Study Title: Self-management of postnatal anti-hypertensive treatment: a trial development pilot study

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No conflicts of interest.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1. SYNOPSIS

Study Title	**Self-management of postnatal anti-hypertensive treatment trial development pilot study**	
Internal ref. no. / short title	**SNAP-HT trial development pilot study**	
Study Design	Non-blinded, randomised, controlled trial-development pilot study	
Study Participants	Women in the postnatal period, with gestational hypertension or pre-eclampsia requiring on-going anti-hypertensive treatment.	
Planned Sample Size	100 women	
Planned Study Period	December 2014 – March 2016 (15 months)	
	Objectives	**Outcome Measures**
Primary	Feasibility of study	Recruitment rate Retention rate Loss to follow up rate Withdrawal rate Compliance/adherence rate in the self-monitoring group
Secondary	Does BP self-management postpartum period improve BP control?	Number of blood pressure readings in target range BP at day 10, 4 weeks, 6 weeks, 12 weeks and 26 weeks postpartum Number of urgent visits, and timing of these, to GP or hospital requiring medication increase due to BP > 150/100, or medication decrease due to BP < 100 systolic
	Can BP self-management postpartum reduce postnatal readmissions to hospital with poorly controlled hypertension?	Postnatal readmission rate
	To assess patient experience of self-management of blood pressure in the postpartum period.	EQ-5D-5L health questionnaire results Structured interviews (participants)
	To assess vascular outcomes, and determine whether better blood pressure control correlates with improved vascular risk markers	Cardio-ankle vascular index Radial arterial tonometry Capillaroscopy
	Safety	Reporting of serious adverse events Side effect reporting
Exploratory analysis	To explore percentage time spent in range as a marker for blood pressure control in this setting	Assess percentage time spent in target BP range in both groups; use the home monitoring data from the intervention arm to explore the validity of this measure and

		the relationship between the trial blood pressure readings taken at two time points
	Setting BP thresholds for future trials	Difference between home and clinic BP recordings

2. ABBREVIATIONS

BP	Blood Pressure
CAVI	Cardio ankle vascular index
CDMS	Computerised Data Management System
CI	Chief Investigator
CRF	Case Report Form
CTRG	Clinical Trials & Research Governance, University of Oxford
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NRES	National Research Ethics Service
PCCTU	Primary Care Clinical Trials Unit, University of Oxford
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TMG	Trial Management Group

3. BACKGROUND AND RATIONALE

Gestational hypertension, defined as blood pressure (BP) of $\geq$ 140/90mmHg, affects between 6 and 15% of pregnancies. A recent population-based retrospective study in the USA found the rate of pre-eclampsia (BP $\geq$ 140/90mmHg and new onset significant proteinuria $\geq$ 300mg/24hr) to be 3.4% [1]. In England in 2008 there were 665,800 pregnancies, and NICE estimates that 89,900 of these were affected by gestational hypertension [2].

There has been considerable focus, both within the primary literature and from the NICE guidance, on BP control during pregnancy, especially with respect to pregnancy outcome. However, it has been shown that severity of hypertension in later life is associated with the degree of hypertension during the first six weeks postpartum [3]. Work is on-going which suggests that those with above-average BP at six weeks postpartum have an approximately 30% increase in aortic stiffness. NICE guidance highlights that very few clinical studies have addressed the management of BP postpartum and clinical care is typically to continue antepartum BP medication and monitor BP in the community with a focus on prevention of over-treatment [4].

Previous work by Prof McManus' group has shown that self-monitoring and self-titration of anti-hypertensive medications in essential hypertension in the non-pregnant population is both feasible and more effective than usual care. The TASMINH2 randomised controlled trial demonstrated that self-management of BP in patients with poorly controlled essential hypertension resulted in a statistically significant reduction in mean systolic BP compared with patients undergoing usual care (difference between groups at 12 months 5.4mmHg, P = 0.0004) [5]. Results from a further RCT in patients at high cardiovascular risk have demonstrated an even greater effect of self-management in this cohort (TASMIN-SR) [6]. No research to date suggests that this intervention should pose any risks to participants i.e. that blood pressure control should be impaired through self-monitoring and self-management.

The proposed study aims to apply this experience to postpartum women with gestational hypertension and pre-eclampsia where both high and low BP can lead to adverse outcomes, and where detection of on-going hypertension is essential. Most women will be treatment-free by 3 months postpartum [7]. This poses an additional challenge in terms of how best to manage this down-titration, and use of the self-management approach to assist with this will also be addressed.

To date research in self-monitoring and self-management of hypertension in non-pregnant patients has shown that it is feasible, acceptable to patients and produces better BP control when compared with conventional monitoring in a clinic setting [5]. The results of this study will be utilised in the planning of a large scale randomised controlled trial investigating self-management of BP in the postpartum period. Women with medicated gestational hypertension and pre-eclampsia would seem to be an ideal cohort in whom to apply this work: the disease has, in general, a limited time course meaning that intensive monitoring is more reasonable and more likely to be adhered to. Pregnant women are by definition in a younger age group than the majority of those with essential hypertension, and may be more comfortable with the use of technology to assist in disease monitoring. Women might also be more driven in the setting of a recent pregnancy to take greater responsibility for their health.

BP control in the postpartum period can be challenging due to other pressures on women and healthcare professionals, and as a result of the need to wean medication appropriately in response to changing BP over a relatively short time-frame. If self-monitoring in the postpartum period proves to be a feasible, acceptable and a successful strategy for management of BP, it could lead to a reduction in the length of inpatient stay, readmissions and the number of postpartum visits, with cost-saving implications for both primary and secondary care. Furthermore as the importance of BP control in the immediate postpartum period has already been demonstrated to affect women's cardiovascular risk up to 15 years after delivery, any strategy, which successfully increases women's adherence to an effective treatment regimen, has the potential to influence their healthcare needs well into the future.

