-Ramsden, Knight et al. 2019). A cross-sectional analysis of 7,025 women reported that hypertensive disorders in pregnancy were strongly associated with severe maternal morbidity in a dose-dependent relationship, and that prevention strategies

focused on hypertension may also impact medically indicated preterm deliveries (Hitti, Sienas et al. 2018).

1.2.2. Rationale for primary outcome

The clinical importance of optimal blood pressure control is primarily through reducing episodes of severe hypertension, a common occurrence. Severe hypertension can lead to hospital admission, preterm birth (if blood pressure is uncontrolled) and major maternal complications such as stroke (Martin Jr, Thigpen et al. 2005) and death, which occur very rarely but are catastrophic. Improved blood pressure control can reduce costs, with complications of uncontrolled blood pressure being costly for the woman, their family and the health service (Law, McCoy et al. 2015, Stevens, Shih et al. 2017). Avoiding severe hypertension may also be advantageous for the baby, reducing fetal growth restriction and rare events such as placental abruption and perinatal death (Magee, von Dadelszen et al. 2016).

For pregnant hypertensive women, blood pressure readings (even on a single day) drive major clinical decisions. This acute management of hypertension is in contrast with management out of pregnancy where high blood pressure readings and treatment decisions are made on a longer-term basis, and further justifies our chosen population for the study, pregnant hypertensive women.

1.2.3. Justification for design

Our group completed a four-centre feasibility study (ISRCTN40973936), comparing modified release nifedipine versus labetalol in 114 pregnant women with chronic hypertension (Webster 2017). The trial recruited 2.6 women/centre/month (range 1.2 to 3.7), with 66% of women approached agreeing to participate, which included those willing to switch from their current antihypertensive drug. This feasibility study informed the recruitment rate, acceptability and primary outcome event rate for Giant PANDA.

The pragmatic study design will help to assess clinical effectiveness of the treatments in a real-world setting within usual clinical care in order to make the results instantly generalisable to the UK population with pregnancy hypertension.

The open-label design is to ensure that women are effectively and safely treated, with healthcare professionals and women aware of their treatment allocation, as dose titration, switching, or adding additional agents to the randomised antihypertensive drug may be required throughout pregnancy as clinically indicated.

1.2.4. Choice of intervention

In the UK, the most widely used and recommended antihypertensive drug in pregnancy is labetalol (a mixed alpha/beta-adrenoceptor blocker) (National Institute for Health and Care Excellence 2019), but outside of pregnancy, beta blockers are recommended as part of Step 4 treatment (National Institute for Health and Care Excellence 2019). Furthermore, infants of women on labetalol at the time of birth may be at risk of hypoglycaemia, a side-effect. Nifedipine (calcium channel blocker) is the second most commonly used antihypertensive drug

in pregnancy, followed by methyldopa, neither of which are routinely recommended out of pregnancy.

National guidance recommends labetalol for pregnancy hypertension, largely because it has a license for use in pregnant women with high blood pressure, with no advice on tailoring the type of antihypertensive drug for ethnicity, as recommended out of pregnancy (National Institute for Health and Care Excellence 2019). Nifedipine has a license for use in treating threatened preterm labour, but not for pregnancy hypertension. Most drugs prescribed in pregnancy are not licensed for use in pregnancy (Webster and Shennan 2013) and licensing does not automatically equate to evidence of optimal effectiveness. The Medicines and Healthcare products Regulatory Agency (MHRA) has estimated that across all classes, only five drugs are licensed for use in pregnancy, as pharmaceutical companies may choose not to pursue licensing, despite widespread use. These recommendations for use of labetalol (first choice), then nifedipine (second choice), then methyldopa (third choice) have been retained in the 2019 NICE update for management of hypertension in pregnancy, as no new evidence has been identified (National Institute for Health and Care Excellence 2019).

1.2.5. Side-effects of the intervention

Common side-effects for labetalol include those for all alpha/beta-adrenoceptor blockers (including somnolence, abdominal discomfort and bradycardia) and drug fever, hypersensitivity and urinary disorders. It is contra-indicated in women with asthma (as given in the Summary of Product Characteristics for the drug).

Common side-effects of nifedipine include those for all calcium-channel blockers (including somnolence, abdominal pain, flushing, headache) and constipation, malaise and oedema. Common side effects of nifedipine also include headache.

Within the PANDA feasibility study adverse events were reported by 38% of women on labetalol compared to 26% on nifedipine.

1.2.6. Public and patient involvement and engagement (PPIE)

A range of PPIE activities, surveys and qualitative interviews with women and clinicians have guided our research questions, choice of participant population, design and intervention, with specific input from Action on Pre-eclampsia. The importance of the topic was confirmed by inclusion as one of the top ten research priorities in the recent James Lind Alliance Priority Setting Partnership for pregnancy hypertension (Blood Pressure in Pregnancy Priority Setting Partnership Steering Group 2018).

2. AIMS AND OBJECTIVES

2.1. Aims and Objectives

Research question
In women with pregnancy hypertension (Population), what is the effect of treatment with nifedipine (Intervention) versus labetalol (Comparator) on severe maternal hypertension

(Outcome) and a composite of fetal or neonatal death, or neonatal unit admissions (Outcome)?

Aim
To evaluate the effect of different antihypertensive drugs in pregnancy hypertension on maternal and fetal/neonatal outcomes.

Objectives
Primary objective: To evaluate if treatment with nifedipine (calcium channel blocker), compared to labetalol (mixed alpha/beta blocker) in women with pregnancy hypertension, reduces severe maternal hypertension without increasing fetal or neonatal death, or neonatal unit admission.

Secondary objectives:
- To investigate the effect of treatment with nifedipine versus labetalol on other secondary maternal and fetal/neonatal outcomes including patient-reported outcome measures.
- To evaluate the cost-effectiveness of nifedipine versus labetalol as antihypertensive drugs from an NHS perspective.

3. STUDY DESIGN AND SETTING

3.1. Study Design

A prospective, late phase, pragmatic, parallel group, open-label, multicentre, two-arm randomised controlled trial of treatment with nifedipine versus labetalol by random allocation (1:1) in women with pregnancy hypertension, with two co-primary outcomes: a maternal outcome assessing superiority and a fetal/neonatal outcome assessing non-inferiority. We will conduct an economic evaluation alongside the trial to determine whether nifedipine is a cost-effective alternative to labetalol for the NHS.

If a woman declines randomisation in the trial then she will be offered participation in an observational study, involving data collection only. In addition, women excluded from randomisation due to contraindication to either labetalol or nifedipine, or women taking both labetalol and nifedipine not able to be randomised to a single drug, who are otherwise eligible, can be offered participation in the observational study. Some sites may offer the observational study only either prior to or instead of the trial. All aspects of data collection study processes will be the same except for the randomisation step.

3.2. Study Setting

The study will be conducted in around 50 consultant-led maternity units across the UK.

3.3. Identification of participants

For the study, pregnant women up to 35^{+6} weeks' gestation with a diagnosis of pregnancy hypertension requiring antihypertensive treatment, will be identified and approached by members of the direct clinical care team or the local maternity research team (who are integrated within the direct clinical care team) through referral letters and/or at antenatal clinics (including at antenatal booking, Early Pregnancy Assessment Unit attendances and

Maternity Assessment Unit attendances). These women are routinely referred to obstetric clinics in secondary care. All eligible women (inclusion criteria discussed in section 4.1) will be invited to participate. For the trial, randomisation will be undertaken from 11^{+0} weeks' gestation onwards.

3.4. Assessment of Risk of trial

This trial is categorised as type A (no higher than the risk of standard medical care). A study risk assessment will be performed and reviewed at regular intervals during the course of the study and updated as required.

Both labetalol and nifedipine are recommended for use (as first and second line, respectively) in the latest NICE guidelines (2019) for management of hypertension in pregnancy, which followed consultation with MHRA. A detailed comparison of all antihypertensive agents was undertaken for the NICE guidelines and shared with the MHRA (for information, see the following link:
https://www.nice.org.uk/guidance/ng133/evidence/a-interventions-for-chronic-hypertension-pdf-6836186126)

The use of these two antihypertensive drugs are standard clinical care, as the NICE guideline (2019) committee recommended that women with sustained blood pressure of 140/90mmHg should be offered antihypertensive treatment.

Labetalol is licensed for use in hypertension, including hypertension in pregnancy. Labetalol crosses the placental barrier and the possible consequences of alpha- and beta- adrenoceptor blockade in the fetus and neonate should be considered; many hospital trusts now recommend screening for hypoglycaemia in babies born to women taking labetalol at the time of delivery, as part of usual clinical care, using guidelines from the British Association of Perinatal Medicine. Other risks include hypoglycaemia unawareness in women with type 1 diabetes. The UK Teratology Information Service has summarised the information for women on labetalol here:
https://www.medicinesinpregnancy.org/Medicine—pregnancy/Labetalol/

Nifedipine is licensed for use in hypertension and is licensed for use in pregnancy for postponement of premature labour. The British National Formulary states: 'manufacturer advises avoid before week 20, but risk to fetus should be balanced against risk of uncontrolled maternal hypertension'. It is noted that for women with asthma (in whom labetalol is contra-indicated) or those of Black ethnicity (in whom calcium channel blockers are first line treatment outside of pregnancy), nifedipine is commonly used before week 20 as the preferred agent for controlling maternal hypertension, in the absence of other recommended treatments. The UK Teratology Information Service has summarised the information for women on nifedipine here:
https://www.medicinesinpregnancy.org/Medicine—pregnancy/Calcium-channel-blockers/

Side-effects of labetalol and nifedipine are detailed in section 1.2.5. Both drugs are already used in clinical practice in the first trimester, and throughout the pregnancy; randomisation within the trial occurs at or after 11 weeks of gestation, and therefore beyond the time period when teratogenesis is considered as a concern. Informed consent for randomisation to either drug will be taken by an appropriately trained healthcare professional who will prescribe the allocated antihypertensive drug as in usual clinical care.