This study is a pilot study: it has been set up in order to inform the planning of a large-scale multi-centre randomised controlled trial by testing the feasibility of methods and procedures for later use on a large scale. We want to increase our experience of applying this management approach in this subset of patients; to select the most appropriate primary outcome measure and to estimate the effect size of this intervention; to assess recruitment potential; and to evaluate feasibility of coordinating this trial across several centres. The primary objective of the large-scale trial will be to determine whether the self-management approach can improve blood pressure control in women with medicated hypertensive disorders of pregnancy in the postnatal period.

4. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Specific objectives and outcome measures for this pilot study are listed in the table below. The overall objectives of this pilot study are [8, 9]:

- **Process:** recruitment and retention rates; acceptability of the intervention; randomisation procedure; integrity of the protocol
- **Resources:** testing of questionnaires; length of time required to conduct study procedures
- **Management:** testing of data collection forms and data management system; centre willingness and capacity;
- **Scientific:** selection of the most appropriate outcome measure; safety of the intervention; were any important variables omitted; estimate of the treatment effect

Objectives	**Outcome Measures/Endpoints**	**Time point(s) of evaluation of this outcome measure (if applicable)**
Primary Objective		
Feasibility of study	Recruitment rate *Number of participants randomised / number of consenting participants* *Number of participants randomised / number of potential participants approached* Retention rate *Number of participants completing trial follow up / number of participants randomised* Attrition rate *Number of participants lost to follow-up or withdrawn / number of participants randomised* Compliance rate *Number of study visits attended / total number of intended study visits*	End of trial period
Secondary Objectives		
To investigate whether self-management of hypertension in the postpartum period leads to improved blood pressure control	Blood pressure at day 10, 4 weeks, 6 weeks, 12 weeks and 26 weeks postpartum Number of blood pressure readings in target range 'Time to event': number of urgent visits, and timing of these, to GP or hospital requiring medication increase due to BP > 150/100, or medication decrease due to BP < 100 systolic	End of trial period

To assess whether self-management of blood pressure in the postpartum period can reduce postnatal readmissions to hospital with poorly controlled hypertension.	Postnatal readmission rate in each group *Number of postnatal readmissions / number of randomised participants*	End of trial period
To assess patient experience of self-management of blood pressure in the postpartum period	EQ-5D-5L health questionnaire results Structured interviews (participants)	End of trial period End of trial period for those participants in patient experience sub-study
To determine whether better blood pressure control correlates with improved vascular risk markers	Arterial stiffness indices (CAVI and arterial tonometry) Microvascular changes (capillary density)	End of trial period for those participants in vascular sub-study
Safety	Reporting of serious adverse events Reporting of side effects	Ongoing throughout trial period
Exploratory analysis		
To explore percentage time spent in range as a marker for blood pressure control in this setting.	Assess percentage time spent in target BP range in both groups, and use the home monitoring data from the intervention arm to explore the validity of this measure and the relationship between the trial blood pressure readings taken at two time points	End of trial period
Setting BP thresholds for future trials	Difference between home and clinic BP recordings	End of trial period

5. STUDY DESIGN

Non-blinded randomised controlled trial. The participants will not be blinded as the nature of the intervention precludes this. All results will be analysed on an intention to treat basis. In order to assist with recruitment numbers, and to assess the feasibility of running a multi-centre trial, we are planning to run this study within several hospitals local to Oxford.

Women with gestational hypertension or pre-eclampsia requiring on-going anti-hypertensive medication in the postpartum period will be randomised to one of two treatment arms: usual care, or self-management of blood pressure.

Women randomised to usual care will have their blood pressure monitored by their community midwife, and will have their anti-hypertensive medication adjusted by their general practitioner.

Women randomised to self-management of blood pressure will have an individualised medication adjustment schedule (based on NICE guidance for medication adjustment postpartum). They will be provided with, and taught to use, a validated home blood pressure monitor, and perform daily blood pressure readings until they have discontinued treatment. The monitor used will be Microlife WatchBP® Home as these have been validated for use in pregnancy. These monitors have been purchased by the Nuffield Department of Primary Care Health Sciences. Women will be provided with written instructions about use of the monitor. When treatment is discontinued we will ask them to continue weekly blood pressure measurements for 1 week, and provided these are normal (<140/90) they will then be asked to

check their blood pressure weekly for the remainder of the trial period. The self-monitoring BP data will be collated centrally through the use of a smart phone app or text messaging based system. This service will respond to participants regarding the level of their BP and what action is required (if any). At the end of the study period the data from the home BP monitors will also be uploaded to the trial database.

These blood pressure readings will replace those that would normally be taken by their community midwives. If women still require additional support from the GP or community midwife postpartum for other medical, psychiatric or social issues then this will continue.

All women will be followed up at 10 days, then 4, 6, 12 and 26 weeks postpartum and have their blood pressure measured by one of the study team. If women still require anti-hypertensive treatment at 6 weeks postpartum, they will be offered referral to the specialist hypertension clinic.

At the baseline visit, and 12 and 26 week follow up women will be weighed using a standardised set of scales. This is in order to evaluate whether the extent and speed of return to booking weight (a mark of pre-pregnancy weight) correlates with resolution of gestational hypertension.

Women from each group will be asked to complete the EQ-5D-5L Health Questionnaire to assess their quality of life at screening (visit 1), 6 weeks (visit 5) and 26 weeks (visit 7). Additionally we will conduct optional structured interviews with women from both groups in order to assess their experience of management of blood pressure in the postpartum period. Some baseline data will be collected at visit 1 (screening), and structured interviews will be done at the 4 (visit 4) and 26 week (visit 7) visits. We aim to recruit a minimum of 50% of participants in each group (i.e. 50 women, 25 from each group) into this sub-study.

Gestational hypertension and pre-eclampsia are both associated with future cardiovascular disease in the mother [10, 11]. To follow on from the work that suggests that those with above-average BP at six weeks postpartum have an approximately 30% increase in aortic stiffness; we are planning to conduct a sub-study to analyse markers of vascular risk in women from both groups. As it may be assumed that the baseline characteristics of the two groups are then similar, if we demonstrate a treatment effect from the intervention, then it will allow us to analyse the relationship between blood pressure control in the postnatal period and markers of vascular risk to help determine if it is the severity of pathology or effectiveness of control that determines long term outcome. Women will consent to an optional extended visit at baseline (or day 10) and 12 weeks where measures of arterial stiffness and capillary density will be taken. Additionally in women who consent to participating in this element of the study we will take a blood sample to measure circulating biomarkers relevant to cardiovascular health. We aim to recruit a minimum of 15 women from each group into this sub-study.

6. PARTICIPANT IDENTIFICATION

6.1. Study Participants

Women with a diagnosis of gestational hypertension or pre-eclampsia, who require on-going antihypertensive medication in the postpartum period.

6.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Female, aged 18 years or above.*
- Women with **gestational hypertension** (new-onset BP $\geq$ 140/90mmHg) or **pre-eclampsia** (new onset BP $\geq$ 140/90mmHg and significant proteinuria $\geq$ 300mg/24hr), prior to their discharge from hospital post-delivery.
- Require antihypertensive medication during pregnancy, which needs to continue in the postpartum period.

*The justification for the lower age limit is that we do believe that in this pilot study additional benefit would be derived from conducting the research in under-18s, compared with conducting it in adults (as per guidance from the General Medical Council) [10].

6.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Hypertension prior to pregnancy.
- Poor English language skills.
- More than three anti-hypertensive agents at discharge from hospital postpartum.

7. STUDY PROCEDURES

7.1. Recruitment

Women undergoing obstetric care at the John Radcliffe Hospital (Oxford), Horton General Hospital (Banbury), Royal Berkshire Hospital (Reading), Stoke Mandeville Hospital (Aylesbury) and Northampton General Hospital (Northampton) will be approached during pregnancy. The study will be advertised through the use of posters in patient areas, and Information leaflets will be available for both patients and healthcare professionals at these sites (through the Antenatal Clinics, Antenatal Wards and Day Assessment Units). The direct care team will make the initial approach to potential participants, will provide interested women with a participant information sheet and take verbal consent to share their details with the research team. These women will then be consented and screened by the research team according to the criteria detailed above.

Eligible women who wish to participate in the study will be seen at a baseline visit in hospital following delivery. At this stage there will be formal confirmation of consent and randomisation will take place.

Women who suffer an adverse perinatal outcome (Special Care Baby Unit admission, intrauterine fetal death or neonatal death) will not be automatically excluded from the study, but there will be careful consultation with the midwifery and obstetric teams before these women are approached, and they will be handled sensitively.

7.2. Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent Form (ICF) before any study specific procedures are performed (including screening). The original consent process and screening will take place prior to birth, and therefore there will be formal confirmation of consent at the baseline visit in hospital after delivery: Study procedures will be re-discussed, and a second copy of the participant information sheet provided if necessary. Confirmation of consent will be verbal, but will be documented in the participant's maternity records.

Written and verbal versions of the participant information and informed consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will have time between first approach and delivery of their baby to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Written informed consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the informed consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. One copy of the signed informed consent will be given to the participant and one copy will be included in the participant's maternity records. The original signed form will be stored at the PCCTU (with participants' consent).

We will inform GPs and community midwives in writing of their patient's involvement in the study.

Patient experience qualitative sub-study: participants will consent to optional extended visits at 4 weeks and 26 weeks where structured interviews to assess their experience of self-management of blood pressure in the postpartum period will be conducted. Some baseline data will also be collected at the screening appointment.

Vascular risk sub-study: Women will consent to an optional extended visit at baseline and 12 weeks where measures of arterial stiffness and capillary density will be taken, and a fasting blood sample will be taken.

7.3. Visit 1: Screening and Eligibility Assessment

Screening (post consent) will involve collecting the demographics, age at entry to the study (years and months), weight at booking, height, BMI at booking, ethnicity, medical history, obstetric history, drug history and social history. We will ask women whether or not they are involved in any other medical research projects. Involvement in other research projects does not exclude women from this trial.

Personal data as follows will be collected and stored separately. This is to facilitate contact with participants during the study, and to arrange home follow-up visits (if participants agree):

- Forename and surname
- Address including postcode
- Medical record number (to allow access to patient's medical records)
- Telephone number

Details of the following aspects of the diagnosis of gestational hypertension / pre-eclampsia will be recorded:

- Blood pressure at booking
- Gestation at diagnosis of gestational hypertension or pre-eclampsia
- Gestation at which anti-hypertensive treatment was started
- Which anti-hypertensive drugs used
- What doses of anti-hypertensive drugs (and dose increases)
- Hospital admissions for gestational hypertension / pre-eclampsia
- Whether intravenous anti-hypertensive treatment was required
- Whether magnesium sulphate was required as eclampsia prophylaxis
- HDU or ICU care
- Significant proteinuria (record level)?
- Maternal complications of gestational hypertension / pre-eclampsia: renal dysfunction, HELLP syndrome, eclampsia, placental abruption
- Fetal complications of gestational hypertension / pre-eclampsia: in-utero growth restriction, placental insufficiency, intrauterine fetal death

Participants will be asked to complete the standardised Eq-5D-5L quality of life questionnaire at this visit.