4. ELIGIBILITY

4.1. Trial Inclusion Criteria

- Pregnancy between 11^{+0} and 35^{+6} weeks' gestation inclusive
- Diagnosis of pregnancy hypertension (chronic/gestational hypertension or pre-eclampsia)
- Clinician decision to initiate or continue use of antihypertensive drugs
- Aged 18 years or over
- Able to give informed consent

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

4.2. Trial Exclusion Criteria

- Contraindication to either labetalol or nifedipine
- Already taking both labetalol and nifedipine, and not able to be randomised to a single drug

4.3. Observational study Inclusion/Exclusion Criteria

Women who meet the inclusion criteria but would not be eligible (due to the exclusion criteria) or who decline randomisation will be able to participate in the Giant PANDA observational study. In addition, women are able to take part in the observational study prior to 11^{+0} weeks gestation. There is no randomisation element to the observational study; use of any antihypertensive drugs prescribed in clinical care will be recorded.

Wherever relevant all processes within the observational study will be the same as the interventional trial, with the exception aspects related to randomisation as there is no randomisation to antihypertensive drugs.

4.4. Co-enrolment

Any woman participating in the Giant PANDA study can participate in any other observational study. Co-enrolment in other trials can be considered, after discussion with the Trial Management Group.

5. INFORMED CONSENT

It will be the responsibility of an appropriately trained healthcare professional (on the 'Trial Signature and Delegation Log') to obtain informed consent (on paper or electronically) for each participant prior to performing any trial related procedure in the trial (following confirmation of eligibility by a medically qualified individual) or the observational study.

A Participant Information Sheet (PIS) (enabled for both paper and electronic versions) will be provided to facilitate this process. A trial-specific animated video can be offered as part of additional material (to widen accessibility), but all participants will still need to access the PIS and sign the consent form. The aims, trial treatment, anticipated benefits and potential risks of taking part in the study will be explained to the woman. It will be made clear that participation is voluntary, and that the woman is free to decline to take part and may withdraw from the study (trial or observational 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). The participant must give explicit consent for the regulatory authorities, members of the research team and or representatives of the sponsor to be given direct access to the participant's medical records. In previous trials, following PPIE and with the approval of the Research Ethics Committee (REC), this has been on the same day as this option is preferred by many pregnant women who do not wish to return for further visits to start or switch treatment.

If the woman wishes to participate in the trial or observational 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. An appropriately trained healthcare professional will then sign and date the ICF (which will include the participant's study number, date of discussion and name of the study). If completed by electronic consent a copy will be transmitted to the woman's email address (stored within the database), a record made in the medical notes and it will be electronically stored in the site-specific section of the database. If completed by paper, a copy of the ICF 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), with a copy transmitted to the BCTU; agreement (or not) to each section of the ICF will be inputted onto the 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 trial or observational study, the woman will have the opportunity to ask questions about the study. 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 onto headed paper of the local institution. Details of all women approached will be recorded on the **Giant PANDA Participant Screening/Enrolment Log** and with the woman's prior consent other relevant healthcare professionals will also be informed that they are taking part in the trial or observational study, through the electronic or handheld maternity record.

6. RECRUITMENT, ENROLMENT AND RANDOMISATION

6.1. Recruitment

Women will be identified in the antenatal care setting (detailed in section 3.3), confirmed as eligible to participate (by a medically qualified individual) and provided with a PIS with information on the study and given appropriate time to make the decision to participate. An appropriately trained healthcare professional on the 'Trial Signature and Delegation Log' will obtain informed consent (on paper or electronically) for participation (informed consent detailed in section 5).

6.2. Enrolment and Screening

Eligible women will be approached to take part as described above (section 5).

6.3. Trial Randomisation

After eligibility has been confirmed and informed consent has been received, the woman can be randomised into the trial.

Randomisation will be provided by a secure online randomisation system at the Birmingham Clinical Trials Unit (BCTU) (available at *<insert web address>*). Unique log-in usernames and passwords will be provided to those who wish to use the online system and who have been delegated the role of randomising women into the trial as detailed on the 'Trial Signature and Delegation Log'. The online randomisation system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance. A telephone toll-free randomisation service ((0044) 0800 953 0274) is available Monday to Friday, 09:00 to 17:00 UK time, except for bank holidays and University of Birmingham (UoB) closed days.

Women will be randomised by computer at the level of the individual participant in a 1:1 ratio to either nifedipine or labetalol. A minimisation algorithm will be used within the online randomisation system to ensure balance in the treatment allocation over the following variables:

- maternity unit
- hypertension type (chronic, gestational, pre-eclampsia)
- diabetes (yes, no)
- singleton (yes, no)
- self-reported ethnicity (Black, all other)
- gestational age (11^{+0} to 19^{+6}, 20^{+0} to 27^{+6}, 28^{+0} to 35^{+6} weeks' gestation)

A 'random element' will be included in the minimisation algorithm, so that each woman has a probability (unspecified here), of being randomised to the opposite treatment that they would have otherwise received. Full details of the randomisation specification will be stored in a confidential document at BCTU.

Following randomisation, a confirmatory e-mail will be sent to the randomising clinician, research team member, site Principal Investigator (PI) and trial manager.

6.4. Informing the participant's GP and other relevant healthcare professionals

Information on the prescription of the study antihypertensive drug 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).

6.5. Trial Masking

This is an open-label trial and, all trial participants, care providers, and outcome assessors will be unmasked to allocation. The open-label design is to ensure that women are effectively and safely treated, with healthcare professionals and women aware of their treatment allocation. Any appropriately trained healthcare professional may up- or down-titrate, switch, or add to, the randomised antihypertensive drug if clinically indicated. We will provide guidance and support on treatment regimens (detailed in the study handbook).

We have considered other designs but given the dynamic blood pressure changes in pregnancy (distinct and more frequent than those outside of pregnancy), an alternative would not be feasible or acceptable. It would be unfeasible to mask those delivering clinical care or outcome assessors to trial allocation as maternity notes, by necessity, contain documentation of antihypertensive treatment alongside blood pressure measurements.

All data analysts will be masked to allocation unless required by the Data Monitoring Committee for the purposes of analysis and/or data cleaning.

7. TRIAL TREATMENT / INTERVENTION

7.1. Treatment(s) and Dosing Schedule

This is a trial of treatment with one of two antihypertensive drugs, nifedipine versus labetalol, the two most commonly used antihypertensive drugs in pregnancy in the UK.

Both interventions are specifically licenced for hypertension and are very widely used. As an open-label trial, healthcare professionals and women will be aware of their allocation and following randomisation, the appropriately trained healthcare professionals will provide a prescription (as used in usual clinical care) for the allocated antihypertensive drug to be dispensed from a pharmacy. The method of dispensing the trial drugs across sites is varied, with initial prescription usually taking place at the hospital (at the time of randomisation), or via a GP practice, with repeat prescriptions via hospital or community pharmacies. None of the trial drugs are being modified or masked in any way, and are prescribed according to their antihypertensive indication. The allocated interventions will be taken from normal, non-trial stock and the standard NHS labelling for dispensed medicines will apply. Participants will be provided with information that identifies their participation in the giant PANDA study, with relevant contact details. Product liability will rest with the holders of the manufacturing authorisations.

Apart from the trial treatments allocated at randomisation, all other aspects of clinical management are entirely at the discretion of the local healthcare team, including additional prescriptions or changes to the prescription provided, as required, throughout the pregnancy

according to current clinical practice. Patients are managed in whatever way appears best for them, with no other special treatments, no special investigations, and no extra follow-up visits.

Intervention group: Oral nifedipine modified release preparations (no brand specified) to be taken twice daily.
The starting dose will be left to the discretion of the responsible healthcare professional, guided by blood pressure on the day, previous antihypertensive dose (where applicable) and any other relevant factors. The starting dose is usually nifedipine modified release 10mg twice a day, increased to a maximum of 40mg twice daily.

Active control group: Oral labetalol (no brand specified) to be taken twice to three times daily.
The starting dose will be left to the discretion of the responsible healthcare professional, guided by blood pressure on the day, previous antihypertensive dose (where applicable) and any other relevant factors. The starting dose is usually labetalol 100mg twice a day, increased to a maximum of 2,400mg total daily dose, divided into three or four times a day regimen.