7.4. Randomisation, blinding and code-breaking

A secure web-based randomisation system will be provided by the Oxford Primary Care Clinical Trials Unit. The system will allow for the allocation of patients to the two treatment groups: standard care or self-management on a 1:1 basis and for this allocation to be stratified according to recruitment site. Due to the nature of the intervention it will not be possible to blind patients, the recruiting clinician or data management staff within the clinical trials unit to the group allocation.

7.5. Visit 2: Baseline

The baseline visit will take place in hospital as soon as is practical after delivery (day 3, -2 or +3 days). There will be verbal confirmation of consent, and this will be documented in the participant's maternity notes.

Further baseline data will be collected at this visit:

- Days since delivery
- Date of delivery
- Mode of delivery
- *Any change from screening appointment?*
    - *Significant proteinuria (record level)?*
    - *Hospital admissions for gestational hypertension / pre-eclampsia*
        - *Number*
        - *Duration of each*
        - *Total duration*
    - *Whether intravenous anti-hypertensive treatment was required*
    - *Whether magnesium sulphate was required as eclampsia prophylaxis*

- *HDU or ICU care*
- *Maternal complications of gestational hypertension / pre-eclampsia:*
  - *Renal dysfunction (peak creatinine)*
  - *HELLP syndrome (peak alanine transaminase, lowest platelets, lowest haemoglobin, peak lactate dehydrogenase)*
  - *Disseminated intravascular coagulation*
  - *Neurological dysfunction: eclampsia, altered GCS, blindness, stroke, hyperreflexia + clonus, severe headache + hyperreflexia, persistent visual scotomata*
  - *Placental abruption*
- *Perinatal complications of gestational hypertension / pre-eclampsia:*
  - *In-utero growth restriction*
  - *Placental insufficiency i.e. abnormal dopplers*
  - *Premature delivery*
  - *Special Care Baby Unit admission (ICU, HDU or LDU) and length of stay*
  - *Intrauterine fetal death*
  - *Intrapartum stillbirth*
  - *Neonatal death*

We will measure participants left mid arm (or right if left cannot be used for blood pressure monitoring) in order to guide choice of blood pressure cuff size.

Participants will have their blood pressure checked after 5 minutes rest using the automated mode of a sphygmomanometer. 6 blood pressure readings will be taken at intervals of 1 minute. For the outcome measure of blood pressure control the mean of the second and third readings will be used. The mean of readings 2-6 will also be calculated as this has the potential to reduce the white coat effect. It may be anticipated that the intervention group may become more habituated to blood pressure monitoring, thereby reducing the white coat effect in this group. This approach attempts to reduce the potential bias that this habituation introduces.

Participants will be weighed at this visit using a standardised set of scales.

At each visit participants will be asked about:

- What anti-hypertensive medication they are currently taking
- Any side effects
- Any adverse events
- Concomitant medications

It is at this visit that participants will be randomised, and participants randomised to the intervention arm will be provided with a blood pressure self-monitor, and taught to use it. Prior to discharge from hospital participants in the intervention group will be given an individualised down titration schedule. This will be written by the research team in conjunction with the participant's direct care team.

If participants consent to participate in the vascular sub-study then this visit will be extended and will take place at the Cardiovascular Clinical Research Facility at the John Radcliffe Hospital, Oxford. A fasting blood sample (ideally 6 hours clear fluid only) will be taken to measure circulating biomarkers relevant to cardiovascular health, and three vascular assessments will be performed:

- Cardio-ankle vascular index (CAVI)
- Arterial tonometry
- Capillaroscopy

7.6. Visits 3-7: Follow-up

Participants will be followed up at 10 days, -2 or + 4 days (visit 3), 4 weeks +/- 1 week(visit 4), 6 weeks +/- 1 week (visit 5), 12 weeks +/- 1 week (visit 6) and 26 weeks +/- 2 weeks (visit 7) postpartum.

If women are discharged home after day 14 post delivery (i.e. beyond the timing of visit 3), then an additional visit or telephone call will be arranged at the participant's convenience between discharge and visit 4 to ensure the participant's safety.

At each visit the participants will be seen by a member of the research team, and their eligibility and consent will be confirmed. At these visits, participants will have their blood pressure checked after 5 minutes rest using the automated mode of a sphygmomanometer. 6 blood pressure readings will be taken at intervals of 1 minute. For the outcome measure of blood pressure control the mean of the second and third readings will be used. The mean of readings 2-6 will also be calculated and recorded.

At each visit participants will be asked about:

- What anti-hypertensive medication they are currently taking
- Any side effects
- Any adverse events
- Concomitant medications

Visits 3, 4, and 7 will all be home visits or alternatively in the clinic or local general practice, at the woman's discretion. The visit at day 10 (visit 3) will aim to coincide with the routine community midwife appointment.

The visit at 6 weeks (visit 5) will be a clinic visit, and ideally will be scheduled alongside the routine postnatal check with the GP. If participants remain on anti-hypertensive treatment at this visit they will be offered referral to the specialist hypertension clinic for investigation for any underlying cause of secondary hypertension.

At visits 6 and 7 (12 and 26 weeks) participants will be weighed using a standardised set of scales.

At visits 5 and 7 (6 weeks and 26 weeks) participants will be asked to complete the EQ-5D-5L questionnaire.

If patients consent to participate in the vascular sub-study then visit 6 will take place at the Cardiovascular Clinical Research Facility at the John Radcliffe Hospital, Oxford. They will have the same vascular assessments performed as at baseline. If participants have not consented to participate in the vascular sub-study visit 6 will be at a participant's home.

If participants consent to participate in the qualitative patient experience sub-study then extended appointments at visits 4 and 7 will include structured patient experience interviews.