Women can be consented to the observational study once they are confirmed to be pregnant but can only be randomised to a treatment group within the trial from 11 weeks' gestation (as a first trimester dating and screening scan is offered from 11 weeks' gestation). Treatment will continue throughout pregnancy and so the maximum duration of treatment would be 31 weeks (if randomised at 11 weeks and the pregnancy continued to 42 weeks' gestation). Women can be changed from any current antihypertensive drug(s) to their new randomised treatment on the day of recruitment, as per routine clinical practice. No wash-out period is possible because the woman requires an antihypertensive that day.

Units will be asked to follow standard NICE care pathways (National Institute for Health and Care Excellence 2019), for management of pregnancy hypertension.

Subsequent to enrolment in the trial, in order to ensure that women are effectively, and safely treated, any appropriately trained healthcare professional in clinical practice may up- or down-titrate, switch, or add to, the randomised antihypertensive drug if clinically indicated.

Standard clinical advice on adherence to antihypertensive tablets will be provided by the healthcare professional; no additional advice specific to the trial will be given.

7.2. Drug Interaction or Contraindications

As no brand of modified release nifedipine or labetalol will be specified, and treatment is within usual clinical care, healthcare professionals will review drug interactions or contraindications within usual clinical practice. Links to current drug information will be included in the study handbook and will be updated as necessary (annually as a minimum).

7.3. Accountability Procedures

No stock recording will be undertaken as all antihypertensive drugs will be dispensed from usual care pharmacies. Usual clinical practice will be followed (in which women are usually asked about tablets taken, side-effects and adherence) and this information will be recorded on the CRF where provided (at case note review following birth).

7.4. Treatment Modification

Usual clinical care will be provided for antihypertensive treatment (following NICE guidelines) and no trial specific treatment modifications are planned.

7.5. Discontinuation of Treatment

Stopping or switching antihypertensive treatment is a common part of usual clinical care in pregnancy and will be undertaken within usual practice. It will be recorded in the eCRF at case note review but will not need to be reported unless related to a reportable Serious Adverse Event. A woman can continue in the study (for collection of further data) after discontinuation of treatment.

7.6. Treatment Supply and Storage

7.6.1. Treatment Supplies

All antihypertensive drugs will be supplied by usual care pharmacies.

7.7. Packaging and Labelling

No specific packaging or labelling will be required as usual care pharmacy supplies will be used.

7.7.1. Drug Storage

Antihypertensive drugs will be stored within usual care pharmacies.

8. OUTCOME MEASURES AND STUDY PROCEDURES

For the purposes of assessing the effect of the randomised allocation to labetalol or nifedipine within the trial, outcomes will be collected from randomisation up to primary hospital discharge for each of the woman or baby post-birth, or 28 days post-birth if remains in hospital, whichever occurs sooner. For the observational study outcomes will be collected from consent up to primary hospital discharge for each of the woman or baby post-birth, or 28 days post-birth, whichever occurs sooner. All safety data (adverse events and serious adverse events) will be collected from consent. Outcomes have been chosen to align with those from the Core Outcome Set for Pre-eclampsia wherever possible (Duffy, Cairns et al. 2020).

8.1. Co-Primary Outcomes

Maternal: Severe hypertension (proportion of days with a healthcare professional measured systolic blood pressure reading ≥160mmHg between randomisation and birth).

For outpatient visits: the highest systolic blood pressure reading at each visit will be recorded; for inpatient admissions, the highest systolic blood pressure reading per day will be recorded inclusive of the day of birth (up to the time of birth). All included blood pressure readings will be measured by healthcare professionals.

Fetal/neonatal: Composite of fetal loss before birth or known neonatal death, or neonatal unit admission involving separation of the baby from the mother between randomisation up to primary hospital discharge or 28 days post-birth, whichever occurs sooner (with no double counting of outcomes).

8.2. Secondary Outcomes

Outcomes indicated by an asterisk (*) will be presented with a treatment effect and confidence intervals. All other outcomes will be presented with summary statistics only.

Clinical outcomes
Maternal:
Up to birth:

- Mean antenatal systolic blood pressure (using highest systolic blood pressure per day as collected for the primary outcome)*
- Severe maternal hypertension* (defined as any episode of severe maternal hypertension (systolic blood pressure ≥160 mmHg between randomisation and birth))
- Mean antenatal diastolic blood pressure (using highest diastolic blood pressure per day)
- Proportion of days with an antenatal systolic hypertension blood pressure reading ≥140mmHg
- Proportion of days with an antenatal diastolic hypertension blood pressure reading ≥90mmHg
- New diagnosis of pre-eclampsia*
- Diagnosis of eclampsia
- Diagnosis of Haemolysis, Elevated Liver enzymes, Low Platelets syndrome
- Placental abruption
- Severe maternal morbidity (fullPIERS consensus definition (von Dadelszen, Payne et al. 2011))*
    - Components of severe maternal morbidity
- Maternal death
- Maternal stroke
- Prescription of additional antihypertensive drug(s)
- Prescription of alternative antihypertensive drug(s)
- Persistence with allocated antihypertensive (time from randomisation to first discontinuation)
- Discontinued allocated antihypertensive drug*
- Undesirable effects of allocated (and other) antihypertensive drug(s) (number of women* and number of undesirable effects)
- Total number of antenatal hospital inpatient days

Medication-related self-reported outcomes (measured at 2 weeks post-randomisation, if prior to birth) using validated tools (see 8.3, 10.3 and Appendix 1)

- Treatment satisfaction with allocated antihypertensive drug
- Beliefs about allocated antihypertensive drug
- Adherence to allocated (and other) antihypertensive drug(s)

At delivery/birth:

- Indicated delivery (induction of labour or prelabour rupture of membranes (PROM) with stimulation of labour or pre-labour Caesarean section)*

- Mode of onset of birth (spontaneous, induction of labour, PROM with stimulation of labour, pre-labour Caesarean section)
    - Indication for onset of birth

Between birth and primary hospital discharge or 28 days post-birth, whichever occurs sooner:

- New episodes of severe maternal morbidity (fullPIERS consensus definition (von Dadelszen, Payne et al. 2011))
    - Components of severe maternal morbidity
- Maternal death

Fetal and neonatal:

Between birth and primary hospital discharge or 28 days post-birth, whichever occurs sooner, unless otherwise specified, using denominator of all fetuses/ infants:

- Fetal loss prior to 24 weeks' gestation
- Fetal loss $\geq 24^{+0}$ weeks' gestation (stillbirth)
- Known early neonatal death (up to 7 days from birth)
- Known late neonatal death (between 7 and up to 28 days from birth)
- Neonatal unit admission (separation of baby from mother)*
    - Principal recorded indication for neonatal unit admission
    - Length of stay in neonatal unit (and level of care)
- Major congenital abnormality as defined by EUROCAT*
- Mode of birth (spontaneous vaginal,* assisted vaginal, Caesarean section)
    - Indication for mode of birth
- Gestational age at birth*
- Preterm birth (<37 completed weeks' gestation)
- Preterm birth (<32 completed weeks' gestation)
- Birthweight
- Birthweight centile*
- Birthweight small for gestational age ($<10^{th}$ centile for gestational age)
- Umbilical arterial pH <7 at birth
- Apgar score at 5 mins after delivery
- Need for additional resuscitation at birth: intubation in the delivery room, resuscitation drugs or chest compressions
- Need for respiratory support
    - Type of respiratory support needed
- Need for treatment for neonatal hypoglycaemia (in those having blood glucose monitoring)*
    - Type of treatment for hypoglycaemia
- Lowest blood glucose measurement within the first 48 hours after birth
- Neonatal seizures
- Intracranial haemorrhage
- Necrotising enterocolitis

Process outcome:

- Number of babies in whom blood glucose monitoring was indicated at birth
- Indication for blood glucose monitoring
- Blood glucose test performed
- Acceptability of digital data capture method: proportion of completed responses over expected total number (adjusted for time between enrolment and delivery)

Adverse events:

- Adverse event recorded (number of women and number of adverse events)

- Adverse event recorded (number of fetuses/neonates and number of adverse events)

Health economic outcomes

Maternal:

Up to birth:

- Health-related quality of life (EQ-5D-5L)
- Number of outpatient contacts
- Hospital inpatient length of stay by level of care (ITU, HDU, or ward)

Between birth and primary hospital discharge or 28 days post-birth, whichever occurs sooner:

- Hospital inpatient length of stay by level of care (ITU, HDU, or ward)

Neonatal:

Between birth and primary hospital discharge or 28 days post-birth, whichever occurs sooner:

- Hospital inpatient days by level of care (NICU, HDU, SCBU, and postnatal ward)

8.3. Schedule of Assessments

Figure 1: Schedule of Assessments

Visit	Screening	Randomisation	Antenatal period	Post delivery
Eligibility check	x			
Valid informed consent*	x			
Randomisation and prescription of antihypertensive drug*†		x		
Two weeks post enrolment contact*			x	
Six weeks post enrolment contact (four weekly thereafter)*			x	
Safety reporting (as needed)			x	x
Case note review (safety and other outcomes)				x

***visits with contact with the participating woman;** † in trial only

Women will be contacted after randomisation (or after consent for women participating in the observational study) by a member of the research team, with the option of face-to-face review (where this fits with an existing antenatal appointment), telephone or other virtual consultation method. Women will be asked to complete the following using electronic data capture wherever possible. At two weeks they will be asked to complete:

- Antihypertensive medication prescribed
- EuroQol- 5 Dimension, EQ-5D-5L (Health-related quality of life)
- Treatment Satisfaction Questionnaire for Medication, TSQM Version II (Treatment satisfaction)
- Beliefs about Medicines Questionnaire, BMQ-Specific (Cognitive representations of medication)
- Medication Adherence Report Scale, MARS-5 (Medication adherence)
- Side-effects over the previous 2 weeks

At subsequent contact points six weeks after randomisation (or after consent for women participating in the observational study) and four weekly thereafter they will be asked to complete:

- Antihypertensive medication prescribed
- EuroQol- 5 Dimension, EQ-5D-5L (Health-related quality of life)

Reminders will be sent if women are not able to attend on the scheduled contact date.