7.7. Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may seek external review regarding discontinuing a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Pregnancy
- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with study requirements*
- Loss of capacity to consent to involvement in research, for example due to developing puerperal psychosis
- Withdrawal of Consent
- Loss to follow up

*Non-compliance in either group would be defined as missing a trial visit, and not being contactable to reschedule the visit. Non-compliance in the intervention arm is defined as failing to report 3 consecutive blood pressure readings in the first 14 days after birth, or 5 consecutive blood pressure readings from this point onwards. The definition of 'significant non-compliance' necessitating withdrawal from the study will be an individualised judgement made by the research team in conjunction with a participant's direct care team. This judgement will be made on the basis of concerns regarding patient safety, and therefore will be influenced by the nature, frequency and clinical impact of a particular participant's non-compliance.

If a participant from the intervention arm withdraws from the study we will ensure that they return to usual blood pressure monitoring with their community midwife and GP. All participants will have their day 10 postnatal check with their midwife, and 6-week postnatal check with their GP as normal.

If a participant withdraws from the study their data will still be included in the data set unless they request their data be removed. As this is a trial-development pilot study withdrawn participants will not be replaced, as accurate assessment of the numbers of participants withdrawn and lost to follow is an important part of this study.

The reason for withdrawal will be recorded in the CRF if available.

7.8. Definition of End of Study

The end of study is the date of the last visit of the last participant.

8. INTERVENTIONS

8.1. Self-management of blood pressure

Participants in the usual care arm with have normal clinical care of their BP with their community midwife and GP. There will be no intervention in this group.

Participants in the intervention arm will be asked to perform daily BP readings at the same time each morning, at a time that is convenient to them: After 5 minutes rest they will perform two readings, more than 1 minute apart, and the second reading acted upon, in terms of how to adjust their medication. The self-monitoring BP data will be communicated centrally through the use of a smart phone app or text messaging based system. This service will respond to participants regarding the level of their BP and what action is required (if any). Participants in this group will be provided with an individualised medication adjustment schedule based on:

- Current treatment (which drugs, what doses)
- NICE guidance for management of hypertension in pregnancy [4]
    - If < 130/80 reduce / stop treatment
    - If < 140/90 consider reducing / stopping treatment
    - If ≥ 150/100 increase / start treatment
    - If ≥ 160/110 requires hospital review

The individualised medication adjustment schedules for each participant will be created by the research team in conjunction with the participant's usual care team. See Appendix D for standardised BP thresholds for medication adjustment (based on NICE guidance as above).

Participants will be provided with a toll-free telephone number to contact for any trial-related queries.

Participants will be advised to attend their local maternity unit for urgent review if blood pressure is ≥ 160/110 or they develop symptoms, which may be associated with hypertension (headache, visual disturbance, vomiting or upper abdominal pain). When on antihypertensive treatment, they will be advised to see their GP if their blood pressure is 150-159/100-109, or systolic < 100.

In the self-management arm we are withdrawing part of their usual blood pressure management by their GP and midwife. Therefore for safety it is important that participants in this arm adhere to the monitoring schedule. In the first 14 days after birth NICE recommends that BP is monitored on at least alternate days. Therefore if participants fail to report 3 consecutive blood pressure readings via the text message service or smart phone app, this will trigger the research team to contact them. From 14 days after delivery until treatment is discontinued, failure to report 5 consecutive blood pressure readings will trigger the research team to contact a participant.

9. SUB-STUDIES

9.1. Patient experience structured interviews

Additionally we will conduct structured interviews with participants in both arms who consent to participate in the qualitative sub-study to assess their experience of either usual care or self-management of blood pressure in the postnatal period, and to identify and explore factors related to the successful (or unsuccessful) implementation of the intervention. This embedded study will provide data regarding the views of patients as to the acceptability of self-monitoring in the routine management of gestational hypertension and pre-eclampsia after birth once they have been discharged from hospital.

Participants in both arms will be interviewed to explore barriers and facilitators to this self-management intervention at two stages during the trial. The control group will be interviewed to allow comparison of patient experience in the two arms.

Baseline data (5 questions) will be collected at visit 1 (screening). The structured interviews will be done at the 4 and 26 week visits (visits 4 and 7), and will take approximately 10-15 minutes on each occasion. There will be 5 questions for both groups, and an additional 5 questions in the intervention group.

An important focus of the interviews will be on identifying: perceived barriers; where similarities and differences in perception lie; appropriate behaviours and information sharing between patient, practitioner and practice staff necessary to maximise successful management; and patient satisfaction. We will use a structured interview approach with free text options, as this provides a reproducible format for consistency across interviews, while also allowing for further (free text) explanation. Structured responses will be entered on to a pre-coded scoring sheet. Free text responses will be audio-recorded and transcribed into Nvivo in order to capture all participant experiences.

At the interviews at screening and 4 weeks we will ask for the structured response first followed by any comments. At the final follow-up visit at 6 months we will aim to gather more detailed answers about participants' experiences so we will ask for their views followed by the structured response.

Structured, coded responses will be analysed using descriptive statistics (e.g. frequencies and cross-tabulations). Free text responses and interviewer notes will be analysed thematically. This dual approach will bring out both 'articulated' data i.e. direct responses to questions on the areas described above, as well as new 'emergent data'.

All women being enrolled into the trial will be asked if they consent to participate in this optional sub-study. All women who consent will be interviewed at visits 1 and 4. If more than 50 women (i.e. 25 from each group) consent to participate, then we will purposively sample these women to determine who undergoes the more detailed interview at the 6 month follow up visit. This sampling will be based on age, index of multiple deprivation, severity of hypertensive disorder of pregnancy (amount of medication at discharge from hospital, using WHO defined daily dosages) and in the intervention group adherence to self-monitoring.