Clinical data are routinely collected in maternity care during the antenatal period and birth up to primary hospital discharge or 28 days post-birth, whichever occurs sooner. Data 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. Postpartum data are less easy to capture due to a wider variety of healthcare professionals being involved in care across hospital and community

settings, and a proportion of women moving location away from their maternity unit immediately after birth. As antihypertensive treatment is often switched immediately after birth (and therefore extended postnatal data are unlikely to reflect effects of the intervention), data collection will be up to primary hospital discharge only.

Data collected 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. It is anticipated that the majority of babies will be delivered in the unit where they are randomised; we have successfully previously utilised the CRN network to locate outcomes for women and babies delivered at other units.

As part of wider study procedures relating to engagement with healthcare professionals, we will enable sharing of information on the Giant PANDA study via social media, other digital channels from official site or other central sources (eg trusted NHS trust websites or BCTU/ giant PANDA twitter account). Although the intended audience is healthcare professionals, this material may be viewed by the public due to the nature of social media and digital channels. We are not proposing that this is a primary recruitment method, as all women still need to be approached within a healthcare setting at approved sites.

8.4. Participant Withdrawal of Consent

If a woman wishes to withdraw consent for further contact (e.g. for the contact at 2 weeks post randomisation) or for 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.

It is recognised that discontinuation of allocated treatment is a recognised aspect of usual clinical care for a proportion of these women (either at the request of the woman, or the clinician) and that this is different to withdrawal of consent (see section 7.5).

9. ADVERSE EVENT REPORTING (TRIAL PARTICIPANTS ONLY)

Adverse events and Serious Adverse Events will be collected for Giant PANDA trial participants only, not women participating in the Giant PANDA observational study, who will be receiving usual care.

9.1. Reporting Requirements

The collection and reporting of Adverse Events (AEs) will be in accordance with the Medicines for Human Use Clinical Trials Regulations 2004 and its subsequent amendments. The PI (or other medically qualified delegate) will assess the seriousness and causality (relatedness) of all AEs against the Summary of Product Characteristics (SmPC) for the interventions as experienced by the woman and this will be documented in the source data. Safety population includes participating women from consent up to primary discharge after birth for whom we will collect AEs.

When reviewing causality of a Serious Adverse Event (SAE) the options used between a suspected causal relationship are definitely related; probably related; possibly related; unlikely to be related or unrelated (detailed in 9.4 below).

9.2. Adverse Events (AE) and Serious Adverse Events (SAEs)

AEs are commonly encountered in this population of pregnant women. As the safety profiles of labetalol and nifedipine used in this trial are well characterised, a strategy of targeted reporting of AEs will therefore not affect the safety of participants. Only some SAEs (detailed in section 9.3) experienced during treatment will be reported as SAEs.

The following are considered expected in this population of pregnant women as a part of the clinical condition of pregnancy, hypertension in pregnancy (and its complications). These will be clearly recorded on the case note review (including where a woman offers information to a research team) but not reported as AEs, consistent with aims of the trial:

Maternal:

- Admission in active labour
- Admission for cervical ripening or induction of labour
- Admission for caesarean section
- Admission for assessment for suspected fetal compromise, including poor growth, or reduced fetal movements
- Admission for monitoring for hypertension or pre-eclampsia, antepartum haemorrhage, suspected preterm labour, pre-labour rupture of the membranes or other reasons for monitoring
- Admission for psychiatric or social reasons
- Admission for unstable lie or external cephalic version
- Admission for postpartum complications
- Known complications of pregnancy and pregnancy hypertension that are collected for every woman as part of outcome collection

Maternal undesirable effects of allocated antihypertensive drugs will be recorded at the two-week post randomisation contact and will be extracted from case note review (post-birth) as part of outcome collection recorded within the eCRF.

Fetal and neonatal:

Known fetal and neonatal complications of pregnancy that are collected for every infant as part of outcome collection, including, but not limited to:

- Neonatal unit admission
- Stillbirth after 24 weeks' gestation
- Neonatal death up to 28 days
- Preterm delivery (<37 completed weeks' gestation)
- Neonatal complications (including but not limited to hypoglycaemia, seizures, encephalopathy, need for respiratory support, sepsis, intraventricular haemorrhage, confirmed infection, necrotising enterocolitis, retinopathy of prematurity, congenital anomaly, intraventricular haemorrhage)

9.3. Serious Adverse Advents (SAE)

9.3.1. Events that require expedited (immediate) reporting

Although the following SAEs are known to occur in this population they will still be required to be reported (expedited reporting):

- Maternal death
- Maternal stroke
- Stillbirth after 24 weeks' gestation
- Neonatal death up to 28 days

9.3.2. Events that do not require expedited (immediate) reporting

Events that do not require reporting (including those of an expedited nature) are detailed in section 9.2.

9.3.3. Monitoring pregnancies for potential Serious Adverse Events

All women and babies will be followed up to primary hospital discharge or 28 days post-birth, whichever occurs sooner (or pregnancy loss) until completion of the trial or study. All outcomes, including potential AEs and SAEs as outlined above, will be collected at this point or sooner or where a woman offers information to a research team member.

9.4. Reporting period

SAEs will be reported between consent and primary hospital discharge or 28 days post-birth (or pregnancy loss), whichever occurs sooner.

9.5. Reporting Procedure – At Site

9.5.1. Adverse Events

Adverse events will be recorded in the study database.

9.5.2. Serious Adverse Events

AEs defined as serious and which require reporting as an SAE should be reported on an SAE form. Relatedness and severity of the SAE will be assessed by the PI (or medically qualified delegate) and the Chief Investigator (CI) (or medically qualified delegate). The following categories will be used to define the relatedness (causality) of the SAE:

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out	Related
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely	
Possibly	There is some evidence to suggest a causal relationship, however, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events or medication)	
Unlikely	There is little evidence to suggest there is a causal relationship; there is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant events or medication)	Unrelated
Not related	There is no evidence of any causal relationship	

On becoming aware that a woman has experienced an SAE, the PI or delegate(s) should report the SAE to their own Trust/Health Board in accordance with local practice and to the BCTU Trials Office as per the requirements of sections 9.3.1 and 9.3.2 above. To report a SAE to the BCTU Trials Office, the PI or delegate(s) must complete, date and sign the trial specific BCTU SAE form. The completed form will be completed on the study database as soon as possible and no later than 24 hours after first becoming aware of the event.

On receipt of an SAE form, the BCTU trials team will allocate each SAE a unique reference number and return this via email to the site as proof of receipt. If the site has not received confirmation of receipt of the SAE from the BCTU or if the SAE has not been assigned a unique SAE reference number within 1 working day, the site should contact the BCTU trials team. The site and the BCTU trials team should ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the SAE. Where an SAE Form has been completed by someone other than the investigator, the original SAE form will be required to be countersigned by the investigator to confirm agreement with the causality and severity assessments.

9.5.3. Provision of follow-up information

Following reporting of an SAE for a participating woman, the woman or infant should be followed up until resolution or stabilisation of the event (or 28 days after birth, which occurs sooner). Follow-up information should be provided using the SAE reference number provided by the BCTU trials team. Where significant new information is reported on a follow up, the PI (or medically qualified delegate) should also consider review and update of relatedness and causality as applicable.

9.6. Reporting Procedure – BCTU Trials Office

On receipt of an SAE Form the CI or delegate will independently determine the seriousness and causality of the SAE. An SAE judged by the CI or delegate(s) to have a reasonable causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The causality assessment given by the PI will not be downgraded by the CI or delegate(s). If the CI or delegate(s) disagrees with the PI's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

The CI or delegate(s) will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

9.7. Reporting SAEs to third parties

9.7.1. Suspected Unexpected Serious Adverse Reactions

BCTU will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the MHRA, REC, and Research Governance Team within 7 days. Detailed follow-up information will be provided within an additional 8 days. All other events categorised as non-life threatening SUSARs will be reported within 15 days.

9.7.2. Serious Adverse Reactions

BCTU will report details of all SARs (including SUSARs) to the MHRA, REC, and Research Governance Team annually from the date of the Clinical Trial Authorisation, in the form of a Development Safety Update Report.

9.7.3. Adverse Events

Details of all AEs will be reported to the MHRA on request.

9.7.4. Other safety issues identified during the course of the trial

The MHRA, REC and Research Governance Team will be notified immediately if a significant safety issue is identified during the course of the study.