9.2. Vascular risk

The following interventions will take place at baseline (visit 2) or day 10 (visit 3) and 12 weeks (visit 6):

- Cardio-ankle vascular index (CAVI) will be used to give a global assessment of arterial stiffness, independent of blood pressure. This involves placing blood pressure cuffs on both upper arms and ankles, with ECG monitoring and heart sound monitoring. Each measurement takes approximately 5 minutes.
- Radial arterial tonometry will be used to measure aortic blood pressure and augmentation index. This involves 3 lead ECG monitoring and using the Sphygmacor machine to analyse the radial arterial waveform. Each measurement takes approximately 10 minutes.
- Capillaroscopy will be used to study capillary density as a marker of microvascular changes related to hypertension. This involves using a microscope to look at the capillaries on the back of the finger at rest (functional capillary density) and with a pressure cuff inflated to 50mmHg (anatomical capillary density). Each measurement will take approximately 30 minutes.

- Investigators trained in venepuncture will take a 40ml fasting blood sample (ideally a minimum of 6 hours clear fluid only) to measure circulating biomarkers relevant to cardiovascular health. Venepuncture is considered necessary, as there is no other way that certain features of cardiovascular risk can be assessed. Lipid profile and glucose homeostasis (assessed by fasting insulin, glucose and HOMA) will be measured by standard techniques. Samples will also be used to measure routine inflammatory indices such as CRP and if considered appropriate novel proposed risk factors such as adhesion molecules, adipokines etc. Samples will be stored at -80^{o}C in facilities within the Department of Cardiovascular Medicine. Measurements will be performed in batches, as appropriate, by laboratories in the University of Oxford, John Radcliffe Hospital or subcontracted laboratories under the direction of the investigators. With the explicit consent of participants for the gifting of samples, samples will then be transferred to a tissue bank for future use.

10. SAFETY

10.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

10.2. Expected Serious Adverse Events

The following SAEs (which must also fulfil at least one of the criteria listed in section 10.1) may be expected to occur in this patient population.

Potentially related to BP management	Unrelated to BP management
BP $\geq$ 160/110	Vaginal bleeding
BP < 90/50 whilst on treatment	Endometritis
Seizure	Sepsis
Intracranial haemorrhage	Pyelonephritis
Stroke	Mastitis
Faint	Surgical site infection
Fall	Paralytic ileus

Headache Vomiting Upper abdominal pain	Visceral injury (ureter, bladder, bowel) Pelvic collection Haematoma

10.3. Recording and Reporting Procedures for Adverse Events and Serious Adverse Events

Safety reporting will be from baseline to the 26 week follow up visit.

Adverse events may also be recorded by the participant using the trial telephone number, email, or via the text message service or smart phone app. Participants will be directly asked about adverse events at each study visit.

All serious adverse events, whether 'expected' (see table above in section 9.2.) or 'unexpected', need to be reported. All serious adverse event (SAE) information will be recorded on the PC-CTU SAE report form by the site or the CI and faxed to the Trials Unit's dedicated fax line, which is monitored during office hours. SAEs will be reported to the PC-CTU as soon as possible, preferably within 24 hours of the site becoming aware of the event. The PC-CTU will perform an initial check of the report, request any additional information from the reporting clinician and ensure that the CI or safety delegator reviews and evaluates the report for expectedness and relatedness. All SAE reports will also be reviewed routinely by the Data Monitoring and Ethics Committee, and all SAEs will be followed up until resolution or the end of the study period.

A SAE occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Related and unexpected SAEs will also be reported to the sponsor. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event.

11. LONE WORKING POLICY

As part of the trial follow up visits the research team will conduct home visits if this is acceptable to participants. These will be conducted in line with the University of Oxford Safety Office 'Safety in fieldwork' policy (UPS S5/07 http://www.admin.ox.ac.uk/safety/policy-statements/s5-07/).

12. STATISTICS AND ANALYSIS

12.1. Description of Statistical Methods

The analysis will be carried out on the basis of intention-to-treat (ITT). This is, after randomisation, participants will be analysed according to their allocated intervention group irrespective of what they actually receive. The analyses for this pilot study will be primarily descriptive and will not include any hypothesis testing or presentation of P-values for group comparisons.

Continuous variables will be reported as means with standard deviations (or medians with Interquartile ranges if skewed). Categorical variables will be reported as counts and percentages. Differences between

groups will be calculated and described with 95% confidence intervals only and will not include significance tests with P-values.

12.2. The Number of Participants

A formal sample size calculation is not required for this pilot study. We will aim to recruit 100 women (i.e. 50 women will be randomised to each arm).

12.3. Analysis of Outcome Measures

The primary objective is to assess feasibility issues. For this analysis, descriptive statistics will be calculated and assessed for each group.

Criteria for success of this pilot study:

- Recruitment rate:
  - Minimum of 3 participants recruited per week across all sites
  - No centre to contribute < 5% of study participants
- Attrition rate of < 10%
- Compliance rate > 90%
  - *Number of study visits attended by all participants / total number of intended study visits (n x 7)*

Potential outcomes for this pilot study:

- Stop – main study not feasible
- Continue, but modify protocol – feasible with modifications
- Continue without modifications but monitor closely – feasible with close monitoring
- Continue without modifications – feasible as is

Difference in blood pressure between groups, to inform the planned future main trial, will be estimated using a mixed effect model and described with 95% confidence intervals only. Further we will explore the validity of a 'time in range' measure as previously described in the analysis of the management of oral anticoagulant therapy by Rosendaal et al in 1993 [13].

A detailed statistical analysis plan will be written with our statistical team and will be completed before receipt of the data.

12.4. Interim analysis

There is no planned interim analysis for this study. All Serious Adverse Events reports will be reviewed by a Data Monitoring and Ethics Committee. This committee will meet annually or more if required, receiving reports in order to facilitate trial oversight and safety assessment. The trial team will be blinded to this data, and no statistical analysis will be conducted.