9.8. Investigators

Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to PIs. A copy of any such correspondence should be filed in the Site File.

9.9. Data Monitoring Committee

The independent Data Monitoring Committee (DMC) will review all SAEs.

10. DATA HANDLING AND RECORD KEEPING

10.1. Source Data

In order to allow for the accurate reconstruction of the study and clinical management of the woman, source data (defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial) will be accessible and maintained.

Data	Source
Participant Reported Outcomes	The original participant-completed CRF is the source and will either be: - Completed electronically (the original record of the questionnaire completion is the source, held on BCTU servers as part of the electronically-enabled questionnaire completion). - Completed on paper at site (the original record of the questionnaire will be kept with the participant's trial record at site, and copies posted to the BCTU Trial Office). - Completed on paper by post (the original record of the postal questionnaire will be returned to the BCTU Trial Office directly.
Clinical event data	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), should be documented in the source documents.
Recruitment	The original record of the randomisation is the source, held on BCTU servers as part of the randomisation and data entry system.
Drop out	Where a participant expresses a wish to withdraw, the conversation should be recorded in the source documents.

10.2. Electronic Case Report Form 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.

10.3. Participant completed Questionnaires (Appendix 1)

These will be completed around two weeks after enrolment (in the study) or randomisation (in the trial).

- EuroQol- 5 Dimension, EQ-5D-5L (Health-related quality of life)
- Treatment Satisfaction Questionnaire for Medication, TSQM Version II (Treatment satisfaction)
- Beliefs about Medicines Questionnaire, BMQ-Specific (Cognitive representations of medication)
- Medication Adherence Report Scale, MARS-5 (Medication adherence)
- Side-effects over the previous 2 weeks

10.4. Data Management

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. Coding and validation will be agreed between the trial's manager, statistician and programmer and the study database will be signed off once the implementation of these has been assured.

10.5. Data Security

The security of the System is governed by the policies of the UoB. The University's Data Protection Policy and the Conditions of Use of Computing and Network Facilities set out the security arrangements under which sensitive data should be processed and stored. All studies at the UoB have to be registered with the Data Protection Officer and data held in accordance with the General Data Protection Regulation 2018. The University will designate a Data Protection Officer upon registration of the study. The BCTU has arrangements in place for the secure storage and processing of the study data which comply with the UoB policies.

The System incorporates the following security countermeasures:

- Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up formatted data 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 etc.
- Network security measures: including site firewalls, antivirus software, separate secure network protected hosting etc.
- System Management: the System shall be developed by the BCTU Programming Team and will be implemented and maintained by the BCTU Programming Team.
- System Design: the system shall 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 the BCTU (UoB).
- Data processing: Statisticians will only have access to anonymised data.
- System Audit: The System shall benefit from the following internal/external audit arrangements:
    - Internal audit of the system
    - Periodic IT risk assessment
- Data Protection Registration: The UoB has Data Protection Registration to cover the purposes of analysis and for the classes of data requested. The University's Data Protection Registration number is Z6195856.

10.6. 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

The CI is required to sign a UoB CI agreement to document the expectations of both parties. The UoB CI agreement document must be completed prior to participation. The CI is required to sign a Clinical Trials Task Delegation Log which documents the agreements between the CI and BCTU. In addition, all local PIs will be asked to sign the necessary agreements including a 'Trial Signature and Delegation log' between the PI and the CTU and supply a current CV

and Good Clinical Practice (GCP) certificate to BCTU. All members of the site research team are required to sign the 'Trial Signature and Delegation Log', which details which tasks have been delegated to them by the PI.

Prior to commencing recruitment, each recruiting site will undergo a process of initiation, either a meeting, a teleconference or online training, at which key members of the site research team are required to attend, covering aspects of the design, protocol procedures, AE 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. The BCTU trials team must be informed immediately of any change in the site research team.

11.2. Onsite Monitoring

Monitoring is carried out as required following study-specific risk assessment by BCTU and as documented in the monitoring plan. Given the low-risk nature of this study, central monitoring will be routine. The monitoring plan will be approved by the QA Manager before it is implemented. Any monitoring activities will be reported to the trials team and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered, for example by poor eCRF return, poor data quality, excessive number of withdrawals or deviations. If further monitoring is required, the BCTU study team will contact the site to arrange for more detailed review of source data. PIs will allow the Giant PANDA study staff access to source documents as requested. The monitoring will be conducted by UoB.

11.3. Central Monitoring

Trials staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trials staff will check ICFs and eCRFs for compliance with the protocol, data consistency, missing data and timing. Sites will be sent data clarification queries requesting missing data or clarification of inconsistencies or discrepancies. On occasion source data may be requested for central monitoring (e.g. for checking eligibility or outcomes). Such source data should be redacted and labelled with the participant's trial number before sending to the Trials Office.

11.4. Audit and Inspection

The PI will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents. The PI will comply with these visits and any required follow up. Sites are also requested to notify BCTU of any relevant inspections.

11.5. Notification of Serious Breaches

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments, the Sponsor is responsible for notifying the licensing authority in writing of any serious breach of the conditions and principles of GCP in connection with the trial or the protocol relating to the trial, within 7 days of becoming aware of that breach.

For the purposes of this regulation, a "serious breach" is a breach which is likely to affect;

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial

Sites are therefore requested to notify the Trials Office of any suspected trial-related serious breach of GCP and/or the protocol. Where the Trials Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Trials Office in providing sufficient information to report the breach to the MHRA 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. Any major problems identified during monitoring may be reported to the Trial Management Group (Trial Steering Committee if appropriate), the REC and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the protocol to the REC and MHRA. A copy is sent to the UoB Clinical Research Compliance Team at the time of reporting to the REC and/or relevant regulatory bodies.

12. END OF STUDY DEFINITION

The end of study will be 3 months after the database lock. The BCTU trial team will notify the MHRA, main REC, HRA and UoB Research Governance Team that the study has ended within 90 days of the end of trial. Where the study has terminated early, the Trials Office will inform the MHRA and REC within 15 days of the end of trial. The Trials Office will provide them with a summary of the clinical trial report within 12 months. The Trials Office will provide them with a summary of the clinical trial report within 12 months of the end of trial.

13. TRIAL STATISTICAL CONSIDERATIONS

13.1. Sample Size

The sample size calculations are driven by the fetal/neonatal co-primary outcome. Assuming a control group event rate for fetal or neonatal death or neonatal unit admission of 25% (Magee, von Dadelszen et al. 2015, Webster, Myers et al. 2017), to test a non-inferiority hypothesis on this fetal/neonatal outcome, a total sample size of 2,190 babies will have 90% power to detect a non-inferiority margin of 6%, with a 2.5% one-sided significance level. This would provide robust, clinically meaningful evidence to assess the impact of women taking nifedipine on neonatal outcomes compared to those taking labetalol. Based on ONS birth statistics, the proportion of women in the target population expected to have multi-fetal pregnancies is around 1.5%, but the proportion recruited to this trial is uncertain. A sample size of 2,190 women will provide a conservative estimate for the number of babies required to address the hypothesis for the fetal/neonatal co-primary outcome. Due to the anticipated small proportion of multi-fetal pregnancies, this sample size will also allow for the dependence between outcomes for infants from the same pregnancy.(Yelland, Sullivan et al. 2018)

For the maternal co-primary outcome, using the dataset from the PANDA feasibility study (Webster, Myers et al. 2017) (112 pregnant women with chronic hypertension), the mean proportion of days with clinic and hospital blood pressure measurements ≥160mmHg was 9.6% with a standard deviation of 16.4%. The inclusion of women with gestational hypertension in the Giant PANDA study is not expected to impact on these estimates substantially. A sample size of 2,190 (which allows for a 6% margin of non-inferiority for the neonatal outcome), will mean that we can detect a 2.3% superiority difference between the

mean proportions, equivalent to an effect size of 0.14 of a standard deviation, based on a two sample t-test (5% two-sided alpha, 90% power), e.g. from around a mean of 9.6% to 11.9%. Although the data are expected to be highly skewed, the approximation to the normal distribution has been shown to produce conservative estimates of the sample size (Cundill and Alexander 2015). With this sample size, a clinically meaningful non-inferiority margin for the fetal/neonatal co-primary outcome can be detected whilst allowing a feasible trial to be conducted (a non-inferiority margin of 5% would require 3,160 women). This sample size also retains power to detect a 5.5% reduction in severe hypertension (from 22% to 16.5%) measured as a binary secondary outcome.

Allowing for up to 5% loss to follow-up, as in similar trials (Webster, Myers et al. 2017, Duhig, Myers et al. 2019), would require a total sample size of approximately 2,300 women, 1150 women per group.

13.2. Analysis of Outcomes

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

The primary comparison groups will be composed of those randomised to nifedipine versus those randomised to labetalol. In the first instance, all analyses will be based on the intention to treat (ITT) principle, i.e. all participants (and all babies of participants) will be analysed in the treatment group to which they were randomised irrespective of compliance or other protocol deviation. An ITT analysis will be undertaken for both the maternal co-primary outcome (on a superiority hypothesis) and the fetal/neonatal co-primary outcome (on a non-inferiority hypothesis) with a sensitivity analysis based on a per-protocol population. The ITT analysis will ensure a comparison that maintains the rigour of randomisation but could risk providing results that are biased towards non-inferiority, and the per-protocol analysis (as a sensitivity analysis) will provide results that minimises this risk (see section 13.2.4).