13. DATA MANAGEMENT

13.1. Access to Data

The delivery of the intervention will involve patient home visits. In order to facilitate these visits the study team will require access to patient identifiable data to include patient names, home addresses and telephone numbers. The consent from will clearly list the data to be collected and for what purpose. Only data required for this defined purpose will be collected and held by the research team. The identifiable data will be held securely at the Primary Care Clinical Trials Unit, University of Oxford, with access to this data restricted to appropriate members of the study team identified on the delegation log. Identifiable data will be held separately from other clinical data and anonymised as soon as no longer required in line with PC-CTU SOPs.

Direct access will be granted to authorised representatives from the Sponsor or host institution for monitoring and/or audit of the study to ensure compliance with regulations.

13.2. Data Recording and Record Keeping

All study data required for analysis will be recorded on paper Case Report Forms (CRFs) and returned to the study team for data entry. CRFs will be held securely in locked filing cabinets, located within office space with restricted entry. All data points will be transferred from paper CRFs to a secure database management system (CDMS) hosted by the PC-CTU. Within the CDMS patients will be identified solely by a unique study identification number. No patient identifiable data will be held within the CDMS. At the conclusion of the trial, following database lock and final analysis all documents will be appropriately archived for at least five years in line with PC-CTU standard operating procedures.

14. QUALITY ASSURANCE PROCEDURES

The CI will ensure the study is conducted in accordance with the current approved protocol, PC-CTU SOPs and all applicable local and national guidelines and regulations. The PC-CTU will conduct a study specific risk assessment prior to study commencement, which will inform the level and nature of monitoring required for this study.

A Trial Management Group (TMG) will be established to support the CI in overseeing the progress and conduct of the study.

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

15.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

15.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

15.4. Reporting

The CI shall submit, once a year throughout the study, or on request, an Annual Progress report to the REC Committee, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

15.5. Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and CDMS. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so. All data generated from the text messaging service and smartphone app will all be anonymised prior to entry into the CDMS.

15.6. Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

15.7. Other Ethical Considerations

In the self-management arm we are withdrawing part of participants' usual blood pressure management by their GP and midwife. Therefore for safety it is important that participants in this arm adhere to the monitoring schedule. In the first 14 days after birth NICE recommends that BP is monitored on at least alternate days. Therefore if participants fail to report 3 consecutive blood pressure readings via the text message service or smart phone app, this will trigger the research team to contact them. From 14 days after delivery until treatment is discontinued, failure to report 5 consecutive blood pressure readings will trigger the research team to contact a participant.

If women in the intervention arm still require additional support from the GP or community midwife postpartum for other medical, psychiatric or social issues then this will continue irrespective of their involvement in the trial. It will only be additional community midwife or GP input for blood pressure management alone that will be withdrawn.

Any incidental findings that arise as a result of study procedures or investigations (for example blood results) will be communicated directly to participants by the CI. With a participant's consent these findings will be passed on to the participant's GP so that appropriate follow up can be arranged if required.

16. FINANCE AND INSURANCE

16.1. Funding

This study is funded by NIHR Collaborations for Leadership in Applied Health Research and Care.

16.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment, which is provided.

17. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by NIHR. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

18. REFERENCES

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[12] General Medical Council '0-18 years: guidance for all doctors' 2007; 16-17
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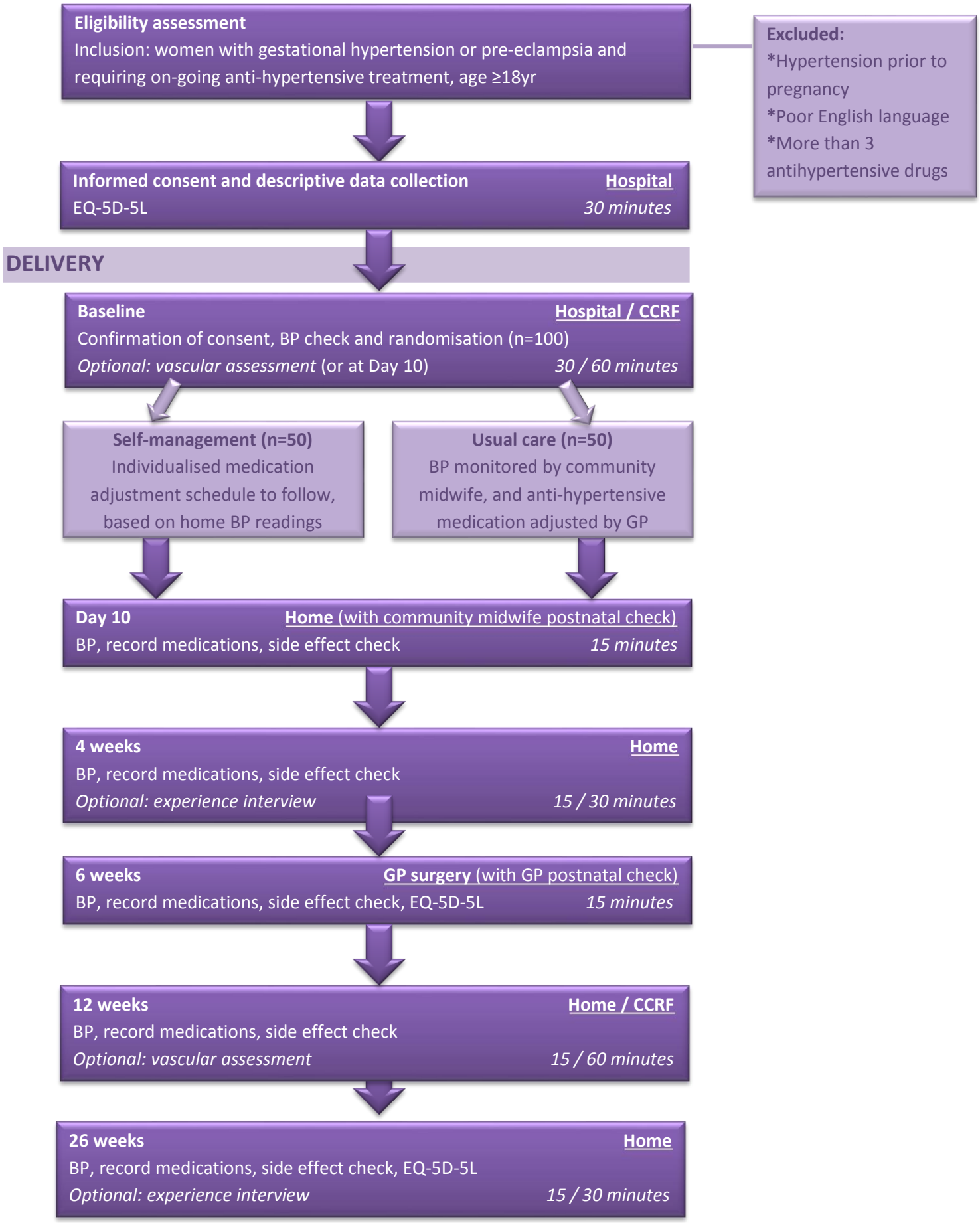
19. APPENDIX A: STUDY FLOW CHART