For all outcome measures, appropriate summary statistics and treatment effects (e.g. mean differences, relative risks) will be presented, along with 95% confidence intervals and p-values as specified below. Treatment effects will be adjusted for the minimisation variables listed in section 6.3 where possible. Correlations between twins will be accounted for in the adjusted model for all fetal/neonatal outcomes. No adjustment for multiple comparisons will be made.

13.2.1. Primary Outcomes

The maternal co-primary outcome will be calculated as the proportion of days with systolic blood pressure readings ≥160mmHg (measured by a healthcare professional) out of the total number of days with blood pressure readings (measured by a healthcare professional) between randomisation and birth. Generalised linear models will be used with a link function that provides the best fit for the data to calculate the mean difference in proportions and 95% confidence intervals (CI). The p-value relating to the treatment group parameter as generated by the model will be presented.

The fetal/neonatal co-primary outcome is binary (i.e. yes or no) and will be analysed using a log-binomial regression model to calculate adjusted risk ratios, risk differences and 95% CI. A p-value will not be presented for this co-primary outcome, as non-inferiority will be assessed

based on the upper limit of the 95% CI. This outcome will include all babies born to a randomised mother, the denominator being the number of fetuses/ infants.

13.2.2. Secondary Outcomes

Secondary outcomes which are binary will be analysed using log binomial regression models and results presented as adjusted risk ratios, risk differences and 95% confidence intervals. Continuous outcomes (e.g. mean antenatal systolic blood pressure, gestational age at birth, birthweight centile) will be analysed using linear regression models if the outcome is sufficiently normally distributed (or where data can be suitably transformed) and results presented as differences in means with 95% confidence intervals. For skewed continuous outcomes, unadjusted median differences and 95% confidence intervals will be presented.

13.2.3. Subgroup Analyses

Subgroup analyses will be undertaken on variables used in the minimisation algorithm except for maternity unit, and will be limited to the co-primary outcomes. 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 subgroups. The results of subgroup analyses will be treated with caution and will be used for the purposes of hypothesis generation only.

13.2.4. Missing Data and Sensitivity Analyses

Every attempt will be made to collect full follow-up data on all participating women; it is thus anticipated that missing data will be minimal. Women with missing primary outcome data will not be included in the primary analysis in the first instance. This presents a risk of bias, and sensitivity analyses will be undertaken to assess the possible impact of the risk. This may include a multiple imputation approach. Full details will be included in the Statistical Analysis Plan.

Sensitivity analyses will be undertaken for the two co-primary outcome measures based on the per-protocol analysis population(s). For the maternal co-primary outcome, this will allow us to examine the robustness of the conclusions. For the fetal/ neonatal co-primary outcome, this approach will enable a robust evaluation of the non-inferiority hypothesis.

To explore the influence, if any, of blood pressure measurement setting on the maternal co-primary outcomes, an additional sensitivity analyses will include an analysis of all blood pressure readings (in clinic and self-measured, reported in a telephone consultation). A further analysis which only includes women who self-monitor their blood pressure will also be considered.

In addition, since there is a risk of measurement bias for the secondary outcome assessing neonatal hypoglycaemia, we will perform a sensitivity analysis on the neonatal hypoglycaemia outcome restricted to babies where testing has been performed as indicated by the BAPM criteria (British Association of Perinatal Medicine 2017) (i.e. excluding babies tested but not satisfying the BAPM criteria).

13.2.5. Analysis of the observational study

The Statistical Analysis Plan will include details of the planned statistical analyses for the observational study. This analysis will be exploratory in nature and will be used to inform hypotheses for further research.

13.3. Planned Interim Analysis

Interim analyses of safety and efficacy for presentation to the independent DMC will take place during the study. This is likely to include the analysis of the primary and major secondary outcomes and full assessment of safety (SAEs) at least at annual intervals. Criteria for stopping or modifying the study based on this information will be ratified by the DMC.

13.4. Planned Final Analyses

The primary analysis for the study will occur once all participants have had their primary hospital discharge or 28 days post-birth, whichever occurs sooner and corresponding outcome data has been entered onto the study database and validated as being ready for analysis. This analysis will include data items up to and including the primary hospital discharge or 28 days post-birth (whichever occurs sooner) assessment and no further.

13.5. Health Economic Analyses

A separate Health Economics Analysis Plan will be produced and will provide a more comprehensive description of the planned health economic analyses. A brief outline of these analyses is given below.

An economic evaluation to understand whether nifedipine represents value for money when compared to labetalol from an NHS perspective will be prepared. Our clinical hypothesis is that nifedipine will be superior with fewer women in this group having severe systolic hypertension, and that the co-primary fetal/neonatal outcome will be no worse for the nifedipine group (non-inferior). Therefore, we also hypothesise no difference in costs for the care received by babies but potential differences in costs and maternal health-related quality of life in favour of nifedipine as a result of better systolic blood pressure control over the trial period. To demonstrate this, we will collect health care resource use for mothers over the trial period and for babies after delivery. For mothers, we will use case notes review to collect data on antenatal care (including outpatient contacts and any hospital admissions before delivery), care received during delivery and days spent in hospital prior to discharge. For babies we will collect data on the number of inpatient days of high, medium and low-level care needed after delivery. Unit costs to value this care will be obtained from national sources.

We will also collect maternal health-related quality of life using the EQ-5D-5L instrument at trial entry, two weeks after randomisation, and every 4 weeks before a woman's expected delivery date. Value sets to derive utility scores for EQ-5D-5L states are currently under evaluation by NICE (National Institute for Health and Care Excellence 2018) but we expect a final value set to be available by the time we need to conduct the analysis.

It is established that in addition to hypertension *per se*, related complications such as pre-eclampsia can also increase the maternal risk of subsequently developing cardiovascular disease (Bhattacharya, Prescott et al. 2012, Wu, Haththotuwa et al. 2017). Cardiovascular disease is a chronic life-long condition with substantial implications for costs, life expectancy,

and health-related quality of life. Therefore, should the trial demonstrate that nifedipine can better control hypertension during pregnancy (either for all women, or only for particular sub-groups of women), the potential exists to reduce associated complications and in turn the longer-term risks of cardiovascular disease. In this case, we shall consider using decision analytic modelling to explore costs and maternal quality-adjusted life years (QALYs) over a life-time horizon for a cost-utility analysis. This model will represent the history of disease of women with raised blood pressure following delivery based on cardiovascular events over time. In order to predict, costs and QALYs, observed risk factors, quality of life estimates and health care resource utilisation from our trial will be used to inform the characteristics of a hypothetical cohort entering the model for each drug therapy. The model will be adapted from an economic model that we are building as part of the BUMP studies (https://www.phc.ox.ac.uk/research/participate/bump-trial). Information about maternal quality of life and costs to inform health states over time will be extracted from literature searches. We will synthesise costs and outcomes using an incremental cost-effectiveness ratio expressed as cost per QALY gained between the two therapies. As a secondary analysis, we will present a cost consequence analysis of key clinical primary and secondary outcomes alongside maternal quality of life, and mother-baby pair health care costs up to primary hospital discharge or 28 days post-birth. This analysis will provide preliminary insights of the potential results of the lifetime economic model.

We will follow current guidance (Husereau, Drummond et al. 2013, National Institute for Health and Care Excellence 2018) when interpreting and reporting this economic evaluation. We will pay special consideration to the handling of uncertainty (Briggs, Weinstein et al. 2012) in both the within-trial and the decision analytical model.

14. INTERNAL PILOT

An embedded internal pilot will run in 17 units (staggered start) over a period of ten months to assess recruitment and retention rates, acceptability and implementation. Pre-specified progression criteria have been agreed as follows:

	Black (<67% of target)	**Red (67-84% of target)**	**Amber (85% of target)**	**Green (actual target)**
Number of sites open	≤11	12-14	15-16	17
Recruitment (per centre/month)*	<2.00	2.00-2.54	2.55-2.99	3.00
Cumulative recruitment target	<195	195-246	247-290	291
Actions	Discuss with TSC and consider stopping trial	Discuss with TSC strategies for improvement and consider changes to processes including opening further sites	Continue, with review of strategies to improve at existing sites	Continue

*Excluding two month lag phase in each centre.

In the light of the ongoing uncertainties during the COVID-19 pandemic and ongoing disruption to maternity care and Research and Development Services, additional actions (e.g. increasing number of sites opened and/or reviewing initiation of intervention delivery through remote means) to support recruitment may be necessary to achieve the pilot targets in an appropriate timeframe.

15. TRIAL ORGANISATIONAL STRUCTURE

15.1. Sponsor

University of Birmingham

15.2. Coordinating Centre

BCTU is the Coordinating Centre.

15.3. Trial Management Group

The Trial Management Group (TMG) will monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The TMG will meet monthly and will be responsible for the day-to-day running of the trial. Each participating centre will have a local PI who will report to the TMG. The TMG will consist of the CI, a senior statistician, a senior trials manager and all other members of the TMG, with oversight from the clinical trials unit director as required. The TMG reports to the Trial Steering Committee.

15.4. Co-Investigators Group

The Co-Investigators' Group (CIG) will meet at regular intervals throughout the duration of the trial; this will comprise all co-applicants and the members of the core TMG. The CIG will advise on broader aspects of the study design, conduct, analysis and dissemination of the trial.

15.5. Trial Steering Committee

A Trial Steering Committee (TSC) will be established to provide oversight of the trial and will meet at least annually and as required depending on the needs of the trial. The TSC will include an independent chair, at least two other independent members, a PPI representative(s), and the CI. Observers from the funding programme will be invited to attend all TSC meetings.

The TSC will operate in accordance with a trial specific TSC Charter. Membership and duties/responsibilities are outlined in the TSC Charter. In summary, the TSC will provide overall oversight of the trial; including the practical aspects of the trial, ensure the trial is run in a way which is both safe for the participants and provides appropriate data to the sponsor and funder. The TSC will consider and act, as appropriate, upon the recommendations of the DMC, and ultimately carries the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy.

15.6. Data Monitoring Committee

An independent data-monitoring committee established for the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

Data analyses will be supplied in confidence to an independent DMC, which will meet prior to trial commencement to agree the manner and timing of such analyses. The DMC will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further women to the trial. The DMC will operate in accordance with a trial specific DMC. The DMC will meet at least annually as agreed by the Committee and documented in the charter unless there is a specific reason to amend the schedule. More frequent meetings may be required for a specific reason and will be recorded in minutes.

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the TSC who will convey the findings of the DMC to funders. The DMC may consider recommending the discontinuation of the trial if any issues are identified which may compromise participant safety. The DMC may recommend early stopping of the trial if the interim analyses shows differences between treatments that are deemed to be convincing to the clinical community.

15.7. Finance

This study is funded by the National Institute for Health Research Health Technology Assessment programme and will be registered on the CRN portfolio.

16. ETHICAL CONSIDERATIONS

The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: *http://www.wma.net/en/30publications/10policies/b3/index.html*).

The study will be conducted in accordance with the UK Policy Framework for Health and Social Care Research 2017, the applicable UK Statutory Instruments, (which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments and the Data Protection Act 2018 and EU Clinical Trials directive) and the principles of the International Conference on Harmonisation Guidelines for Good Clinical Practice. This study will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations. The protocol will be submitted to and approved by the main REC prior to circulation and the start of the study. All correspondence with the MHRA and/or REC will be retained in the Trial Master File/ISF, and an annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given by the REC, and annually until the study is declared ended.

Before any women are enrolled into the study, the PI at each site is required to obtain local R&D approval/assurance. Sites will not be permitted to enrol women until written confirmation of R&D approval/assurance is received by the BCTU trials team.

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 women.

17. CONFIDENTIALITY AND DATA PROTECTION

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.

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.

18. FINANCIAL AND OTHER COMPETING INTERESTS

No financial or other competing interests to declare.

Richard McManus has received BP monitors from Omron for research and is working with them on a telemonitoring system. The telemonitoring system for the BUMP trials has been commercialised by SENSYNE and is currently made available to the NHS during the COVID-19 pandemic. Any income associated with these activities is received by the university of Oxford and not personally by RM.

19. INSURANCE AND INDEMNITY

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

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

The UoB is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry guidelines for participant compensation.

20. AMENDMENTS

Approval for the study will be sought from the MHRA, 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 approval.

21. POST-TRIAL CARE

As antihypertensive treatment is often switched immediately after birth (and therefore extended postnatal data are unlikely to reflect effects of the intervention), outcomes will be collected up to birth and data collection up to primary hospital discharge or 28 days post-birth, whichever occurs sooner. The decision to continue or switch antihypertensive drugs after birth will sit entirely with clinicians within the woman's usual care team.

22. ACCESS TO THE FINAL STUDY DATASET

Individuals with access to the full dataset will include the trial manager and data manager. The CI will have access to the full dataset after database lock. The CI's Institution will be the overall owner of the study data. Site investigators will not have access to the full data set and must not use, disseminate or publish any trial 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. In line with the conditions of use of the following validated questionnaires: Beliefs about Medicines Questionnaire (BMQ-Specific), Medication Adherence Report Scale (MARS-5), copyright holders will receive a copy of the de-identified study datasets relating only to these questionnaire responses.

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 and the BCTU, with input from the co-investigator group where applicable.

23. PUBLICATION POLICY

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.

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.

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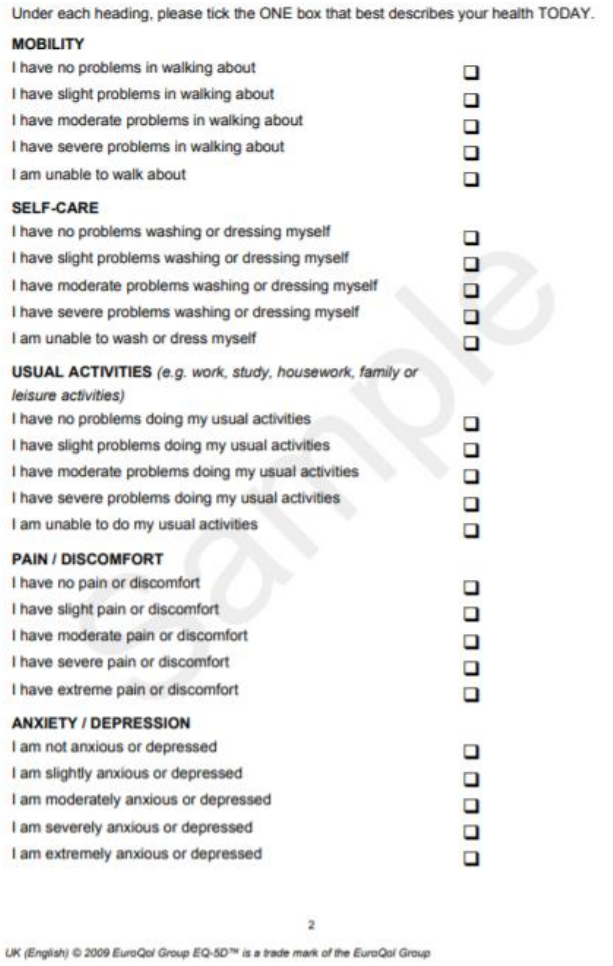
1. APPENDICES

Appendix 1: Questionnaires
EuroQol- 5 Dimension, EQ-5D-5L



Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY
- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE
- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*
- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION
- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

2

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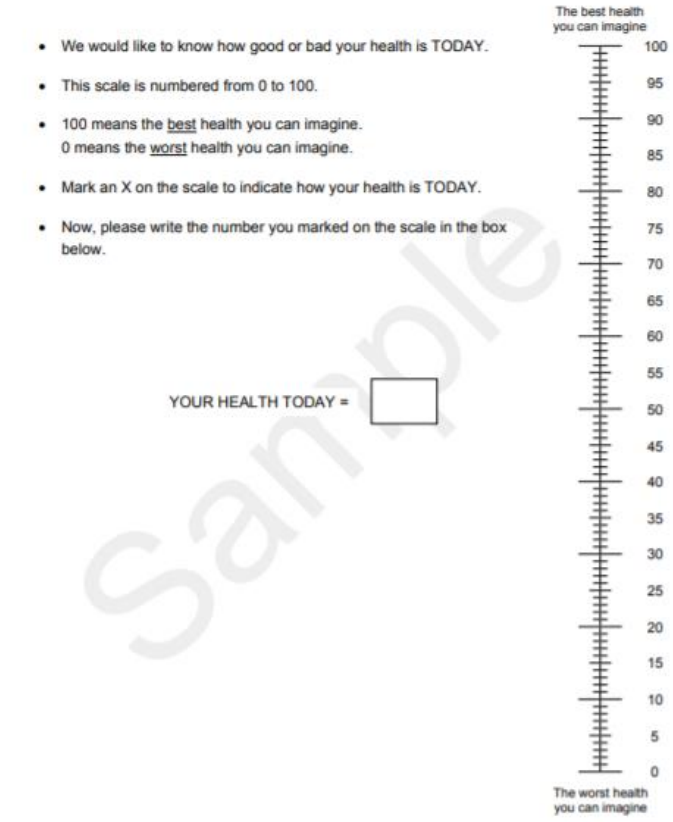

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐

The best health you can imagine
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
The worst health you can imagine