20. APPENDIX B: SCHEDULE OF STUDY PROCEDURES

Procedures	**Visits** *(all timings in relation to date of delivery)*						
	1: Screening	**2: Baseline** Day 3 - 2 or +3d	**3:** Day 10 - 2 or +4d	**4:** 4 weeks +/- 1w	**5:** 6 weeks +/- 1w	**6:** 12 weeks +/- 1w	**7:** 26 weeks +/- 2w
Informed consent	X						
Verbal confirmation of consent		X	X	X	X	X	
Demographics	X	X					
Medical history	X	X					
Eligibility assessment	X						
Eligibility confirmation		X	X	X	X	X	X
Randomisation		X					
Blood pressure check		X	X	X	X	X	X
Document medications	X	X	X	X	X	X	X
Side effect check		X	X	X	X	X	X
Adverse event assessment			X	X	X	X	X
Weight	Record booking weight	X				X	X
EQ-5D-5L	X				X		X
Offer specialist hypertension assessment if on-going treatment					X		
Structured patient experience interview (*optional*)	X			X			X
Vascular risk measurements (*optional*)		EITHER X	OR X			X	

21. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	4.0	19/01/2015	A Cairns	Participants will be weighed at visits 2, 6 and 7.
2	5.0	08/06/2016	A Cairns	• Vascular assessments to take place at baseline or day 10 visit • Windows for visits 2,3 and 4 adjusted • If participants discharged after day 14, additional visit or phone call will be arranged before 4 weeks at the participants' convenience • Serious adverse events: altered to make it clear that symptoms must also fulfil one of the criteria listed in section 10.1 in order to be classified as a serious adverse event Data analysis: No centre to contribute < 5% of study participants
3	5.1	16/06/2016	A Cairns	Protocol amended to reflect the title used in practice for our independent oversight committee from Independent Safety Review Committee to Data Monitoring and Ethics Committee and added a small amount of text to clarify the role of this committee in line with our trial's risk assessment.

22. APPENDIX D: Blood pressure thresholds for self-management

For women on anti-hypertensive treatment:

Colour	Level	Blood pressure	Action
RED	**VERY HIGH**	**SYS 160 or more OR DIA 110 or more OR Symptoms**	Your blood pressure is very high. Sit quietly for 5 min and repeat blood pressure reading. If this is a repeat reading record a RED reading: Contact your local maternity unit immediately and arrange urgent assessment today.
ORANGE	**HIGH**	**SYS 150-159 OR DIA 100-109**	Your blood pressure is high. Sit quietly for 5 min and repeat blood pressure reading. If this is a repeat reading record an ORANGE reading: Contact your GP or midwife urgently and arrange assessment today.
YELLOW	**RAISED**	**SYS 140-149 OR DIA 90-99**	Your blood pressure is raised. Record a YELLOW reading. No change in your medication yet.
GREEN	**HIGH NORMAL**	**SYS 130-139 OR DIA 80-89**	Your blood pressure is in the target range when on treatment. Record a GREEN reading. This is fine provided that you have no side effects.
BLUE	**LOW NORMAL**	**SYS 100-129 AND DIA less than 80**	Your blood pressure is normal but you may require less treatment. Record a BLUE reading. Follow your medication change instructions if two days in a row in BLUE.
PURPLE	**LOW**	**SYS less than 100 AND DIA less than 80**	Your blood pressure is too low. Sit quietly for 5 min and repeat blood pressure reading. If this is a repeat reading record a PURPLE reading: Contact your GP or midwife urgently and arrange assessment today.

For women off anti-hypertensive treatment:

Colour	Level	Blood pressure	Action
RED	**VERY HIGH**	**SYS 160 or more OR DIA 110 or more**	Your blood pressure is very high. Sit quietly for 5 min and repeat blood pressure reading. If this is a repeat reading record a RED reading: Contact your local maternity assessment unit for urgent review today.
ORANGE	**HIGH**	**SYS 140-159 OR DIA 90-109**	Your blood pressure is high. Sit quietly for 5 min and repeat blood pressure reading. If this is a repeat reading record an ORANGE reading: If 2 or more consecutive readings in this range contact your GP or maternity assessment unit for review within 48 hours.
GREEN	**NORMAL**	**SYS less than 140 AND DIA less than 90**	Your blood pressure is normal. Record a GREEN reading.