3

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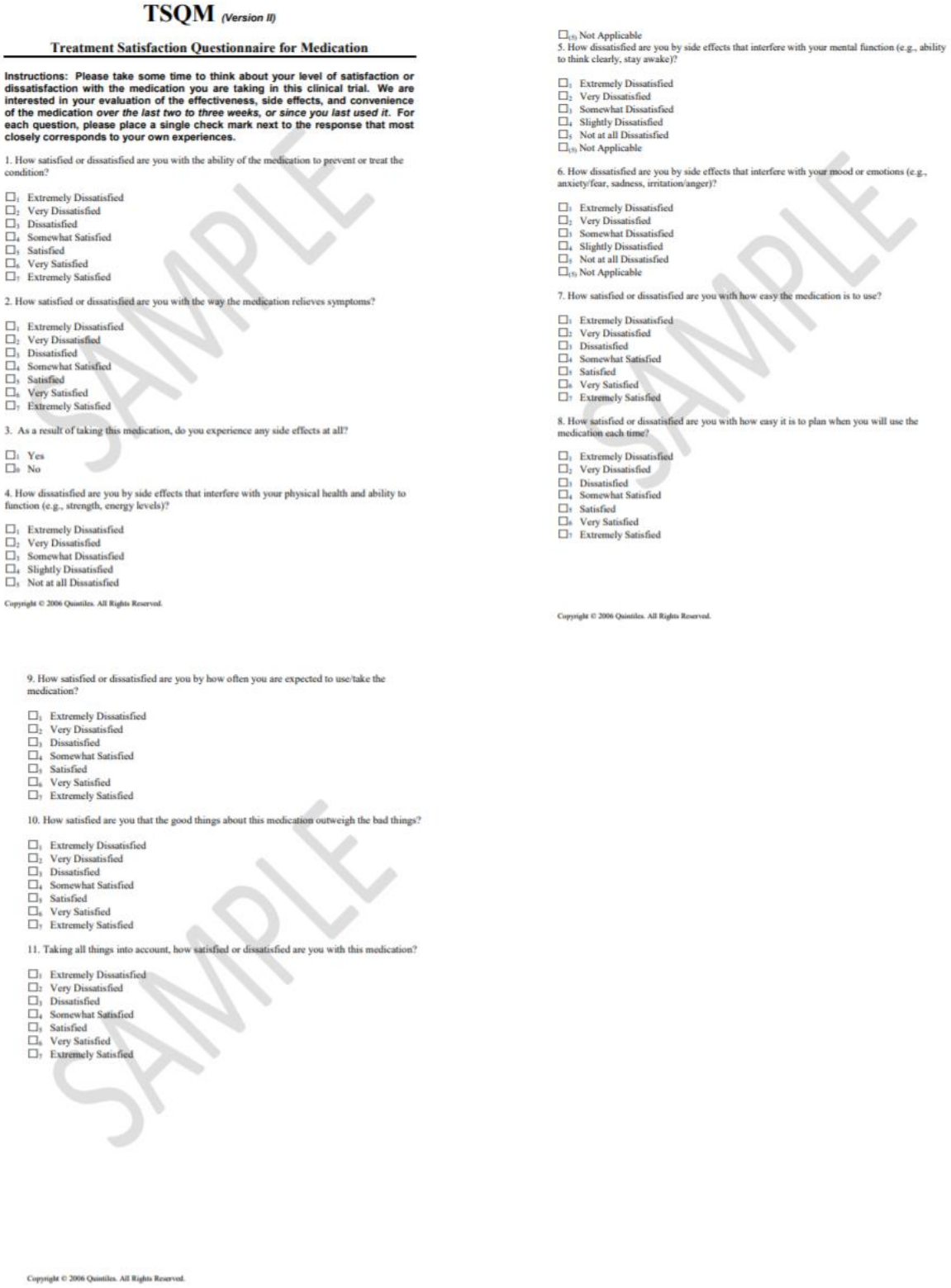
Screenshots of questionnaire sample from the EuroQol website (https://euroqol.org/). Copyright requested.

Treatment Satisfaction Questionnaire for Medication, TSQM Version II



TSQM *(Version II)*

Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication *over the last two to three weeks, or since you last used it*. For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat the condition?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves symptoms?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

3. As a result of taking this medication, do you experience any side effects at all?

☐1 Yes
☐0 No

4. How dissatisfied are you by side effects that interfere with your physical health and ability to function (e.g., strength, energy levels)?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Somewhat Dissatisfied
☐4 Slightly Dissatisfied
☐5 Not at all Dissatisfied

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☐(0) Not Applicable

5. How dissatisfied are you by side effects that interfere with your mental function (e.g., ability to think clearly, stay awake)?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Somewhat Dissatisfied
☐4 Slightly Dissatisfied
☐5 Not at all Dissatisfied
☐(0) Not Applicable

6. How dissatisfied are you by side effects that interfere with your mood or emotions (e.g., anxiety/fear, sadness, irritation/anger)?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Somewhat Dissatisfied
☐4 Slightly Dissatisfied
☐5 Not at all Dissatisfied
☐(0) Not Applicable

7. How satisfied or dissatisfied are you with how easy the medication is to use?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

8. How satisfied or dissatisfied are you with how easy it is to plan when you will use the medication each time?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

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9. How satisfied or dissatisfied are you by how often you are expected to use/take the medication?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

10. How satisfied are you that the good things about this medication outweigh the bad things?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

11. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

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Screenshots of questionnaire sample from IQVIA contact (https://www.iqvia.com/landing/treatment-satisfaction-questionnaire-for-medication-tsqm). Copyright requested.

Beliefs about Medicines Questionnaire, BMQ-Specific

BMQ-S11-singular Project Number .....

YOUR VIEWS ABOUT THE MEDICINE PRESCRIBED FOR YOU

- We would like to ask you about your personal views about the medicine prescribed for you.
- These are statements other people have made about this medicine.
- Please show how much you agree or disagree with them by ticking the appropriate box.

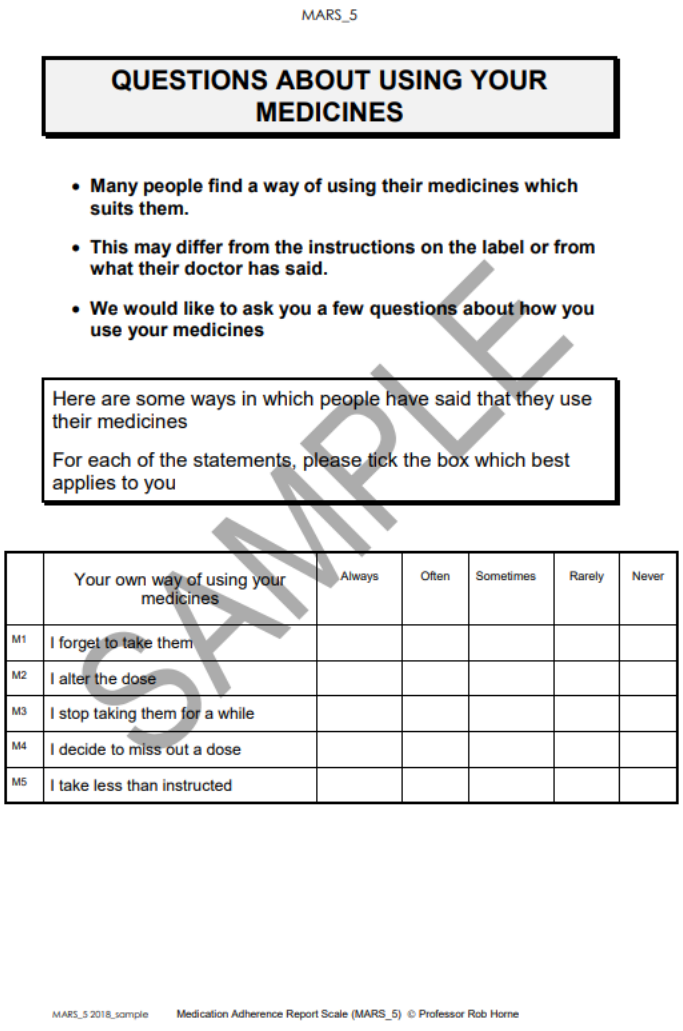
There are no right or wrong answers.
We are interested in your personal views

	Views about the MEDICINE PRESCRIBED FOR YOU:	Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
N1	My health, at present, depends on this medicine					
C1	Having to take this medicine worries me					
N2	My life would be impossible without this medicine					
C2	I sometimes worry about long-term effects of this medicine					
N3	Without this medicine I would be very ill					
C3	This medicine is a mystery to me					
N4	My health in the future will depend on this medicine					
C4	This medicine disrupts my life					
C5	I sometimes worry about becoming too dependent on this medicine					
N5	This medicine protects me from becoming worse					
C6	This medicine give me unpleasant side effects					

Screenshots of questionnaire from contact with Professor Robert Horne (BMQ © Rob Horne University of Brighton 1996. All rights reserved). Copyright requested.

Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. Psychol Health. 1999;14(1):1–24

Medication Adherence Report Scale, MARS-5



MARS_5

QUESTIONS ABOUT USING YOUR MEDICINES

- **Many people find a way of using their medicines which suits them.**
- **This may differ from the instructions on the label or from what their doctor has said.**
- **We would like to ask you a few questions about how you use your medicines**

Here are some ways in which people have said that they use their medicines

For each of the statements, please tick the box which best applies to you

	Your own way of using your medicines	Always	Often	Sometimes	Rarely	Never
M1	I forget to take them					
M2	I alter the dose					
M3	I stop taking them for a while					
M4	I decide to miss out a dose					
M5	I take less than instructed					

MARS_5 2018_sample Medication Adherence Report Scale (MARS_5) © Professor Rob Horne

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Chan AH, Horne R, Hankins M, Chisari C. The Medication Adherence Report Scale: A measurement tool for eliciting patients' reports of nonadherence. British Journal of Clinical Pharmacology. 2020 May 18.